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Occurrence, Fate and Transformation of Emerging Contaminants in Water: An Overarching Review of the Field

John Wilkinson[1,2]*, Peter S. Hooda[1], James Barker[3], Stephen Barton[3] and Julian Swinden[3]

[1] Kingston University London, School of Natural and Built Environments, Kingston-Upon-Thames, U.K.
[2] University of York, Environment Department, York, UK
[3]Kingston University London, School of Life Sciences, Pharmacy and Chemistry, Kingston-Upon-Thames, U.K.
*Corresponding author, University of York, Environment Department, York, U.K., email: john.wilkinson@york.ac.uk

Abstract

Many of the products and drugs used commonly contain chemical components which may persist through sewage treatment works (STW) and eventually enter the aquatic environment as parent compounds, metabolites, or transformation products. Pharmaceuticals and personal care products (PPCPs) and other emerging contaminants (ECs) have been detected in waters (typically ng/L) as well as more recently bound to sediment and plastic particles (typically ng/g). Despite significant advancement of knowledge since the late 1990s, the fate of these contaminants/transformation products once introduced into the aquatic environment remains relatively unresolved.

This review provides a unique focus on the fate of seven major groups of PPCPs/ECs in the aquatic environment, which is frequently not found in similar works which are often compound or topic-specific and limited in background knowledge. Key findings include: a) some replacements for regulation precluded/banned chemicals may be similarly persistent in the environment as those they replace, b) the adsorption of potentially bioactive chemicals to micro- and nanoplastics is a significant topic with risks to aquatic organisms potentially greater than previously thought, and c) micro-/nanoplastics are likely to remain of significant concern for centuries after regulatory limitations on their use become active due to the slow degradation of macro-plastics into smaller components.

An interdisciplinary perspective on recent advances in the field is presented here in a unique way which highlights both the principle science and direction of research needed to elucidate the fate and transport patterns of aquatic PPCPs/ECs. Unlike similar reviews, which are often topic-specific, here we aim to present an overarching review of the field with focus on the occurrence, transformation and fate of emerging contaminants. Environmental presence of seven major classes of contaminants (analygesics, antibiotics, antineoplastics, beta-blockers, perfluorinated compounds, personal care products and plasticisers), factors affecting contaminant fate, association with plastic micro-/nanoparticles and photochemical transformation are comprehensively evaluated.

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Keywords: Pharmaceuticals and personal care products; emerging contaminants; microplastics; photochemical transformation; aquatic pollutants; emerging contaminant fate

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1.0 Introduction and background of the field

Pharmaceuticals, personal care products (PPCPs), and many other synthetic organic compounds have revolutionised modern life and their use is now an indispensable component of a healthy society. Pharmaceutical use in particular is an integral component of establishing and maintaining a healthy population of both humans and livestock. In recent years, PPCPs and other emerging contaminants (ECs) have been detected in sewage effluents, surface- and ground-waters, precipitation, and occasionally drinking waters at trace levels (Ternes, 1998; Mohle et al., 1999; Stackelberg et al., 2004; Thomas and Hilton, 2004; Weigel et al., 2004; Lindqvist et al., 2005; Fent et al., 2006; Jjemba et al., 2006; Nikolaou et al., 2007; Kasprzyk-Hordern et al., 2008; Benotti and Brownawell, 2009; Mahmoud et al., 2009; Silva et al., 2011; Lopez-Serna et al., 2013; Tijani et al., 2016). Furthermore, these compounds are also shown to be present in suspended solids and river sediment (McClellan and Halden, 2010; Walters et al., 2010; Silva et al., 2011; Wilkinson et al., 2017).

The seemingly ubiquitous environmental presence of pharmaceuticals and other so-called 'emerging contaminants', albeit in trace or ultra-trace (below ng/L) concentrations, has become of great concern in recent years (Tijani et al., 2016). Furthermore, the extent of PPCPs and other ECs found in the environment, as well as their often largely unknown transformation products, is virtually limitless as new drugs and replacements for regulatory limited compounds are continually being introduced to market.

Many pharmaceuticals and personal care products contain complex chemical structures, often in combination. The original source of these products can be traced to respective manufacturing plants (e.g., 3303 tonnes of paracetamol were produced in France in 2008). However, after leaving manufacturing plants, their routes of environmental exposure become more complex, less understood, and differ between urban and rural environments (Figure 1). Every human represents a source of PPCP and other emerging contamination, particularly with increasing use of pharmaceuticals (Table 2). From use of soaps and plastics to prescription and non-prescription pharmaceuticals, the personal care products and pharmaceuticals we use in everyday life will inevitably enter the environment after use and excretion. Un-used pharmaceuticals, disposed of in toilets or drains, as well as partially or un-metabolised medication excretions by humans have been shown to be a significant source of prescription and non-prescription drug contamination, representing up to 90% of input (National Association of Clean Water Agencies, 2012). Olsen et al. (2009) found urine to be the most significant source of PPCP elimination in humans. Pharmaceuticals are often not completely metabolised in the body resulting in some proportion of the parent compound (or conjugated derivative) entering sewage treatment facilities (Table 3) via renal (urine) and biliary (faeces) excretions then introduced into the environment (by STW effluent) after incomplete degradation (Jjemba, 2006; Silva et al., 2011).

Virtually every human and veterinary pharmaceutical, either prescription or non-prescription, has been detected in sewage treatment works (STW) effluent (Table 1) and the aquatic environment at levels typically not exceeding upper ng/L. Personal care product (PCP) contamination often includes residues of surfactants used in detergents and soaps, plasticisers used in product packaging and linings, musk compounds used as fragrances, personal insecticides, disinfectants, among others. So-called other ECs include non-commonly monitored agricultural chemicals (for example many herbicides, pesticides and

pharmaceuticals used in animal husbandry) and even residues of recreational drugs and their metabolites (Rosi-Marshall et al., 2015). Recent concern regarding groundwater/aquifer contamination by chemicals used in the hydraulic fracturing of shale (e.g., naphthalene used as a surfactant and tetramethyl ammonium chloride as clay stabiliser) may be considered novel emerging contaminants (Gordalla et al., 2013).

Once in the aquatic environment, other than some well-researched compounds (e.g., BPA and ethinylestradiol), their ultimate fate (i.e., bioaccumulation, spatial distribution, and partition between dissolved and bound to suspended particulate material phases) in aquatic ecosystems is relatively unclear. Most reviews on the study of ECs tend to be limited to a certain chemical (e.g. BPA: Corrales et al., 2015), group of chemicals (e.g. endocrine disrupting compounds: Patisaul and Adewale, 2009; Fisher and Eugster, 2014) or on certain specific aspects of PPCPs/ECs (e.g. removal/degradation during sewage treatment: Luo et al., 2014). This review critically examines the most influential research, encompassing seven major groups of PPCPs and ECs, with a particular focus on occurrence, association with micro-/nanoplastic particles, and bio- and photochemical transformation.

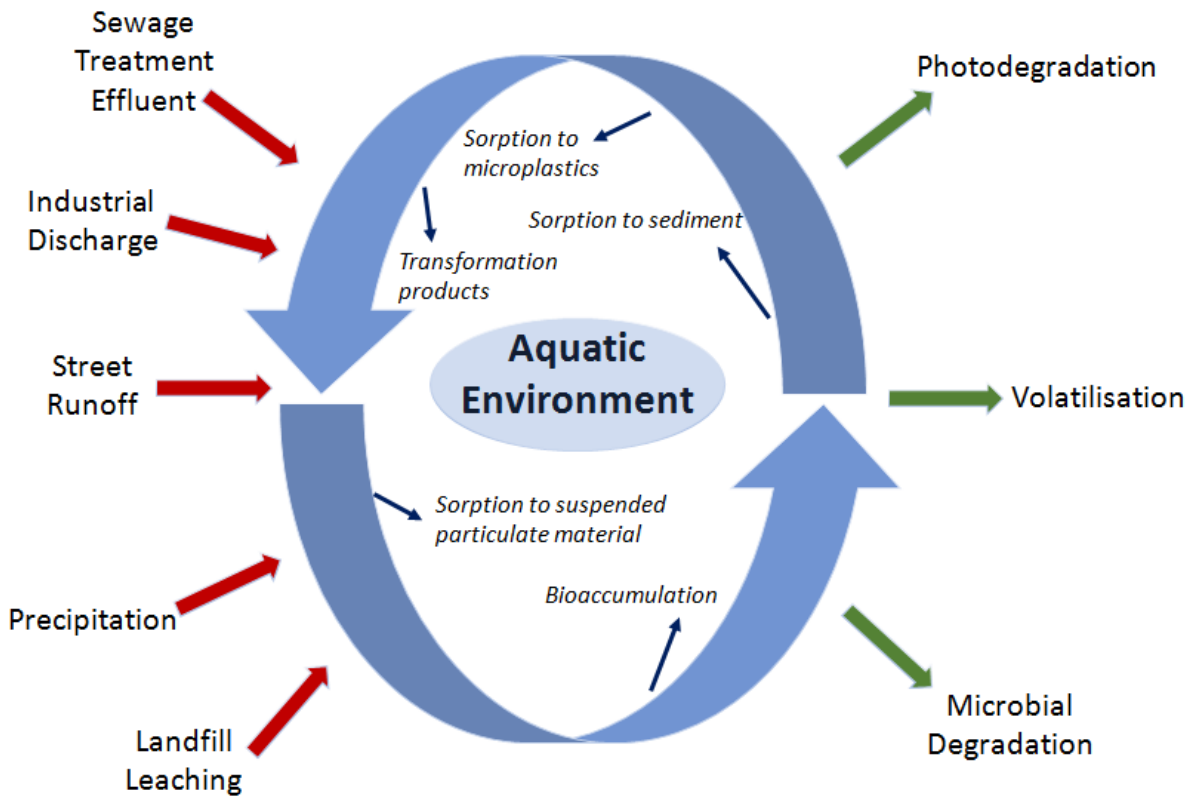

Figure 1. Sources and fate of PPCP and other ECs in the aquatic environment.

Table 1. Comparison of influent and effluent concentrations of 10 commonly reported pharmaceuticals in wastewater

Compound	STW Influent (ng/L)	STW Effluent (ng/L)	Source
Atenolol	1250*	800*	Jelic et al. (2011)
	795	330	Vieno et al. (2007)
Bezafibrate	800*	400*	Jelic et al. (2011)
	4700	600	Metcalfe et al. (2003)
Carbamazepine	1050*	750*	Jelic et al. (2011)
	1900	2300**	Metcalfe et al. (2003)
Diclofenac	1550*	900*	Jelic et al. (2011)
	1300	ND	Metcalfe et al. (2003)
Gemfibrozil	170*	420**	Jelic et al. (2011)
	2100	1300	Metcalfe et al. (2003)
Ibuprofen	8600	510	Guerra et al. (2014)
Ketoprofen	2650*	800*	Jelic et al. (2011)
	5700	ND	Metcalfe et al. (2003)
Metoprolol	130*	80*	Jelic et al. (2011)
	1060	755	Vieno et al. (2007)

2.0 The profile of PPCP Contamination: What's in the Water?

Since the use of synthetic compounds such as pharmaceuticals and personal care products started, these contaminants have been present in the natural and built environments (Jelić, 2012). More than 80 compounds and several metabolites have been found in the aquatic environment and some in drinking water, which indicates that not all contaminants are removed during water treatment (Heberer, 2002). While their presence is not a new phenomenon, noticeable attention has been drawn to them within the last decade (Jelić, 2012). Arguably much of this novel interest is due to recent research into the ecotoxicological effects on aquatic organisms of other synthetic compounds such as herbicides and pesticides. Product proliferation and ease of access to pharmaceuticals and personal care products have significantly increased the loading of such compounds in both the natural and built environments (National Association of Clean Water Agencies, 2012). The exact combination of compounds in sources of water varies from location to location and concentrations are consistently higher in ground and surface water than in drinking water (Benotti and Brownawell, 2009; National Association of Clean Water Agencies, 2012).

Worldwide, few such compounds have been inventoried or regulated as contaminants (Caliman and Gavrilescu, 2009). Thus, a lack of knowledge exists regarding the occurrence, proliferation, impacts and fate of synthetic pharmaceuticals and personal care products in the environment (Caliman and Gavrilescu, 2009). Benotti and Brownawell (2009) found 21 different synthetic compounds in 19 different municipal water supplies in the United States. In this study, 51 pharmaceuticals were tested for, of which nearly half were detected (Benotti and Brownawell, 2009). The ten most commonly found pharmaceutical contaminants were: atenolol, estrone, carbamazepine, meprobamate, gemfibrozil, naproxen, phenytoin, sulfamethoxazole, trimethoprim, and TCEP (Benotti and Brownawell,

2009). Of the ten most commonly found, median concentrations were less than 10 µg/L (Benotti and Brownawell, 2009). While such concentrations may seem low, some compounds (e.g., ethinylestradiol) have been shown to be endocrine disruptors during critical periods of biological development in fish at concentrations as low as ≤1 ng/L (Parrott and Blunt, 2005; Baumann et al., 2014). Thus, particularly in terms of hormonal disruption, concentrations of synthetic contaminants can have biological effects at concentrations detected in environmental samples.

In the United Kingdom, Jones et al. (2002) modelled aquatic concentrations of the 25 most frequently used pharmaceuticals in the nation. Compounds ranged from sodium valproate, an anti-epileptic drug, to ibuprofen, an analgesic (Jones et al., 2002). Surface water concentrations of all contaminants were modelled with conservative estimates and exceeded 1 ng/L (Jones et al., 2002). Some of the most commonly used drugs in the United States alone are asthma medication for children, central nervous system stimulants, antidepressants, and cholesterol lowering medication, all of which have been detected in US waters (Centers for Disease Control, 2010). In 2000, the U.S. Geological Survey (USGS) began one of the first and perhaps still most significant reconnaissance studies of the 95 most common PPCPs in the United States focusing on 136 different streams and rivers running through intensive livestock production and urban centres (Barnes et al., 2002; Kolpin et al., 2002). During the study, 82 of the 95 PPCPs were detected (Kolpin et al., 2002). While concentrations were generally low and did not often surpass U.S. drinking water guidelines (where guidelines exist for such contaminants), known endocrine disrupting compounds were discovered at physiologically active concentrations (Kolpin et al., 2002). Furthermore, mixtures of PPCPs present in water were common as a median of 7 contaminants and as many as 38 were found in individual streams or rivers bringing to light possible combination/synergistic effects (Kolpin et al., 2002). In recent years, research has commonly focused on elucidating the presence, concentrations, and at times spatial distribution of such contaminants in the aquatic environment (Musolff et al., 2009; Sánchez-Avila et al., 2010; Al Aukidy et al., 2012; Li, 2014). Such research serves to indicate that contamination of the aquatic environment with synthetic compounds is a worldwide phenomenon. Several commonly reported classes of PPCPs have been observed and are discussed in greater detail within this chapter. Table 4 shows concentrations of 42 commonly detected PPCP/ECs in surface, ground and drinking water of five different countries.

2.1 Analgesics

Non-Steroidal Anti-inflammatory Drugs such as ibuprofen, paracetamol (acetaminophen), naproxen, and diclofenac are commonly used and relatively easily accessible. Prior to STW discharge, ibuprofen appears to be readily degraded into its two main metabolites: carboxyibuprofen and hydroxyibuprofen. Concentrations of parent-ibuprofen have been found at levels up to 24600 ng/L (4000 ng/L median) in STW effluents and at levels of 700 ng/L in seawater (Metcalfe et al., 2003; Weigel et al., 2004). While paracetamol appears to be well removed during sewage treatment, Kolpin et al. (2002) identified levels of the parent compound of paracetamol at median levels of 110 ng/L in 24% of sampled U.S. streams and rivers. Other analgesics, such as codeine, were found in the same study at median levels of 10 ng/L in 7% of sampled streams and rivers. Analgesics such as naproxen, ibuprofen and paracetamol have also been detected in rivers and canals of Spain at levels of 81 ng/L, 470 ng/L and 40 µg/L respectively (Al Aukidy et al., 2012; Li, 2014). In six Canadian STWs, Guerra et al. (2014) identified acetaminophen, ibuprofen, hydroxyibuprofen and

naproxen at respective median levels of 92000 ng/L, 8600 ng/L, 24000 ng/L and 6280 ng/L in all collected influent samples and 2200 ng/L, 510 ng/L, 4200 ng/L and 580 ng/L in 58%, 92%, 67% and 100% of respective effluent samples. In the same study, acetaminophen, ibuprofen, 2-hydroxy-ibuprofen and naproxen were extracted from biosolids collected in the same sewage treatment facilities at respective median levels of 23 ng/g dry weight (dw) biosolid, 150 ng/g dw, 79 ng/g dw and 24 ng/g dw in 25%, 100%, 13% and 75% of collected samples (Guerra et al., 2014). Environmental levels of common analgesics appear relatively constant over recent years with median levels of naproxen and ibuprofen reported at 550 ng/L and 200 ng/L respectively in rivers and canals of both New Jersey and Canada (Li, 2014).

2.2 Antibiotics

Antibiotics are one of the oldest, most successful, and most commonly used classes of pharmaceuticals. Both human and veterinary antibiotics are commonly found in the aquatic environment (Baquero et al., 2008; Kümmerer, 2009; Martinez, 2009; Jiang, 2013; Berglund, 2014). In addition to parent compounds, metabolites of antibiotics such as erythromycin and penicillin (e.g., penicilloic acid) have also been detected at levels, up to 30 ng/L in both ground and surface waters (Focazio et al., 2008). Sulphonamides sulfamethoxazole and sulfapyridine have been found in Spanish STW effluents at levels up to 18 ng/L and 28 ng/L as well as their acetylated metabolites at 9 ng/L and 52 ng/L respectively (Garcia-Galan et al., 2012). Kolpin et al. (2002) found residues of several common antibiotic contaminants in US streams and rivers (see Table 4) including triclosan at 2300 ng/L. Trimethoprim and sulfamethoxazole have also been detected at levels of 2 ng/L and 46 ng/L respectively in Canadian groundwater (Van Stempvoort et al., 2013), 6 ng/L and 3 ng/L respectively in rivers and canals of Spain (Li, 2014), and 2000 ng/L and 39 ng/L respectively in STW effluent in Taiwan (Li, 2014). Despite the typically low concentration of such compounds, their occurrence in the aquatic environment is suggested to influence the development of antibiotic resistance in microorganisms (Hong et al., 2013; Berglund, 2014). However, such findings are debated and warrant further investigation.

2.3 Antineoplastic Compounds (ACs)

Antineoplastic (anticancer) pharmaceutical contamination of the aquatic environment is of concern as their use continues to increase (Brezovsek et al., 2014). Several compounds used in chemotherapy have been identified in hospital wastewater, surface waters, STW facilities, and even estuarine waters (Thomas and Hilton, 2004; Roberts and Thomas, 2006; Fent et al., 2006). Among those identified include, ifosfamide, daunorubicin etoposide and methotrexate at concentrations of <2-10647 ng/L, <5-380 ng/L and <2-4689 ng/L respectively in hospital wastewater (Yin et al., 2010). In the UK, tamoxifen, a drug used in the treatment of breast cancer, was identified by Roberts and Thomas (2006) at levels ranging between 146 and 369 ng/L in STW effluents. Furthermore, levels of the same drug were identified in the Tyne estuary (Tyne and Wear, UK) at levels of 27-212 ng/L, indicating a strong environmental persistence and likely low degradation in STW facilities (Thomas and Hilton, 2004; Roberts and Thomas, 2006). Antineoplastic compounds appear to be incompletely removed by sewage treatment and not readily biodegradable (Besse et al., 2012). Liu et al. (2010) show maximum STW influent and effluent levels of anastrozole of 0.32 ng/L and 0.30 ng/L respectively indicating the compound is poorly removed from

Chinese STW. Surface water concentrations of antineoplastic compounds are typically low and have been reported up to 64.8 ng/L for cyclophosphamide (Moldovan, 2006), 0.14 ng/L for ifosfamide (Buerge et al., 2006), and 25 ng/L for tamoxifen (Coetsier et al., 2009). Zounkova et al. (2010) suggest some antineoplastic compounds may be found in hospital effluents at biologically significant concentrations to common aquatic bacteria however it should be noted that such biologically significant levels are currently not well-established or researched.

2.4 Beta-Blockers

Beta-blockers, or beta-adrenergic receptor antagonists, are used for the treatment of high blood pressure and heart attack recovery and have been identified in sewage and surface waters (Fent et al., 2006; Maurer et al., 2007). Such compounds commonly include sotalol, atenolol, metoprolol, propranolol, and bisoprolol. Atenolol and metoprolol have been identified at highest levels of up to 33100 ng/L and 1520 ng/L respectively in STW influent and 7600 ng/L and 250 ng/L respectively in STW effluents (Luo et al., 2014). Beta-blockers appear to be relatively degradable in STW facilities showing removal efficiencies from 56.4% for metoprolol to 85.1% for atenolol, for example (Maurer et al., 2007; Luo et al., 2014). Atenolol has been reported in multiple countries including in the ground water of France up to 30 ng/L (Vulliet and Cren-Olivé., 2011), Korea up to 690 ng/L (Kim et al., 2009), and the United Kingdom up to 680 ng/L (Kasprzyk-Hordern et al., 2009).

2.5 Perfluorinated Compounds

Perflourinated compounds (PFCs) are characterised by a fluorinated carbon chain of variable length and are commonly used as anti-stick or water repellent liners for clothing, packaging, automobiles, among other uses. PFCs include compounds such as perfluorooctanoic acid (PFOA), used in fluoropolymers such as Teflon, and perfluorooctane sulfonate (PFOS), a fluorosurfactant used in stain repellents and fire-fighting foams. Other PFCs may be used in cosmetics and hydrophobic coatings, such as used with some clothing items (Inoue et al., 2004). Research has shown these compounds frequently detected in the environment, even being found in deep arctic seas (Rudel et al., 2003; Skutlarek et al., 2006; Farré et al., 2008; Jahan et al., 2008; Arvaniti et al., 2015; Wilkinson et al., 2017). Perfluorinated compounds are not limited to the aquatic environment. PFOA and PFOS have been consistently detected in the vacuum cleaner dust of Japanese homes at levels up to 3700 ng/g and 2500 ng/g respectively (Moriwaki et al., 2003). In addition, Fluorotelomer alcohols (FTOHs), such as 8:2 FTOH, have been detected in Japanese precipitation at concentrations up to 1.97 ng/L indicating the atmosphere as both a medium of transport and source of contamination (Mahmoud et al., 2009). Fluorotelomer alcohols are common precursors to many fluorosurfactants, a component of many personal care products and are so too used in the production of stain repellents and hydrophobic product coatings.

Typically, PFCs are found in rivers at levels below 100 ng/L but PFOA has been identified in the Moehne River, Germany, at up to 3640 ng/L and perfluoropentanoic acid up to 1638 ng/L (Skutlarek et al., 2006). PFCs including PFOS, PFOA, and perfluorononanoic acid (PFNA) have been detected in port and coastal sea water at concentrations typically not exceeding 0.75 ng/L but have been detected by Sánchez-Avila et al. (2010) up to 8.38 ng/L (PFOS) in port seawater and 3.93 ng/L (PFOS) in coastal seawater. Recent evidence suggests levels of PFCs may be elevated in street water runoff during periods of rainfall where levels

of PFNA and PFOA have been reported as high as 648 and 1160 ng/L respectively in areas of heavy transport vehicle activity (Wilkinson et al., 2016b). Many PFCs are, at times, detected at higher concentrations in river water than in STW effluent water indicating their sources may not always be predominately wastewater-driven (Sánchez-Avila et al., 2010). Zushi and Masunaga (2009) suggest that concentrations of PFCs in rivers are highest in areas receiving runoff from heavy transportation land use (in particular near train stations). Thus, land use may be associated with the introduction of PFCs to rivers via runoff (rainfall-driven) events.

Table 2. Amounts (in tonnes) of twelve common pharmaceuticals consumed annually

		Country, (Year), [Population]				
Drug Class	**Compound** (in Tonnes)	**England**[1] (2000) [58,789,194]	**Germany**[2] (2001) [82,350,000]	**France**[3] (2008) [64,370,000]	**Germany**[4,5] (2010) [81,780,000]	**Spain**[5] (2010) [47,020,000]
Analgesic	Diclofenac	26.12	85.8	22.64	78.58	17.4
	Ibuprofen	162.2	344.89	58.35	250.79	218.53
	Naproxen	35.07	n/a	37.33	n/a	56.7
	Paracetamol	390.9	621.65	3303.08	n/a	1065.84
Antacid	Ranitidine	36.32	85.81	n/a	n/a	n/a
Antibiotic	Amoxicillin	n/a	n/a	333.22	n/a	187.76
	Clarithromycin	n/a	n/a	16.89	12.36	10.86
Anticonvulsant	Carbamazepine	40.35	87.6	33.36	83.3	20.95
Antidiabetic	Metformin	205.8	516.91	n/a	n/a	n/a
β-Blocker	Atenolol	28.98	n/a	n/a	n/a	n/a
	Metoprolol	n/a	92.97	n/a	n/a	n/a
Lipid lowering	Bezafibrate	n/a	n/a	20.85	39.16	6.25

[1]Jones et al. (2002)
[2]Huschek et al. (2004)
[3]Vulliet and Cren-Olivé, (2011)
[4] ter Laak., (2010)
[5]Ortez de Garcia et al. (2013)
*n/a, not available

Drinking water treatment does not appear to be an absolute barrier to PFCs. Zafeiraki et al. (2015) quantified concentration of 11 PFCs in treated drinking water and found ΣPFCs up to 54 ng/L in 48.6% of tested waters near Amsterdam, Netherlands. Here, short-chain PFCs such as perfluoropentanoic acid and perfluorohexanoic acid were detected more frequently than long chain (C>8) PFCs, particularly in areas using purified surface water over groundwater (Zafeiraki et al., 2015).

PFCs, and their metabolites are shown to be persistent and bioaccumulative in the aquatic environment and not easily degraded by microbiological or chemical treatment in sewage and drinking water treatment (Skutarek et al., 2006; Arvaniti et al., 2015). Schultz (2006) showed that mass flow of 6:2 fluorotelomer sulfonate and perfluorooctanoate remained unchanged through STW trickling filtration and primary clarification. Mass flow of perfluorooctane and perfluorodecane sulfonates increased during trickling filtration and activated sludge treatment due to degradation of their precursor molecules, mainly fluorotelomer alcohols (Schultz et al., 2006). Many PFCs appear to be metabolised to their sulfonate and carboxylic acid metabolites (Farré et al., 2008).

In recent years, many long-chain (>C7) carboxylic and sulfonic acid PFCs (e.g., perfluorooctanoic acid- PFOA) have been replaced by shorter, less bioaccumulative derivatives (Sun et al., 2016). However, resent evidence suggests that new generation short-chain replacements such as perfluoro-2-propoxypropanoic acid (which has replaced PFOA for many uses) are similarly persistent through wastewater treatment and found at concentrations exceeding those of long-chain 'legacy' PFCs 630 ng/L in river water (Sun et al., 2016). Similarly, Wilkinson et al. (2017) quantified concentrations of short chain replacement perfluorobutanesulfonic acid between 1.4 to 1.7-fold higher than long-chain alternatives in sewage treatment effluent and receiving water bodies of southern England. While study indicates that long-chain PFCs may be highly persistent and bio-/accumulative in the aquatic environment (Sun et al., 2016), future research should focus on determining the environmental fate and accumulation of short-chain alternatives to traditional (>C7) PFCs. While no clear and significant statutory regulation of long-chain PFCs exists, government bodies have encouraged use of short-chain analogues through programmes such as the US EPA's PFOA Stewardship Programme and the Stockholm Convention's Persistent Organic Review Committee's guidance on replacements for PFOS. Ultimately, the use and manufacture of long-chain PFCs has been phased out of most OECD countries with some production shifted to other locations (Stockholm Convention on Persistent Organic Pollutants, 2010). Additionally, over 150 potential short-chain and other chemical replacements for PFOA alone have been established under the EPA's PFOA Stewardship Programme (United States Environmental Protection Agency, 2017).

2.6 Personal Care Products (PCPs)

Common PCPs include fragrances (musk compounds), UV filters (sunscreens), detergents, lotions, personal insecticides, deodorants, and cleaning products which are typically released through household wastewater (Peck, 2006; Roosens et al., 2007). Cleaning products used in domestic and industrial applications (detergents and soaps) can include non-ionic surfactants such as alkylphenol ethoxylates (AEOs), of which more than 90% are nonylphenol ethoxylates (NPEOs) (Farré et al., 2008). Compounds of interest include 4'-nonylphenol, a well-known metabolite of NPEOs which has recently been detected up to 80 ng/L in the Vaal River, South Africa (Chokwe et al., 2015).

Synthetic Musk Compounds (SMCs) are commonly used in personal care products and are widely occurring in the environment with varying chemical structures (Roosens et al., 2007; Lee I. et al., 2010). These compounds were first developed at the end of the 19th century and have since been continually produced for fragrance in cosmetics, soaps, perfumes, detergents and lotions (Lee I. et al., 2010). Some of the most commonly occurring SMCs include Tonalide (AHTN), Galaxolide (HHCB), musk xylene (MX), and musk ketone (MK) and have been detected in PCPs such as lotions, perfumes, and deodorants at levels up to 8000 µg/g, 22000 µg/g 26 µg/g, and 0.5 µg/g respectively (Roosens et al., 2007). Typically, SMCs occur in Sewage treatment works (STW) influent at levels of 3690-7330 ng/L, effluent at levels of 960-2960 ng/L, and surface water at 150-16700 ng/L (Lee I. et al., 2010).

Ultraviolet (UV) filters, such as benzophenone-4 (BP-4) and 2-Phenylbenzimidazole-5-sulphonic acid (PBSA), have only relatively recently been reported in STW influent, effluent, surface- and at times in drinking-waters (Giokas et al., 2007; Kasprkyz-Hordern et al., 2008; Rodil et al., 2008; 2012). Residues of UV filters are thought to be largely seasonally introduced through bathing and other recreational use of water (Rodil et al., 2012). In

northwest Spain, Rodil et al. (2012) detected BP-4 and PBSA in all sampled STW influents at median concentrations of 2100 ng/L and 200 ng/L respectively. Similarly, median concentrations of 1200 ng/L BP-4 and 240 ng/L PBSA were found in treated STW effluent and up to 600 ng/L BP-4 and 20 ng/L PBSA in surface water (Rodil et al., 2012). Among UV filters detected in drinking water (frequency between 12-46% of samples) concentrations are typically below 10 ng/L except BP-4, which has been detected up to 60 ng/L in northwest Spain (Rodil et al., 2012).

The implications of such PCPs in the aquatic environment is somewhat unclear when compared to the relatively large amount of research conducted elucidating the aquatic toxicity of human pharmaceuticals (Brausch and Rand, 2011). Toxicity of trace-level (ng/L to low µg/L) PCPs in the aquatic environment are highly debated and are reviewed in greater detail elsewhere (e.g., Brausch and Rand, 2011). Further research is warranted particularly in assessing potential endocrine disruption associated with exposure to UV-filters and bioaccumulation of PCPs in the aquatic environment (Brausch and Rand, 2011).

2.7 Plasticisers

Plasticisers are compounds which increase the plasticity of a material and are often involved in the production of plastic products/packaging, epoxy resins (coating cans for food and beverage), water pipe lining, thermal printing paper, implanted medical devices and in the production of CDs and DVDs, mobile phones, plastic food containers, eye glass lenses, drinking bottles, food packaging, dental sealants, among many others (Barraza, 2013; American Dental Association, 2016; Testai et al., 2016). Common plasticisers found in surface water include bisphenol-A (BPA), bisphenol-S (BPS), and bisphenol-F (BPF) which have recently been detected up to 98 ng/L, 135 ng/L, and 1110 ng/L respectively in the Pearl River, China (Yamazaki et al., 2015). Bisphenol-A has also been detected at levels of up to 50 ng/L (average of <9 ng/L) in <5% of 291 sampled tap waters across France (Colin et al., 2014). BPA in particular is made at one of the highest volumes of any PPCP in the world with more than 2 million metric tonnes produced annually (Lang et al., 2008; Maia et al., 2009). Despite government restrictions being placed on BPA use, the market for BPA, and hence the compound's production, is poised for continued growth (see a comprehensive market analysis of BPA use and production: Merchant Research and Consulting, 2015). In 2011, in response to widespread concern over safety in the public and scientific sectors, the European Commission restricted the use of BPA as a monomer in the manufacture of polycarbonates (Grignard et al., 2012). However, since 2011, worldwide production of BPA has increased 5.25% annually showing total production of 4.4 million tonnes in 2011, 4.6 million tonnes in 2012 and 5.4 million tonnes in 2015 (Merchant Research and Consulting, 2015). Approximately 53% of BPA is produced in Asia with major centres of production in Taiwan, South Korea, China and Japan (Merchant Research and Consulting, 2015).

In response to concern over environmental toxicity of BPA and the compound's widespread use in thermal printer paper, the USEPA released a report outlining 19 possible replacements for BPA (most other plasticisers) and their associated toxicity (USEPA, 2014). Possible replacements include BPS, 2,4'-bis(hydroxyphenyl)sulfone (2,4-BPS), BPF, 2,2'-bis(4-hydroxy-3-methylphenylphenyl)propane (BPC), and 4,4'-(1-Phenylethylidene)bisphenol (BPAP) among others (USEPA, 2014). However, it should be noted that the USEPA report outlines potential replacements with similar toxicity to that reported for BPA (such as for BPS, BPC and BPAP) or toxicity potentially higher than that reported for BPA such as in the

case of BPF (USEPA, 2014). Bisphenol-S is now commonly used as a plasticizer; however, BPS has not been extensively evaluated in terms of its environmental presence and persistence in surface, ground, and drinking waters (Grignard et al., 2012). Recent evidence suggests BPS, BPF and BPAF are present at concentrations up to 19 ng/L, 3.4 ng/L and 246 ng/L respectively in Chinese rivers and that BPF and BPAF may more readily associate with sediment at concentrations of up to 30 ng/g and 2010 ng/g respectively (Yang et al., 2014). In the same study BPA was quantified up to 75 ng/L in river water and 43 ng/g in sediment (Yang et al., 2014). Plasticisers such as BPA and BPS have also been detected in street runoff during times of rainfall at levels up to 2410 and 50 ng/L respectively in greater London, UK (Wilkinson et al, 2016b). As replacements for plasticisers limited by regulatory bodies come to market, further and increasing research is needed to determine the environmental distribution as well as fate in sediment, suspended material and biota.

Table 3. Proportion of the parent compound excreted for 60 common pharmaceuticals (Upton et al., 1980; Baker et al., 1999; Jjemba, 2006)

	Low: (≤5%)	Moderately low: (6-39%)	Relatively high: (40-69%)	High: (≥70%)
Analgesics	Aspirin, Ibuprofen, Paracetamol, Ketoprofen, Neproxen	Cromoglycate, Diclofenac	Dexamethasone	Morphine
Anesthetics		Lidocaine		
Antimicrobials	Acylovir, Chloramphenicol	Ampicillin, Clindamycin, Sulfamethoxazole	Dicloxacillin, Ethambutol, Didanosine, Fluconazole, Metronidazole, Minocycline, Norfloxacin, Trimethoprim, Valaciclovir	Amoxacillin, Ciprofloxacin, Doxycycline, Cephalexin, Flucytosine, Genaconazole, Tetracycline
Antineoplastics	Idarubicin	Temozolomide		
Cardiovascular	Atorvastatin (Lipitor), Labetalol, Quinapril, Verapamil	Enalapril (Vasotec), Hydrochlorothiazide, Procainamide, Qiunidine, Ramipril, Simvastatin (Zocor)	Bezafibrate, Clonidine, Digoxin, Furosemide	
Dopamirgics		Nimodipine		
Gastrointestinal		Domperidone, Rinitinide (Zantac)		
Reproductive			Testosterone	
Sedatives/ antipsychotics	Carbamazepine, Valium, Fluoxentine (Prozac), Naltrexone	Phenobarbitone, Primidone	Atropine	Baclofen
Uricosuric	Probenecid			

3.0 Environmental Transport and Fate of PPCP and other Emerging Contaminants

Traditionally, the contamination and fate of PPCPs and other emerging contaminants in river systems are studied through analysis of liquid samples. This is usually limited to monitoring parent compounds in the water (as opposed to rarer studies involving sediment, suspended solids and other mediums, e.g. biofilms, and other aquatic biota) of river ecosystems. Such an approach, while still informative in regard to contaminant attenuation within the water component of a river, does not represent the complete dynamics of PPCPs transport. Contaminant transport and fate in aquatic systems is still an evolving research area of PPCP environmental pollution, likely due to the relatively poorly understood and complex interactions between micro-organic contaminants and the environment within which they exist. The attenuation of contaminants in a river is very dynamic and dependent on specific factors relating to season, location, river hydrology, flow, biodegradation, association with other environmental compartments such as sediment and suspended particulate material, as well as river and contaminant-specific chemistry (Osenbruck et al., 2007; Musolff et al., 2009; Luo et al., 2011).

Point source contamination (e.g., sewage treatment facility effluent) is conceptually the simplest transport pathway to evaluate. After introduction into a river, contaminant concentrations are typically higher when effluent is discharged into tributaries with lower volume and slower flow rates than the main rivers, likely due to dilution effects (Silva et al., 2011). As contaminants flow down-stream, their interaction with the aquatic environment becomes more complex and less well understood. Ultimate fate and attenuation of contaminant concentrations can occur through several pathways/mechanisms, often depending on the properties of each individual compound, each individual river or aquatic system, biotic and abiotic contaminant degradation, how and when the compound was introduced to the environment, and its partition to solid components of the aquatic environment such as suspended solids and sediment (Osenbruck et al., 2007; Musolff et al., 2009). Much research is needed to further characterise the conditions leading to specific pathways of river transport and contaminant fate.

Table 4. Concentration ranges of 42 commonly detected pharmaceuticals, personal care products and other emerging contaminants in surface water (adapted from Wilkinson et al., 2016a)

Contaminant Class	Contaminant	Surface water (ng/L)
Analgesic	Ibuprofen	1-2370[a]
	Diclofenac	<0.5-253[a,g]
	Paracetamol	110-10000[b,c,g]
	Codine	12-1000[b,c]
	Naproxen	<1-81[o]
Antibiotic	Amoxicillin	<2.5-245[a]
	Erythromycin	<0.5-159[a]
	Triclosan	140-2300[b,c]
	Trimethoprim	<1-2[p]
	Sulfamethoxazole	<1-46[p]
Antidepressant	Amitriptyline	66-207[a]

	Fluoxetine	5.8-120[a,b]
	Venlafaxine	1.1-35[a]
Antineoplastic	Ifosfamide	0.05-.14[d]
	Cyclophosphamide	0.05-0.17[d]
	Tamoxifen	<0.05-25[n]
Alkylphenols	4-nonylphenol	165.8-1187.6[e]
	4-t-octylphenol	2.4-14.5[e]
Beta Blocker	Metoprolol	<0.5-10[a]
	Atenolol	<1-487[a]
Hormones/Steroids	17α-ethynylestradiol	<0.98-10.2[g]
	17β-estradiol	0.1-200[a,b]
	19-norethisterone	48-872[a,b]
	Coprostanol	<1-2717[h]
Lipid regulator	Bezafibrate	<10-60[a]
	Gemfibrozil	48-790[b,c]
Musk Compounds	Linalool	<0.5-0.6[q]
	Isobornyl acetate	<0.18-0.65[q]
	Aroflorone	<0.17-0.48[q]
Perfluoroalkyls	8:2 Fluorotelomer Alcohol	<0.9-1.97[m]
	Perfluorobutane sulfonic acid*	2.4-125[f,g]
	Perfluoro-2-propoxypropanoic acid*	<1-630[l]
	Perfluorononanoic acid	0.03-209[f,g]
	Perfluorooctanoic acid	0.16-189[f,g]
	Perfluorooctane sulfonic acid	0.4-2709[f,g]
Plasticiser	Bisphenol-A	140-12000[a,b,c,g]
	Bisphenol-S**	<1.02-306[g]
	Bisphenol-AF**	<1-246[i]
	Bisphenol-F**	<1-1110[j]
	Diethyphthalate	200-420[b,c]
Ultraviolet Filters	Benzophenone-4	<1-600[k]
	2-Phenylbenzimidazole-5- sulfuric acid	<1-20[k]

*Compound used or proposed as a replacement for long-chain (>C7) perfluorinated compounds
** Compound used or proposed as a replacement for bisphenol-A

[a]Petrie et al. (2015); [b]Kolpin et al. (2002); [c]Boyd et al. (2004); [d]Buerge et al. (2006); [e]Wang et al. (2012); [f]Llorca et al. (2012); [g]Wilkinson et al. (2017); [h]Peng et al. (2008); [i]Yang et al. (2014); [j]Yamazaki et al. (2015); [k]Rodil et al. (2012); [l]Sun et al. (2016); [m]Mahmoud et al. (2009); [n]Coetsier et al. (2009); [o]Li (2014); [p]Van Stempvoort et al. (2013); [q]Relic et al. (2017)

3.1 Atmospheric Transportation and Precipitation

The atmosphere has been indicated as both a transport mechanism and source of several volatile PPCPs and other ECs (Hayes et al., 2002; 2003; Oono et al., 2008; Mahmoud et al., 2009). Fluorotelomer alcohols (FTOHs) are commonly reported emerging contaminants in the atmosphere and precipitation. FTOHs are widely produced with an estimated global production of 1.1-1.4 million kg/year and are commonly used as fluorotelomer-based acrylic polymers in water repellents for cloths, paper, packaging and carpet (Oono et al., 2008). The two most common FTOH compounds found in the atmosphere, 8:2 FTOH and 6:2 FTOH, were detected across 33 locations in Japan at concentrations of 32-247 pg/m^3 and <LOD-768 pg/m^3 respectively (Oono et al., 2008). FTOH compounds have also been detected in Japanese precipitation and surface waters at concentrations ranging from 0.21-1.97 ng/L and 0.16-3.38 ng/L respectively (Mahmoud et al., 2009).

Volatile emerging contaminants may enter the atmosphere via volatilisation from surface water or STWs as well as atmospheric emission during manufacture or incineration. Reviewing recent trends in the analysis and occurrence of PPCP/ECs in air, Salgueiro-González et al. (2015) suggest many common endocrine-disrupting compounds may associate with airborne particulate material (PM) less than 10 µm in diameter. Furthermore, such contaminant-PM associates may be a potential source of such compounds to humans and other air-breathing organisms (Salgueiro-González et al. 2015). Levels of PM-bound contaminants are often significantly higher in indoor air than outdoor air, potentially due to poor ventilation and the widespread use of many such compounds in plastics and cleaning spray products (Rudel and Perovich, 2009; Salgueiro-González et al., 2015). Levels of commonly detected endocrine-disrupting phthalates, dibutyl phthalate (DBP), di(2-ethylhexyl)phthalate (DEHP) and nonylphenol (NP) have been detected in outdoor air at levels of 55 ng/m^3 (Salgueiro-González et al. 2013), 45 ng/m^3 (Salapasidou et al., 2011) and 30.5 ng/m^3 (Saito et al., 2004) respectively. In indoor air, DBP, DEHP and NP have been detected at significantly higher levels of as much as 2300 ng/m^3 (Bergh et al., 2011), 1000 ng/m^3 (Rudel et al., 2003) and 680 ng/m^3 (Saito et al., 2004) respectively. Further research is warranted to assess whether such airborne endocrine-disrupting compounds may influence inputs into the aquatic environment and indeed health implications on organisms exposed to such compounds, whether in air or water (Salgueiro-González et al. 2015).

Other contaminants, such as the herbicide atrazine, have been detected in precipitation geographically isolated from source areas, potentially entering the atmosphere via their application to land as sprays (Hayes et al., 2002; 2003). Rudel et al. (2003) detected endocrine-disrupting compounds including plasticisers, emulsifiers, nonylphenols, and an adhesive (4-*tert*-butylphenol) in the air of 52 of 89 homes tested at concentrations ranging from 50-1500 ng/m^3. Furthermore, as discussed in section 2.1, agricultural spray drift of certain ECs used, for example in fruit tree production, can also transport such compounds atmospherically (Daughton, 2006). It is unclear how far such volatile compounds can travel in the atmosphere before entering the aquatic environment or being deposited on land through precipitation and more research is needed on this subject.

3.2 River Flow and Adsorption to Sediment and Suspended Solids

PPCPs and other ECs appear to attenuate in rivers at different rates largely depending on their sorption affinity to suspended solid/ sediment material (a higher affinity, indicating increased attenuation) and recalcitrance to biodegradation (a lower recalcitrance indicating

increased attenuation) (Osenbruck et al., 2007). For example, carbamazepine, an antiepileptic, appears to attenuate in river water much slower than galaxolide, a musk compound commonly used in fragrances for soaps and detergents (Osenbruck et al., 2007). However, it is important to note that this attenuation does not necessarily indicate the compound has been removed. Adsorption to suspended solids in river water, sediments and banks can account for PPCP/EC contaminant attenuation, with some compounds preferentially binding to suspended solids rather than remaining dissolved (Luo et al., 2011; Silva et al., 2011). The antibiotic tetracycline, for example, appears to bind more preferentially to suspended solids and sediment than other antibiotic contaminants such as sulfonamides, quinolones and macrolides. Adsorption to suspended solid material is suggested to aid in the transportation of such compounds in the aquatic environment (Gregg et al., 2015). The physiochemical characteristics of contaminants as well as the properties of the adsorbing material itself are important in determining environmental fate (e.g., Luo et al., 2011; Wilkinson et al., 2017).

Luo et al. (2011) describe that cation exchange capacity and organic matter content of suspended solid material and sediment exert a great influence on contaminant adsorption (higher exchange capacity and organic matter indicating increased adsorption) and, in turn, attenuation. Similarly, Wilkinson et al. (2017) found that amphipathic compounds with long (C>7) linear chains and polar moieties were more likely to adsorb to solid material found in the aquatic environment than those with short-chains or particularly non-polar molecules without ionisable functional groups (Wilkinson et al., 2017). High river flow rates are also suggested to decrease contaminant adsorption to solid material by limiting or preventing adequate contact time (Luo et al., 2011). Luo et al., (2011) found sulfonamides, quinolones and macrolide antibiotics were more significantly affected by increased river flow preventing their adsorption onto sediment and suspended solids than tetracycline (Luo et al., 2011). Compounds showing basic (pka>7) and hydrophobic characteristics appear to preferentially bind to suspended solids and sediment (Silva et al., 2011). At times, many preferentially-bound contaminants may not even be detected in the dissolved fraction of the aquatic environment, existing almost exclusively in suspended solids and sediments (Silva et al., 2011). Some common aquatic contaminants such as nonylphenol and nonylphenol monoethoxylate are found in suspended solid material and in sediment up to 21.5 and 4.7 times higher respectively than dissolved in river water (Patrolecco et al., 2006; Silva et al., 2011). Similarly, Gregg et al. (2015) demonstrate that polycyclic aromatic hydrocarbons bind to suspended particles in the Columbia River Estuary (northwest USA) at levels up to 10 times higher relative to those found dissolved in respective water. However, other common contaminants such as diazepam, erythromycin, gemfibrozil and metoprolol are found predominately, if not exclusively, dissolved in the aquatic environment rather than bound to solid fractions (Patrolecco et al., 2006; Silva et al., 2011).

It should be noted however that while levels of chemicals bound to suspended material are commonly reported in mass/mass units (e.g., ng/g dry weight), a more accurate comparison of their distribution may be reported as mass/volume of water the suspended material was separated from (e.g., ng/L water the suspended material is separated from). Where levels of suspended particulate material in water are low, vast amounts of water may be needed to extract as little as 1 g of suspended material, making comparison to dissolved contaminant concentrations in a single litre of water potentially misleading.

Research indicates that PPCP and other EC concentrations are generally lower in river sediment than suspended solids or in water (Silva et al., 2011). However, such findings remain relatively unclear, particularly regarding degradation product adsorption to suspended solids and sediments. Table 5 shows the measured concentration ranges of 14 pharmaceuticals in the surface water, suspended solids, and sediment of various rivers. Such data demonstrate that detection in the dissolved fraction of the aquatic environment alone is not an adequate measure of PPCP/EC occurrence

3.3 Biodegradation of Organic Contaminants

All PPCPs and other ECs will eventually degrade into other, less well-characterised compounds. Biological degradation transitions are generated by human and animal metabolism and by microorganisms present in sewage treatment works (STW), occurring naturally, in suspended solids, or sediments (Ferrando-Climent et al., 2012). Such transformations may occur via hydrolysis, oxidation, reduction and complete mineralization into inorganic carbon, oxygen, nitrogen or hydrogen mediated by microbes (Christensen and Li, 2014). High rates of biodegradation are typically observed in the sediment-water interface, wetlands and swamps with efficiency dependent on factors such as temperature, nutrient availability, pH, river flow and salinity (Christensen and Li, 2014). Traditionally, research has focused on the presence of parent compounds in the aquatic environment rather than biodegradation transitions and much research is still needed to characterise PPCP/EC breakdown pathways and resulting molecules. Pharmaceuticals in particular are expected to breakdown along the metabolism of those taking them, resulting in an initial presence of degradation products in sewage treatment influent as contaminants themselves or glucuronide-transitions.

Microorganisms such as bacteria, fungi, microalgae and protozoa tend to degrade contaminants to a much greater degree (some to mineralization) than humans and animals, which often only transform organic compounds (e.g., via conjugation with glucuronides and sulfates) to a limited degree (Kumar et al., 2012; Christensen and Li, 2014). It is suggested that microbes may facilitate de-conjugation of excreted transformations. Kumar et al. (2012) show that glucuronide-conjugates of estrone and estradiol are completely transformed back to free parent estrogens during activated sludge treatment while sulfate-conjugates are more resistant as only 10-55% were converted to parent estrogens. Similarly, in surface water, de-glucuronidation of estrone and estradiol yielded 60-100% parent estrogens at a half-life of 2 days (Kumar et al. 2012).

Enzymes are indicated to play an important role in the biodegradation of organic contaminants. Although precise degradation pathways are relatively unclear, overall enzyme-dependent degradation of PPCPs/ECs is suggested (Christensen and Li, 2014) to occur via a certain sequence of events: 1) transport of contaminant to microbe in a bioavailable manner (some hydrophobic contaminants may become unavailable for uptake by association with suspended solids), 2) contaminant uptake and diffusion through cell walls (to intracellular enzymes), 3) binding to enzyme reaction site and formation of contaminant-enzyme complex, 4) enzyme-contaminant reaction often mediated by cofactors and coenzymes and 5) release of the transformed product. It should be noted however that reaction sites are highly specific and attachment to and passage through biological membranes are largely dependent on the polarity and chemical composition of the specific contaminant. For example, hydrophobic PPCPs/ECs may more easily attach to

the membrane and become more quickly degraded than hydrophilic compounds when the rate determining step is adsorption-dependent (Christensen and Li, 2014).

Contaminants are known to degrade during sewage treatment, particularly during activated sludge processing. Here microorganisms in biofilms degrade organic contaminants in a similar way as both fixed biofilms (more influential in small streams) and mobile aggregate biofilms (more influential in larger rivers) can degrade such organic compounds in the natural environment (Winkler et al., 2001). It should be noted however that there is a considerable lack of research into the role natural biofilms play in the environmental metabolism of organic contaminants. Within activated sludge treatment, Remberger et al. (2008) found the two main breakdown transitions of ibuprofen, hydroxyl- and carboxyl-ibuprofen, at higher concentrations than the parent compound in sewage effluent. While ibuprofen is relatively well studied and good example of biodegradation, further research is needed to elucidate breakdown transitions and pathways of other common PPCPs and ECs. The toxicity of breakdown products, biodegraded or not, should also be considered as transformation products are indicated to be equally or more toxic (see section 6.4.3) as parent compounds (Ruggeri et al., 2013; Bergheim et al., 2014).

Table 5. Concentrations of 14 PPCP and other ECs in surface water, suspended solids, and sediment (Patrolecco et al., 2006; Silva et al., 2011)

Compound	River Water (ng/L)	Suspended Solids (ng/g)	River Sediment (ng/g)
Acetaminophen	n.d.-872	n.d.-657	n.d.-222
Atenolol	n.d-1237	3.06-34	n.d.-3.78
Diazepam	n.d-2.68	n.d.	NA
Diclofenac	n.d.-148	n.d.-468	<LOQ-2.65
Erythromycin	n.d.-42.4	NA	n.d.-33.5
Gemfibrozil	n.d.-160	n.d.-47.1	n.d.-5.2
Ibuprofen	n.d.-541	n.d.-571	n.d.-20.9
Metoprolol	n.d.-33.88	n.d.-7.59	n.d.-4.1
Naproxen	n.d.-109	n.d.-38.5	n.d.-1.87
Ranitidine	n.d.-84.5	19.4-133	n.d.-25.1
Bisphenol-A	60-90	<LOQ-610	<LOQ
Nonylphenol	150-340	2680-7320	380-970
Nonylphenol monoethoxylate	190-480	1320-2260	250-1780
Nonylphenol diethoxylate	70-400	<LOQ-2430	50-320

LOQ - Limit of Quantification n.d. - Not Detected NA - Not Analysed

3.4 Photochemical Transformation in the Aquatic Environment

Photochemical transformation (or degradation) of organic contaminants in the aquatic environment occurs by both direct absorption of solar radiation and indirectly via reaction with photo-sensitized species. Via both direct and indirect mechanisms, energy from solar radiation results in the transformation of organic contaminants into other molecules by breaking covalent bonds typically resulting in more biodegradable and hydrolysable compounds (Richard and Canonica, 2005). Factors affecting the efficiency of photochemical

transformation include the mechanism of degradation (direct or indirect), chemical nature of the compound being degraded, temperature, pH, depth below the water surface, cloud coverage, altitude, latitude, and time of day (Remucal, 2014; Christensen and Li, 2014). While the degradation of specific contaminants via both direct and indirect photochemical transformation may be calculated or experimentally determined, generalising degradation potential across whole classes of compounds is difficult and often not reliable (Remucal, 2014). It should be noted however that photochemical transformation has been indicated as a means by which to degrade PPCP/ECs in STW effluent. Despite debate regarding the toxicity of some transformation products (Boreen et al., 2003; Latch et al., 2003b; Ruggeri et al., 2013; Bergheim et al., 2014), photocatalysis, photo-Fenton and UV with H_2O_2 have shown promising removal efficiencies and are reviewed in greater detail elsewhere as wastewater treatment strategies (e.g., Pereira et al., 2007; Ikehata et al., 2008; Wang and Xu, 2012).

3.4.1 Direct Photochemical Transformation

Direct photochemical transformation involves the non-reversible bond cleavage or re-arrangement of organic molecules by the energy (photons) contained in sunlight reaching the Earth's surface, atmosphere, and shallow regions of the aquatic environment (Remucal, 2014). It should be noted that direct photochemical transformation of PPCPs/ECs in the aquatic environment is limited by the depth of water in which the compounds are found (Jasper and Sedlak, 2013). The majority of ultraviolent light, for example, is absorbed within the top 2 m of water (Dabrowska et al. 2004).

Sunlight reaching the earth's surface and shallow depths of the aquatic environment ranges in wavelength from about 290 to 600 nm (Dabrowska et al., 2004). Corresponding photo energy is of a similar order to many common covalent bonds found in organic contaminants (400 to 200 kJ/ mol) such as C-C, C-H, C-O, C-Cl and C-Br (Christensen and Li, 2014). The π-bond configuration of organic contaminants in the aquatic environment largely determines the absorptive capability (of sunlight) of the molecule via interaction with un-bound electrons of heteroatoms such as nitrogen and oxygen (Christensen and Li, 2014). Most alcohols, acids, ethers and esters as well as most aliphatic hydrocarbons do not absorb light reaching the earth's surface (Christensen and Li, 2014). However, increased susceptibility to photochemical transformation is observed in molecules containing functional groups (e.g., -CH=CH2, -NO2, -NH2, -N=N-, and -OH) that are capable of donating additional π-electrons, thereby strengthening conjugated bonds (Christensen and Li, 2014). The absorption efficiency of light is assessed by the reaction quantum yield (Φ), calculated by the ratio of transformed moles to the total moles absorbing the light (Bezarez-Cruz et al., 2004). Reaction quantum yields >1 indicate chain reactions and most aquatic organic compounds show reaction quantum yields <0.01 (Christensen and Li, 2014). Not all absorbed energy results in the transformation of absorbing molecules. Christensen and Li (2014) describe three alternative routes for absorbed photo energy: 1) energy may be released when excited molecules deactivate to ground state by either phosphorescence or fluorescence, 2) absorbed energy may be consumed by the respective molecule providing additional kinetic energy, and 3) energy may result in heat produced by collision with other molecules. Many organic contaminants are photodegraded by some combination of direct and indirect mechanisms.

3.4.2 Indirect Photochemical Transformation

This pathway is mediated by chromophoric components in the aquatic environment which are photosensitized (or photo-induced/ excited) by solar radiation and then pass the excited energy on to organic compounds breaking chemical bonds and degrading the molecule (Richard and Canonica, 2005; Remucal, 2014). The occurrence of such reactions is dependent upon the amount of chromophores in the aquatic system and their ability to react (once sensitized) with respective organic contaminants. Such a pathway may be the dominant degradation process for aquatic contaminants that poorly absorb solar radiation directly (Richard and Canonica, 2005). Sensitizers absorb light (photons) becoming reactive photooxidant radicals such as RO•, ROO•, HO•, HOO•, $^1O_2$, O_2^-, and CO_3^- via reaction of bicarbonate and •OH (Jasper and Sedlak, 2013; Christensen and Li, 2014; Remusal, 2014). Dissolved organic matter (DOM) can also act as a sensitizer (triplet DOM) in addition to inorganic species such as NO_2^- and NO_3^- (Dabrowska et al., 2004; Christensen and Li, 2014). Similar to energy lost in direct transformation, not all photosensitized species pass their excited energy on to break down organic contaminants. Photosensitized species may use their energy to deactivate others in a process called quenching making the resulting molecules less reactive (Christensen and Li, 2014). DOM may also decrease the efficiency of phototransformation by acting as an antioxidant and/or a sink for organic contaminants (Remucal, 2014).

3.4.3 Photochemical Transformation of PPCPs/ECs in the Aquatic Environment

The rate of PPCP/EC photochemical degradation is the sum of both direct and indirect transformations (Dabrowska et al., 2004). For example, in addition to thermal dissociation, phenol is degraded into oxalic acid and methanoic acid via both direct absorption of solar radiation and indirectly through oxidation by hydroxyl radicals in water (Wu et al., 2001; Dabrowska et al., 2004). However other PPCPs may undergo photochemical degradation more selectively, if at all. For example, cimetidine is photodegraded in water indirectly via reaction with singlet oxygen and is not susceptible to direct photochemical transformation (Latch et al., 2003a). Diclofenac has been shown to degrade into 1-(8-chlorocarbazolyl)acetic acid via photocyclization with further photochemical transformation via dechlorination resulting in carbazole products (Boreen et al., 2003). However, compounds with a high affinity for solids (such as tetracycline) may avoid photochemical degradation via sorption to suspended particulate materials (Boreen et al., 2003). As mechanisms of degradation and environmental distribution may differ between compounds and within groups of PPCPs/ECs, photoreactivity must be studied on a case-by-case basis (Boreen et al., 2003). It should be noted that study of photochemical degradation rates is often conducted in complete solvent or partial water-solvent systems and care must be taken in applying such findings to real-world conditions (Christensen and Li, 2014). For example, Packer et al. (2003) determined diclofenac readily degraded by direct photochemical transformation and the addition of isopropyl alcohol to the aqueous system resulted in a more rapid transformation, potentially due to formation of other radical species.

While much research has focused on determining photochemical degradation rates and quantum yields rather than elucidating mechanisms and transformation products, detailed review of photochemical transformations is available (e.g., Boreen et al., 2003; Wols and Hofman-Caris, 2012). Detailed research is needed in particular to determine

toxicity of phototransformation products which can be equally, if not more biologically active than parent compounds (Boreen et al., 2003; Latch et al., 2003b; Ruggeri et al., 2013; Bergheim et al., 2014). Ibuprofen is shown to degrade via both direct and indirect photochemical transformation into 4-isobutylacetophenone (IBAP) which is known to adversely affect the central nervous system, red blood cells and connective tissue (Ruggeri et al., 2013). Here, transformation occurs via reaction with hydroxyl radicals (2.3±0.1% yield), direct photolysis (25±7% yield) and reaction with excited DOM (31±4% yield) producing IBAP concentrations up to approximately 15% of ibuprofen levels in respective water (Ruggeri et al., 2013). Similarly, Latch et al. (2003b) determine that triclosan degrades via exposure to UV light into the potentially toxic 2,8-dichlorodibenzo-*p*-dioxin in aqueous medium with condition-specific yields of 1-12%. Noting the difficulty of product identification, Boreen et al. (2003) suggest coupling biological assays with photochemical studies. Here, potential biological effects of photochemical transformation products may be assessed without identifying the products themselves by comparing changes in biological endpoints before and after transformation of the parent compound. Using such methodology, Bergheim et al. (2014) tested the direct photodegradability and toxicity of 14 pharmaceuticals found in the aquatic environment (acyclovir, allopurinol, cetirizine, cimetidine, fluconazole, hydrochlorothiazide, lisinopril, phenytoin, primidone, ranitidine, sotalol, sulpiride, tramadol and valsartane). Of the selected pharmaceuticals, acyclovir, allopurinol and fluconazole resisted direct photochemical transformation via exposure to UV light (Bergheim et al., 2014). Furthermore, irradiated solutions of 8 mg/L cetirizine, cimetidine, tramadol and valsartane demonstrated higher toxicity in growth inhibition assays to bacteria *P. putida* than non-irradiated solutions. Similarly, irradiated solutions of hydrochlorothiazide, ranitidine, sulpiride tramadol and valsartane showed greater inhibition of *V. fischeri* bioluminescence than non-irradiated solutions (Bergheim et al., 2014).

Identification of photochemical transformation products as well as assessment of their potential ecological impacts and environmental occurrence remain relatively under-studied topics (Bergheim et al., 2014). Future research should proceed with focus on the environmental occurrence and toxicology of photochemical transformation products identified by primary laboratory work.

3.5 PPCPs and other ECs in Sewage Biosolids used as Agricultural Additives

Biosolids are an end product of sewage treatment and are used as agricultural conditioners and fertilisers. Agricultural use of such municipal biosolids has increased in the EU since a commission prohibition on their disposal at sea in 1998 (Barron et al., 2010). The U.S. Environmental Protection Agency (USEPA) estimates about 50% of biosolids produced in the USA are used for agricultural purposes on less than 1% of the nation's farmland (USEPA, 2012). Throughout treatment, sewage sludge retains many contaminants, including a complex mixture of PPCPs and other emerging contaminants. The use of such biosolids on agricultural lands inevitably introduces organic contaminants including PPCPs which may ultimately result in soil contamination, groundwater recharge to aquifers, runoff, and possible uptake by agricultural plants (Daughton, 2006; Barron et al., 2010). Introduction of emerging organic contaminants to soil in this manner has raised concern over recent years. Current regulation on the quality of biosolids used for agricultural purposes does not take contamination by PPCP and other ECs into account (USEPA, 2012).

The fate and persistence of biosolid-borne PPCP contaminants in soils appear to be compound-, site/soil-, and climate-specific. While hydrophobicity and soil organic carbon content do affect contaminant adsorption, they are alone not sufficient variables in estimating PPCPs behaviour in soils (Barron et al., 2010). Variables more significantly affecting contaminant adsorption in soils (via the application of biosolids to topsoils) may include the degree of soil water-saturation, rate of percolation, physicochemical properties of both the solid matrix and compounds, temperature of the soil, and pH of the soil/liquid solution (Barron et al., 2010).

Reviewing the use of biosolids in agricultural soil, Clarke and Smith (2011) conclude that despite over 143,000 chemicals being registered for industrial use in the European Union (all of which could potentially be found in biosolids), the risk of contaminant uptake into agricultural plants causing implications on human health is not significant. PPCPs and other ECs are detected in sewage biosolids at concentrations typically not exceeding 10 mg/kg dry weight (dw), although exceptions do exist (Clarke and Smith, 2011). For example, pharmaceuticals ciprofloxacin and ofloxacin have been detected up to 40.8 and 58.1 mg/kg dw sludge respectively in the USA (US EPA, 2009) while plasticisers bisphenol-A (BPA) and bis(2-ethylhexyl) phthalate (DEHP) have been detected up to 325 mg/kg dw (Meesters and Schroder, 2002) and 3514 mg/kg dw (Abad et al., 2005) in Germany and Spain respectively.

Further research is warranted particularly regarding such contaminants leaching into the aquatic environment, including into aquifers. Additionally, with increased demand to recover phosphorus from wastewater treatment facilities, including from sludge (Melia et al., 2017), study should be undertaken to evaluate the effect of phosphorous recovery on concentrations of PPCPs/ECs in biosolids and in phosphorus recovery products.

3.6 Temporal and Seasonal Effects on PPCP and ECs in water

Many of the factors affecting contaminant attenuation can fluctuate with seasonal and meteorological changes (Vieno et al., 2005; Musolff et al., 2009). Most notable fluctuations seemed to be linked to temperature changes in receiving waters, volumes of receiving waters, and changes in seasonal PPCP/EC use (e.g., sunscreens, personal insecticides and caffeine). During warmer months, increased water temperature has been associated with increased attenuation of contaminants in surface waters, potentially due to increased microbial and biofilm activity (Musolff et al., 2009). Changes in river volume can also affect the concentration of contaminants, mainly by dilution. For example, Vajda et al. (2008) describe how the increased stream volume of Boulder Creek (Colorado, USA) during warmer months, due to snowmelt from the Rocky Mountains, reduces the dominance of STW effluent in river volume (and hence PPCP and EC discharge) by as much as >75%.

Last, temporal and seasonal changes in compound use occur and can directly affect concentrations of PPCPs/ECs in the aquatic environment. In the city of Leipzig (Germany), periods of rainfall and colder months saw increased loading of both caffeine and 4-nonylphenol indicating weather and season as factors in contaminant loading (Musolff et al., 2009). It is unclear how seasonal changes in population can affect environmental loading of PPCP and other emerging contaminants. Such population fluctuations could be a factor in cities with seasonal tourism or high student populations (e.g., university towns). However, research is lacking in terms of the exact affect population fluctuation has on contaminant loading.

3.7 Micro- and nanoplastic particles in the aquatic environment

Evidence exists suggesting that certain PPCP and other EC contaminants may bind to plastics particles in the aquatic environment (Mato et al., 2001; Rios et al., 2007; Teuten et al., 2009; Hirai et al., 2011; Wegner et al., 2012; Rochman, 2016). Microplastics are defined by a diameter of 1 μm-5 mm while nanoplastics a diameter of <1 μm (Browne et al., 2008). However, it should be noted that the very definition of nanoplastics is debated as the European Commission defines nanoplastics with a particle diameter between 1 nm-100 nm (Europe Commission, 2015).

Plastic particles, which are ubiquitous in the aquatic environment, do not biodegrade, but do however do degrade (National Oceanic and Atmospheric Administration, 2016). In addition to being used in cosmetic products (i.e., facial scrubs and toothpaste), microplastic particles are formed via the degradation of larger (manufactured state) plastic objects over hundreds of years and may never be completely eliminated from the environment (National Oceanic and Atmospheric Administration, 2016). Both primary production and fragmentation (e.g., via ultraviolet light exposure) of larger plastic particles into micro-and nanoparticles are thought to be major contributors to the substantial amounts present in the aquatic environment (Eriksen et al., 2014). Fragmentation of microplastics into nanoplastics increases surface area to volume ratio which in turn may affect the area of plastic available for organic contaminants to bind (European Union Commission, 2011). Woodall et al. (2014) report abundance of microplastics in ocean sediment up to 4 orders of magnitude higher than that detected in sea-surface water indicating that sediment may be a significant sink for these contaminants. In the same study, plastic microparticles were identified in all sediment samples at abundances ranging from 1.4-40 pieces/50 mL sediment and consisted predominately of rayon and polyester (Woodall et al., 2014).

Some organic contaminants have been shown to bind to plastic particles in the aquatic environment at similar concentrations to suspended solids and sediments (Mato et al., 2001; European Union Commission, 2011; Rochman, 2016). Among the first to demonstrate this, Mato et al. (2001) recovered PCBs, DDE, and nonylphenols bound to plastic particles at concentrations of 4-117 ng/g plastic, 0.16-3.10 ng/g, and 0.13-16 ng/g respectively. More recently, Hirai et al. (2011) found hydrophobic contaminants more likely to accumulate on plastics. In the same study, common ECs were detected on plastic particles at up to 730 ng BPA/g plastic and nonylphenol up to 3936 ng/g (Hirai et al., 2011). However, it is important to note that plasticisers such as BPA and nonylphenol have been shown to leach from plastic material such as polyethylene, silicone (nonylphenol only), polycarbonate and polystyrene (Fasano et al., 2012). Hence, levels of these chemicals found on plastic particles in the environment may only represent desorption from the plastic itself during extraction in the laboratory rather than adsorption of the chemicals to the plastic from the environment, or a combination of both. Study investigating the accumulation of ECs and PPCPs onto micro- and nanoplastics in the environment is limited but is rapidly increasing in recent years. Research is likely most significantly limited by the difficulties in retrieving such particles from environmental matrices.

Aquatic organisms may ingest plastic particles, perhaps mistaking them for eggs, bringing to light a possible route of exposure when PPCPs/ECs are bound to the particles (Mato et al., 2001; Wegner et al., 2012). Boerger et al. (2010) found ingested plastic particles in 35% of plankton-eating fish caught in the North Pacific Gyre. Similar findings

were reported in Brazilian estuaries where 18-33% of collected catfish were found with plastic particles in their stomachs (Possatto et al., 2011). Ingestion of contaminated particles may influence biological disruption in exposed organisms (European Union Commission, 2011) and may result in the bioaccumulation of adsorbed chemicals in animals that consume the particles (Rochman, 2016). The degree to which levels of contaminants attached to plastic particles may affect the biology of the organisms, consuming them is not well-known and may be specific to the species and period of development an individual is exposed (Rochman, 2016).

The presence of plastic micro- and nanoparticles in the environment is likely to remain a key issue in the field longer than many others due to the amounts of the material in the aquatic environment and its inability to fully degrade (National Oceanic and Atmospheric Administration, 2016). In recent years, regulatory and government bodies have begun banning the use of microplastic particles in cosmetic products (Table 6).

Table 6. Summary of significant regulation set on the sale, manufacture and import of products containing plastic microparticles across the world as of early 2017

Country	Implementation Date	Regulation	Comments
Canada	1 July, 2018	Changes to the Canadian Environmental Protection Act	Ban on the sale of shower gels, facial scrubs and toothpaste containing plastic microbeads from 1 July 2018. Manufacture banned six months before the sales ban. Additional ban on natural products and non-prescription drugs containing microplastics from 1 July, 2019.
France	Proposed: 1 January, 2018	Proposed at the time of writing	Prohibit the sale of cosmetic products containing microplastic particles and cotton buds with plastic stems in France.
New Zealand	1 July, 2018	Changes to the Waste Minimisation Act of 2008	Ban on the manufacture and sale of personal care products containing plastic microbeads. Penalty of $73,000 (USD) for any entity found in breach of the ban (Waste Minimisation Act of 2008).
South Korea	Proposed: July 2017 (manufacture and import), July 2018 (cosmetic product sale)	Proposed at the time of writing	Ban on the manufacture and import of cosmetic products containing plastic particles from July 2017 and ban their sale from July 2018.
Taiwan	Proposed: 2017	Proposed at the time of writing by Taiwan's Environmental Protection Agency	Prohibits the sale, import and manufacture of personal care products and toothpastes containing plastic particles.
United Kingdom	Proposed: October 2017	Proposed at the time of writing	Prohibits the manufacture and sale of cosmetic products and personal care products which contain microplastic particles which may cause harm to the marine environment (DEFRA, 2017)
United States	July 2017 (manufacture), January 2018 (cosmetic product sale)	Microbead-Free Waters Act of 2015	Prohibits the manufacture and interstate commerce of cosmetic products with intentionally-added wash-off plastic particles > 5 mm in diameter. Manufacture of microbeads banned from July 2017 and ban of the sale of cosmetic products containing microbeads from January 2018 (Microbead-Free Waters Act of 2015).

3.7.1 Significant legislation regulating the manufacture, sale and import of products containing plastic particles

At the time of writing (early 2017), only the United States, Canada and New Zealand had legislated clear regulation of the manufacture, sale and import of cosmetic products containing plastic particles >5 mm in diameter (Table 6). Other nations including the United Kingdom, Taiwan, South Korea and France have proposed legislation (at the time of writing) which would take effect between late 2017 to mid 2018. Although individual U.S. states including California, Colorado and New York had previously implemented bans on the sale of cosmetic products containing plastic particles, the United States-wide congressional legislation H.R. 1321 (Microbead-free Water Act of 2015) was the first major regulatory decision on plastic microparticles. Much of the following regulation by other nations followed the template of H.R. 1321, which included an initial ban on the manufacture of plastic micropartles followed by a subsequent ban (6 months later) on the sale and import of cosmetic products containing plastic microparticles (Table 6). At the time of writing, no European Union-wide legislation is proposed despite the governments of Austria, Belgium, Sweden, Luxembourg and the Netherlands calling for an EU-wide ban in 2014 (Council of the European Union, 2014).

Despite regulatory decisions, as microplastics are also produced by degradation of larger plastic pieces (National Oceanic and Atmospheric Administration, 2016), such legislation is likely to not have a significant effect on the amount of microplastic particles in the environment for many hundreds of years. Research should focus on determining their possible environmental implications rather than mechanisms to reduce their prevalence.

4.0 Conclusions and Direction for Research

Contamination of water by pharmaceutical, personal care products and other emerging contaminants is unavoidable as long as their uses remain such an indispensable component of a modern and healthy society. Such contaminants are virtually ubiquitous in the aquatic environment and are rarely detected in some drinking waters (Jjemba, 2006; Silva et al., 2011; Raghav et al., 2013; United States Geological Survey, 2016a). Currently, technology and techniques utilised in sewage/wastewater, and potentially drinking water, treatment are not complete barriers to these contaminants. While future research must focus on increasing PPCP/EC removal efficiencies in sewage treatment, complete removal prior to environmental introduction is likely not practical (Radjenovic et al., 2009; Hirani et al., 2013).

Future study may focus on the elucidation of largely unknown breakdown products and their formation during sewage treatment, natural photochemical transformation and biological degradation. The potential environmental toxicity of such breakdown products should also be considered as some transformation products may be equally, if not more toxic than parent compounds (Boreen et al., 2003; Latch et al., 2003b; Ruggeri et al., 2013; Bergheim et al., 2014). Such investigation could be undertaken as suggested by Boreen et al. (2003) where biological assays are coupled with degradation study in such a way that adverse biological outcomes are assessed and compared before and after transformation of parent compounds without having to identify the breakdown products themselves. Subsequently, more detailed study could identify the specific chemical structures of

transformation products produced under study conditions which may mimic those observed in specific sewage treatment facilities. Such STW-specific conditions, when coupled with quantitative structural-activity relationship models and the abovementioned toxicity assessments may inform the creation of novel models for predicting the toxicity of transformation products under defined conditions.

Much remains to be elucidated regarding variables and conditions influencing the environmental fate and attenuation of PPCPs and other ECs. Some contaminants appear to bioaccumulate, preferentially bind to suspended solids or river sediment, volatilise, interact with other environmentally present components (plastics, heavy metals), and breakdown into unknown or poorly understood metabolites, each with potentially independent fates and behaviours. This concept particularly challenges the identification of contaminants present in the environment as some may only exclusively present in certain aquatic matrices leading to great uncertainty regarding where exactly to look (Patrolecco et al., 2006; Silva et al., 2011). Much research and classification is still needed to understand the environmental fate and metabolism of PPCP and other ECs, particularly when associating with media such as biofilms, micro-/nanoplastic particles and distribution between dissolved and less-bioavailable bound fractions in water. Specific work focusing on the factors influencing the uptake of ionisable chemicals into aquatic organisms is warranted.

Four overarching challenges are posed at present which present the need for continued and future, likely highly-interdisciplinary research:

1) Identification of new environmentally present contaminants and both new and existing transformation products is particularly challenging as new drugs and replacements for regulatory limited compounds are continually being introduced to market and subsequently into the environment;

2) Compounds used to replace those which are statutory/regulation-limited must be comprehensively studied to elucidate ultimate environmental fate and potential toxicity. Such research may focus on perfluorinated compounds of <6 carbon chains such as PFBS as well as plasticisers BPS, BPF and BPAF;

3) The presence of antibiotics in the aquatic environment is thought to have a role in the development of antimicrobial resistance (see section 2.2). Study may most efficiently focus on the potential transfer mechanisms of antibiotic-resistant genes originating from bacteria within sewage treatment facilities and urban wastewater systems to bacteria in receiving surface waters and potential risk reduction using disinfection (e.g., UV) at STW facilities; and

4) As regulation will likely not eliminate the presence of plastic particles in the environment for many thousands of years (as plastic does not degrade but simply fragments), specific research is warranted to determine the effects/rate of plastic fragmentation on potential particle toxicity (if any), ability to retain emerging contaminants (if any), uptake by organisms and distribution in the environment.

Since the late 1990s, significant progress has been made in the understanding of the sources, occurrence and fate of pharmaceuticals, personal care products and other

emerging contaminants. Regardless, this topic is likely to dominate emerging environmental chemistry for many years to come as our understanding of the field becomes deeper and ultimately more interdisciplinary.

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