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A review on emerging contaminants in wastewaters and the environment: Current knowledge, understudied areas and recommendations for future monitoring

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ABSTRACT

This review identifies understudied areas of emerging contaminant (EC) research in wastewaters and the environment, and recommends direction for future monitoring. Non-regulated trace organic ECs including pharmaceuticals, illicit drugs and personal care products are focused on due to ongoing policy initiatives and the expectant broadening of environmental legislation. These ECs are ubiquitous in the aquatic environment, mainly derived from the discharge of municipal wastewater effluents. Their presence is of concern due to the possible ecological impact (e.g., endocrine disruption) to biota within the environment. To better understand their fate in wastewaters and in the environment, a standardised approach to sampling is needed. This ensures representative data is attained and facilitates a better understanding of spatial and temporal trends of EC occurrence. During wastewater treatment, there is a lack of suspended particulate matter analysis due to further preparation requirements and a lack of good analytical approaches. This results in the under-reporting of several ECs entering wastewater treatment works (WwTWs) and the aquatic environment. Also, sludge can act as a concentrating medium for some chemicals during wastewater treatment. The majority of treated sludge is applied directly to agricultural land without analysis for ECs. As a result there is a paucity of information on the fate of ECs in soils and consequently, there has been no driver to investigate the toxicity to exposed terrestrial organisms. Therefore a more holistic approach to environmental monitoring is required, such that the fate and impact of ECs in all exposed environmental compartments are studied. The traditional analytical approach of applying targeted screening with low resolution mass spectrometry (e.g., triple quadrupoles) results in numerous chemicals such as transformation products going undetected. These can exhibit similar toxicity to the parent EC, demonstrating the necessity of using an integrated analytical approach which compliments targeted and non-targeted screening with biological assays to measure ecological impact. With respect to current toxicity testing protocols, failure to consider the enantiomeric distribution of chiral compounds found in the environment, and the possible toxicological differences between enantiomers is concerning. Such information is essential for the development of more accurate environmental risk assessment.

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1. Introduction

In surface waters, a broad range of inorganic and organic contaminants are controlled by legislation outlined by the European Commission (European Commission, 2008). These have traditionally been industrial or agricultural chemicals. However, legislation is expected to broaden to encompass a greater number of municipal derived chemicals described as ECs following the recent proposal of the pharmaceuticals 17β-estradiol (E2), 17α-ethinylestradiol (EE2) and diclofenac as priority hazardous substances (European Commission, 2012). Proposed legislative targets for consent were 0.4, 0.035 and 100 ng l^{-1} for E2, EE2 and diclofenac, respectively (European Commission, 2012). Also, dissemination of antibiotic resistant bacteria in the environment caused by the presence of antibacterial drugs is an emerging concern (Marti et al., 2014). This emphasises the level of concern posed by this family of environmental pollutants. Large numbers of non-regulated ECs have been observed mainly in the ng to μg l^{-1} range in surface waters throughout the UK (Ashton et al., 2004; Roberts and Thomas, 2006; Kasprzyk-Hordern et al., 2007, 2008a,b, 2009; Baker and Kasprzyk-Hordern, 2011a, 2013) and across the rest of Europe (Gracia-Lor et al., 2011; Gros et al., 2012; Kunkel and Radke, 2012; Ferrando-Climent et al., 2013; Fenech et al., 2013; Hughes et al., 2013; Loos et al., 2013; López-Serna et al., 2013). To date, >200 different pharmaceuticals alone have been reported in river waters globally, with concentrations up to a maximum of 6.5 mg l^{-1} for the antibiotic ciprofloxacin (Hughes et al., 2013). Single compound acute toxicity testing (including crustaceans, algae and bacteria) conducted under controlled laboratory conditions have found median effective concentrations (EC_{50}'s – concentration at which the toxicological response to an organism is halfway between a normal and maximum response for a pre-set time period) for a number of these ECs to be < 1 mg l^{-1} (Bruce and Versteeg, 1992; Holten Lützhøft et al., 1999; Halling-Sørensen, 2000; Brooks et al., 2003; Andreozzi et al., 2004; Brain et al., 2004; Eguchi et al., 2004; Cleuvers, 2005; Isidori et al., 2005a,b; DellaGreca et al., 2007; Isidori et al., 2007; DeLorenzo and Fleming, 2008; Terasaki et al., 2009; Giudice and Young, 2010). Such effect concentrations classify the chemical as potentially very toxic to aquatic organisms as described under the EU-Directive 93/67/EEC (Commission of the European Communities, 1996; Cleuvers, 2003). The presence of these chemicals in the environment is more concerning considering that they do not appear individually, but as a complex mixture, which could lead to unwanted synergistic effects. The ubiquity of a high number of potentially toxic ECs in the environment underpins the need to better understand their occurrence, fate and ecological impact.

This review describes current knowledge on the occurrence of ECs in wastewaters and surface waters using the UK data set as an example. From the data set and wider literature, areas of concern considered to be understudied are discussed. Among them are: spatial and temporal variability of ECs in wastewater and river water, partitioning of ECs to solid matter during wastewater treatment, fate of ECs in environmental waters and toxicological impact of ECs within the environment. Finally, recommendation for future environmental monitoring approaches is proposed.

2. Current knowledge of EC occurrence in wastewaters and surface waters

The presence of ECs in the environment is mainly attributed to the discharge of treated wastewater from WwTWs. Conventional secondary processes (activated sludge and trickling filters) represent the most extensively used and studied processes and are therefore focused on in this review. However, these processes are not designed to remove ECs resulting in their discharge to receiving surface waters including rivers, lakes and coastal waters. A UK data set is used as a baseline to outline current knowledge of EC contamination within wastewaters and surface waters for a European country.

Approximately 70 pharmaceuticals belonging to a variety of therapeutic classes have been reported in UK environmental waters (Table 1). The most studied are non-steroidal anti-inflammatory drugs (NSAIDs), β-blockers, antidepressants and the antiepileptic carbamazepine. These are highly prescribed (>1000 kg per annum) and ubiquitous to influent wastewaters. Removal varies broadly from low (<50%) to high (>80%) due to their different physicochemical properties and susceptibility to biological attack (Tadkaew et al., 2011; Petrie et al., 2013a). Incomplete removal results in pharmaceuticals being reported in receiving surface waters in the ng to μg l^{-1} range. The analgesic tramadol has been observed in river water at the highest concentration up to a maximum of 7731 ng l^{-1} (Kasprzyk-Hordern et al., 2008b). To date, a total of 15 illicit drugs and licit stimulants have been reported in UK wastewaters (Table 1). Due to the lower consumption of illicit drugs within the community, concentrations observed in influent wastewaters are expectantly lower. Nevertheless, incomplete removal during wastewater treatment has resulted in several of these ECs being found in final effluents and receiving surface waters. The hallucinogen 3,4-methylenedioxy-N-methylamphetamine (MDMA) and the stimulant cocaine have been observed in river water at concentrations of 25 and 17 ng l^{-1}, respectively (Baker and Kasprzyk-Hordern, 2011a,b, 2013). In contrast, antimicrobials, sunscreen agents and preservatives are high usage chemicals due to their application in a broad range of personal care products. These types of chemical are often observed in influent wastewater at >1000 ng l^{-1} (Table 1). Removals during wastewater treatment are generally good and range from 50 to 100%. However, notable concentrations remain in final effluents owing to the relatively high influent concentrations encountered. The sunscreen agent 4-benzophenone has been observed at mean final effluent concentrations ranging from 3597 to 5790 ng l^{-1} (Kasprzyk-Hordern et al., 2008a, 2009). The data set also revealed that the majority of EC analysis is undertaken on the aqueous phase (i.e., a pre-filtered sample) only, and there has been a lack of particulate phase measurements made (e.g., sludge or suspended particulate matter). The observations of the UK data set are typical of EC research reported throughout the rest of Europe (Gracia-Lor et al., 2011; Gros et al., 2012; Ferrando-Climent et al., 2013;

Table 1 – Emerging contaminant occurrence information for wastewaters and surface waters in the UK (all data reported as mean concentrations and aqueous phases unless otherwise stated).

Emerging contaminant	Family/use	Prescription 2012 (kg)[a]	Excretion unchanged (%)	Known metabolites	Influent (ng l^{-1})	Removal (%)	Sludge (ng kg^{-1})	Final effluent (ng l^{-1})	Surface water (ng l^{-1})	Surface water max. (ng l^{-1})
Pharmaceuticals										
Estrone	Steroid estrogen	–	–	Sulfate and glucuronide conjugates	49[c]	L-H[c,m]	–	4.3–12[b,m]	–	–
17β-estradiol	Steroid estrogen	84	–	Sulfate and glucuronide conjugates	20[c]	M-H[c,m]	–	0.4–1.3[b,m]	–	–
17α-ethinylestradiol	Synthetic estrogen	12	–	Sulfate and glucuronide conjugates	1.0[c]	L-H[c,m]	–	0.20–0.47[b,m]	–	–
Propranolol	Beta blocker	9076	<0.5[d]	4-Hydroxypropranolol (active), glucuronide conjugates (20%)[f]	60–638[c,e,g,j]	L-H[c,g,j]	170[c]	93–388[b,e,g,j,k]	<0.5–107[d–g,j,k]	215[k]
Metoprolol	Beta blocker	2311	10–30[d]	No active metabolites[f]	75–110[e,g]	L-M[g]	–	41–69[e,g]	<0.5–10[d–g]	12[f]
Sulbutamol	Beta blocker	182	30[d]	Sulfate conjugate	0.1–130[e,g]	M-H[g]	–	63–66[e,g]	<0.5-2[e–g]	8[f]
Atenolol	Beta blocker	20,725	50[d]	Hydroxylated metabolite (3%)[f]	12,913–14,223[e,g]	M-H[g]	–	2123–2,870[e,g]	<1–487[d–g]	560[f]
Carbamazepine	Antiepileptic	44,498	3[d]	Hydroxylated (10,11-epoxide) (active), conjugated metabolites[f]	950–2,593[e,g]	L[g]		826–3,117[e,g]	<0.5–251[d–g]	684[f]
Gabapentin	Antiepileptic	104,110	100[d]	–	15,034–18,474[e,g]	L-H[g]		2592–21,417[e,g]	<0.6–1,879[d–g]	1,887[f]
Acetaminophen	NSAID	>2,000,000	20[d]	Sulfate conjugate (30%), paracetmaol cysteinate, mercapturate (5%)[f]	6924–492,340[e,g,j]	H[g,j]	–	<20–11,733[e,g,j]	<1.5–1,388[d–g]	2,382[f]
Diclofenac	NSAID	10,652	5–10[f]	Glucuronide, sulfate conjugates[f]	69–1,500[c,e,g,j]	L-H[c,g,j]	70[c]	58–599[b,e,g,j,k]	<0.5–154[e–g,k]	568[k]
Ibuprofen	NSAID	108,435	1[f]	(+)-2-4′-(2-Hydroxy-2-methylpropyl)-phenylpropionic acid (25%) and (+)-2-40-(2-carboxypropyl)-phenylpropionic acid (37%), conjugated ibuprofen (14%)[f]	1681–33,764[c,e,g,j]	H[c,g]	380[c]	143–4,239[b,e,g,j,k]	1–2,370[e–g,j,k]	5,044[k]
Naproxen	NSAID	126,258	<1	6-o-Desmethyl naproxen (<1%), conjugates (66–92%)[f]	838–1,173[g]	M[g]	–	170–370[g]	1–59[f,g]	146[f]
Ketoprofen	NSAID	243	0–50	2-(3-benzoylphenyl)-propanoic acid and glucuronides	28–102[e,g]	M[g]	–	16–23[e,g]	1–4[e–g]	14[f]
Clofibric acid	Metabolite	–	–	–	1–651[e,g,j]	L-H[g,j]	–	6–44[e,g,j]	<0.3–101[e–g]	164[f]
Salicylic acid	Metabolite	–	–	–	5866–52,000[c,e,g]	L-H[c,g]	–	75–209[e]	4–62[e–g]	302[f]

(*continued on next page*)

Table 1 – (*continued*)

Emerging contaminant	Family/use	Prescription 2012 (kg)[a]	Excretion unchanged (%)	Known metabolites	Influent (ng l^{-1})	Removal (%)	Sludge (ng kg^{-1})	Final effluent (ng l^{-1})	Surface water (ng l^{-1})	Surface water max. (ng l^{-1})
Ranitidine	H_2 receptor agonist	35,665	30[d]	N-oxide (3–6%), S-oxide (1–2%) desmethyl ranitidine (1–2%)[f]	<12–5,060[e,g]	L-H[g]	–	<9–425[e,g]	<3–32[d–g]	73[f]
Cimetidine	H_2 receptor agonist	3195	48–75[d]	Cimetidine N-glucuronide (24%), cimetidine suphoxide (7–14%), hydroxymethylcimetidine (4%)[f]	2219–3,452[e,g]	L-M[g]	–	462–2,605[e,g]	<0.5–105[e–g]	220[f]
Furosemide	Diuretic	14,840	Little[f]	Mainly glucuronides[f]	1476–2,789[e,g]	L-M[g]	–	629–1,161[e,g]	<6–129[e–g]	630[f]
Bezafibrate	Lipid regulator	7966	50[f]	Glucuronides (20%)[f]	420–971[e,g]	L-M[g]	–	177–418[e,g]	<10–60[e–g]	90[g]
Simvastatin	Lipid regulator	49,198	Little	β-Hydroxyacid metabolite[f]	<7–115[e,g]	–	–	<3–5[e,g]	<0.6[d,e,g]	–
Fluoxetine	Antidepressant	5319	11[l]	Norfluoxetine	14–86[c,h,i,l]	L-H[c,i]	170[c]	16–29[b,h,i]	5.8–14[h,i]	14[h,i]
Norfluoxetine	Metabolite	–	–	–	3.3–63[h,i,l]	M[i]	–	5.8–13[h,i]	1.3–2.8[h,i]	3.5[i]
Venlafaxine	Antidepressant	16,211	5[l]	Desmethylvenlafaxine	120–249[h,i,l]	L[i]	–	95–188[h,i]	1.1–35[h,i]	85[i]
Dosulepin	Antidepressant	3270	11[l]	Desmethyldosulepin	21–228[h,i,l]	M-H[i]	–	57[h]	0.5–25[h,i]	32[h,i]
Amitriptyline	Antidepressant	10,171	2[l]	Nortriptyline, 10-hydroxyamitriptyline (active), 10-Hydroxynortriptyline (active)[f]	106–2,092[e,g,h,i,l]	M-H[g,i]	–	66–207[e–i]	<0.5–30[d–i]	72[h]
Nortriptyline	Antidepressant	439	3[l]	Hydroxynortriptyline	5.1–114[h,i,l]	M[i]	–	7.6–33[h,i]	0.8–6.8[h,i]	19[h,i]
Valsartan	Hypertension	6484	80[d]	Valeryl 4-hydroxy valsartan[f]	342–1,734[e,g]	L-H[g]	–	192–344[e,g]	<1–55[d–g]	144[f]
Diltiazem	Calcium-channel blocker	21,922	2–4[f]	Desacetyldiltiazem, N-monodemethyldiltiazem (active)[f]	770–1,559[e,g]	L-M[g]	–	95–357[e,g]	<1–17[d–g]	65[f]
Theophylline	Bronchodilator	4[l]	10	Caffeine, 3-methylxanthine	9467–20,400[h,i,l]	H[i]	–	1220–3,169[h,i]	76–558[h,i]	1,439[i]
Tramadol	Analgesic	41,445	15–35[d,l]	Desmethyltramadol (active)[f]	733–48,488[e–i,l]	L[g,i]	–	739–59,046[e,g,h,i]	<30–5,970[d–f,h,i]	7,731[f]
Nortramadol	Metabolite	–	–	–	226–2,457[h,i,l]	M-H[i]	–	145–433[h,i]	11–181[h,i]	410[i]
Codeine	Various	34,626	64–70[d,l]	Codeine-6-glucuronide (main), free/conjugated morphine (10–15%), norcodeine (10–20%)[f]	1088–10,321[e–i,l]	L-H[g,i]	–	372–5,271[e,g–i]	<1.5–347[d–i]	815[f]
Norcodeine	Metabolite	–	–	–	30–112[h,i,l]	M[i]	–	24–33[h,i]	2.1–9.0[h,i]	20[h]
Oxycocodone	Analgesic	–	9[l]	Noroxycocodone, oxymorphone,	5.0–12[h,i,l]	L[i]	–	7–12[h,i]	0.5–3[h,i]	7.1[h]
Oxymorphone	Analgesic	–	11[l]	Noroxycodone, noroxymorphone	11–20[h,i,l]	–	–	<1.7–8.4[h,i]	<0.1–2.3[h,i]	3.5[i]

Morphine	Analgesic	5684	55[l]	Morphine-3-glucuronide, morphine-6-glucuronide, normorphine	340–481[h,i,l]	H[i]	–	59–131[h,i]	1.6–36[h,i]	36[h]
Normorphine	Metabolite	–	–	–	51–203[h,i,l]	H[i]	–	20–62[h,i]	<5–5.7[h,i]	5.7[i]
Dihydrocodeine	Analgesic	9720	54[l]	Dihydromorphine (active)	227–386[h,i,l]	L[i]	–	118–146[h,i]	2.9–36[h,i]	97[i]
Buprenorphine	Various	91	1[l]	Norbuprenorphine and glucuronides	33–47[h,i]	–	–	14[h]	<0.5–15[h,i]	14[i]
Norbuprenorphine	Metabolite	–	–	–	<1–19[h,i]	–	–	<0.7–7.5[h,i]	<0.5–12.2[h,i]	3.4[i]
Methadone	Analgesic	1687	28[l]	EDDP, EMDP	52–88[h,i,l]	L[i]	–	42–50[h,i]	0.6–12[h,i]	24[i]
EDDP	Metabolite	–	–	–	71–193[h,i,l]	L-M[i]	–	32–89[h,i]	1.2–19[h,i]	38[h]
EMDP	Metabolite	–	–	–	1.8–5.7[h,i]	–	–	1.3–1.7[h,i]	0.6–1.0[h,i]	1.1[h]
Fentanyl	Analgesic	1.0	3[l]	Norfentanyl, despropionylfentanyl	1.3–1.7[h,i]	–	–	<0.1–0.5[h,i]	<0.1[h]	–
Norfentanyl	Metabolite	–	–	–	6.9[h]	–	–	1.1[h]	<0.1[h]	–
Propoxyphene	Analgesic	–	1[l]	Norproxyphene	8.2–11[h,i]	–	–	7.1[h]	<0.1[h]	–
Norpropoxyphene	Metabolite	–	–	–	<4.2–184[h,i,l]	L[i]	–	91–106[h,i]	6.5–31[h,i]	80[i]
Temazepam	Hypnotic	833	75[l]	Oxazepam	85–208[h,i,l]	L[i]	–	135–179[h,i]	3.2–34[h,i]	78[i]
Diazepam	Hypnotic	335	Trace[l]	Nordiazepam, temazepam, oxazepam	<0.9–7.6[h,i]	–	–	1.6–5.1[h,i]	0.6–0.9[h,i]	1.1[h,i]
Nordiazepam	Metabolite	–	–	–	12–25[h,i,l]	M[i]	–	5.8–9.9[h,i]	0.7–3.2[h,i]	6.8[i]
7-Aminonitrazepam	Metabolite	–	–	–	<1.9–205[h,i]	–	–	<1.2[h]	<0.5[h]	–
Oxazepam	Hypnotic	85	33[l]	Glucuronide metabolite	22–50[h,i,l]	L[i]	–	33–58[h,i]	2.4–11[h,i]	21[i]
Ketamine	Anaesthetic	64	2[l]	Norketamine	52–235[h,i,l]	L[i]	–	83–130[h,i]	0.6–27[h,i]	54[i]
Norketamine	Metabolite	–	–	–	11–85[h,i,l]	L[i]	–	14–28[h,i]	1.7–5.8[h,i]	14[h]
Sildenafil	Erectile dysfunction	570	<1	N-desmethyl sildenafil	8.3–25[h,i,l]	L[i]		7.0–9.7[h,i]	<1–2.2[h,i]	2.9[i]
Ephedrine/ pseudoephedrine	Various	622	40–90	Cathine	476–966[h,i,l]	H[i]	–	35–70[h,i]	7.7–15[h,i]	17–29[h,i]
Norephedrine	Various	–	80–90	–	40–86[h,i]	H[i]	–	59[h]	<5[h]	–
Amoxicillin	Antibacterial	158,231	30–70	Amoxicilloic acid	<87[e]	–	–	31[e]	<2.5–245[d,e,f]	622[f]
Erythromycin	Antibacterial	41,057	5[d]	Erythromycin-H_2O[f]	71–2,530[c,e,g,j]	L-H[c,g,j]	50[c]	109–1,385[b,e,g,j,k]	<0.5–159[d–g,j,k]	1,022[k]
Metronidazole	Antibacterial	12,300	20[d]	1-(β-hydroxymethyl-5-nitroimidazole, 2-methyl-5-nitroimidazole-1yl-acetic acid[f]	569–2,608[e,g]	L[g]	–	265–373[e,g]	<1.5–12[d–g]	24[f]
Ofloxacin	Antibacterial	219	65–80	Desmethyl, N-oxide metabolites	180[c]	M-H[c]	210[c]	10[b]	–	–
Chloramphenicol	Antibacterial	–	8–12[d]	Glucuronide conjugates[f]	<4–248[e,g]	H[g]	–	<6–21[e,g]	<10[d,f,g]	40[f]
Sulfamethoxazole	Antibacterial	–	30[d]	N_4-acetylated metabolite	<3–115[e,g]	L-M[g]	–	10–19[e,g]	<0.5–2[d–g]	8[g]
Sulfapyridine	Antibacterial	–	<10	Hydroxyl, acetyl metabolites	914–4,971[g]	L-H[g]	–	277–455[g]	<2–28[f,g]	142[f]

(continued on next page)

Table 1 – (*continued*)

Emerging contaminant	Family/use	Prescription 2012 (kg)[a]	Excretion unchanged (%)	Known metabolites	Influent (ng l^{-1})	Removal (%)	Sludge (ng kg^{-1})	Final effluent (ng l^{-1})	Surface water (ng l^{-1})	Surface water max. (ng l^{-1})
Sulfasalazine	Chronic bowel disorders	54,039	15	5-Aminosalicylic acid (active), sulfapyridine (active)[f]	0.2–116[e,g]	L[g]	–	0.3–484[e,g]	<1.5–76[e–g]	168[f]
Trimethoprim	Antibacterial	10,998	80[d]	1,3-oxides, 3′ 4-hydroxy derivatives[f]	213–2,925[e,g,j]	L-M[j,g]	–	128–1,152[e,g,j,k]	<1.5–108[d–g,j,k]	183[f]
Oxytetracycline	Antibacterial	17,143	30	N-desmethyloxytetracycline	3600	H[c]	6710	170[b]	–	–
Tamoxifen	Anti-cancer	453	30	Hydroxytamoxifen (active)	143–215[j]	L[j]	–	<10–369[j,k]	<10–212[j,k]	–
Illicit drugs and licit stimulants										
MDMA	Hallucinogen	–	20[l]	MDA, HMMA, HMA	10–231[h,i,l]	L[i]		13–38[h,i]	0.5–8.7[h,i]	25[h,i]
MDEA	Hallucinogen	–	19[l]	MDA	<0.3–1.4[h,i]	–	–	<0.5[h]	<0.1[h]	–
MDA	Hallucinogen/ metabolite	–	High[l]	–	10–18[h,i,l]	–	–	11–15[h,i]	<0.1–1.7[h,i]	1.7[i]
Amphetamine	Stimulant	–	1–74[d,l]	25% Phenylacetone, benzoic acid, hippuric acid, <10% 4-hydroxy-norephedrine, norephedrine[f]	77–5,236[e–i,l]	H[g,i]	–	2–201[e,g–i]	<1–9[d–i]	4.3[h]
Methamphetamine	Stimulant	–	43[l]	Amphetamine, 4-hydroxymethamphetamine	2–40[h,i,l]	M-H[i]	–	0.8–1[h,i]	<0.1–0.3[h,i]	0.3[i]
Cocaine	Stimulant	–	1–9[f,l]	35–54% benzoylecgonine, 32–49% ecgonine[f] methyl ester (main)	57–526[e,g–i,l]	L-H[i]	–	<1–149[e,g–i]	<0.3–6[d–i]	17[i]
Benzoylecgonine	Metabolite	–	–	–	196–1,544[e,g–i,l]	L-H[g]	–	13–1,597[e,g–i]	<1–92[d–i]	72[i]
Norbenzoylecgonine	Metabolite	–	1[l]	–	6–54[h,i,l]	–	–	3.6–7[h,i]	0.3–2[h,i]	3.1[i]
Norcocaine	Metabolite	–	–	–	1[h]	–	–	<0.2[h]	0.1[h]	0.1[h]
Cocaethylene	Metabolite	–	–	–	3–45[h,i,l]	L-M[i]	–	1.7–3.8[h,i]	0.1–0.6[h,i]	1.4[h]
Benzylpiperazine	Stimulant	–	7(rat)[l]	Hydroxylated metabolite	22–25[h,i]	L-H[i]	–	31–44[h,i]	1.1–26[h,i]	65[h]
Trifluoromethyl-phenylpiperazine	Stimulant	–	<1(rat)[l]	Hydroxylated metabolite	2.4–5.1[h,i,l]	–	–	4.6–6.6[h,i]	0.2–1.2[h,i]	6.1[i]
6-acetylmorphine	Metabolite	–	<1[l]	–	3.0–22[h,i,l]	–	–	<0.3–2.2[h,i]	<0.1[h]	–
Caffeine	Human indicator	–	1[l]	Acids and 1-methylxanthine	9902–25,138[h,i,l]	H[i]	–	1744–2,048[h,i]	163–743[h,i]	1,716[i]
Nicotine	Human indicator	442	–	–	3919–9,684[h,i,l]	H[i]	–	52[h]	12–86[h,i]	148[i]
Personal care products										
Triclosan	Antibacterial	–	–	–	70–2,500[c,e,g]	M-H[c,g]	5,140[c]	25–200[b,e,g]	5–48[e–g]	–
Bisphenol A	Plasticizer	–	–	–	416–2,050[c,e,g]	M-H[c,g]	320[c]	35–86[b,e,g]	<6–34[e–g]	–
1-benzophenone	Sunscreen agent	–	–	–	134–306[e,g]	H[g]	–	12–32[e,g]	<0.3–9[e,f]	–
2-benzophenone	Sunscreen agent	–	–	–	25–194[e,g]	H[g]	–	1–4[e,g]	<0.5–18[e–g]	–
3-benzophenone	Sunscreen agent	–	–	–	638–1,195[e,g]	M-H[g]	–	22–231[e,g]	<15–36[e–g]	–
4-benzophenone	Sunscreen agent	–	–	–	3597–5,790[e,g]	L[g]	–	2701–4,309[e,g]	<3–227[e–g]	–
Methylparaben	Preservative	–	–	–	2642–11,601[e,g]	H[g]	–	<3–50[e,g]	<0.3–68[e–g]	–
Ethylparaben	Preservative	–	–	–	589–2,002[e,g]	H[g]	–	4–50[e,g]	1–13[e–g]	–
Propylparaben	Preservative	–	–	–	598–3,090[e,g]	H[g]	–	26–63[e,g]	<0.2–7[e–g]	–
Butylparaben	Preservative	–	–	–	50–723[e,g]	H[g]	–	<1[e,g]	<0.3–6[e–g]	–

Key: NSAID, non-steroidal anti-inflammatory drug; L, secondary removal is <50%; M, secondary removal is within the range 50–80%; H secondary removal >80%.
[a] Taken from NHS Prescription Cost Analysis information for England (National Health Service, 2012).
[b] Median data reported from 162 WwTWs – Gardner et al., 2012.
[c] Data obtained from 14 WwTWs (inc. activated sludge, trickling filters, membrane bioreactors and biological nutrient removal plants – Gardner et al., 2013.
[d] Kasprzyk-Hordern et al., 2007.
[e] Kasprzyk-Hordern et al., 2008a.
[f] Kasprzyk-Hordern et al., 2008b.
[g] Two WwTWs monitored (activated sludge and trickling filter) Kasprzyk-Hordern et al., 2009.
[h] Baker and Kasprzyk-Hordern, 2011a.
[i] Seven WwTWs (activated sludge and trickling filters), median data reported – Baker and Kasprzyk-Hordern, 2013.
[j] WwTWs is a train of processes (trickling filter, activated sludge and UV treatment) Roberts and Thomas, 2006.
[k] Five WwTWs (oxidation ditch, activated sludge and trickling filters) Ashton et al., 2004.
[l] Baker et al., 2014.
[m] Includes particulate concentrations – Koh et al., 2009.

Fenech et al., 2013; Hughes et al., 2013; Loos et al., 2013; López-Serna et al., 2013).

3. Understudied areas of EC pollution in wastewaters and the environment

The data set described (Table 1), and wider literature was used to identify key areas of concern considered to be understudied. These are discussed to address deficiencies in current knowledge of EC contamination in wastewaters and the environment.

3.1. *Spatial and temporal variability of ECs in wastewater and river water*

3.1.1. *Factors which influence receiving wastewater concentration*

A large variation in influent wastewater concentrations (equivalent to more than an order of magnitude) has been observed for some ECs (Table 1). For example, acetaminophen was found within influent wastewater at mean concentrations ranging from 6924 to 492,340 ng l^{-1} (Roberts and Thomas, 2006; Kasprzyk-Hordern et al., 2008a, 2009) (Table 1). This indicates spatial and/or temporal variations in their usage. However dilution from industrial inputs, degradation within the upstream sewer, rainfall and sampling mode will all contribute to this variability. The use of inappropriate sampling strategies is considered the greatest weakness of reported occurrence data. Ort et al. (2010a,b) gave an excellent account of uncertainties associated with different sampling modes. Current approaches tend to use discrete grab sampling of low inter-day frequency and often no intra-day repetition. To demonstrate, all reported data in Table 1 was obtained using a grab sampling approach. This approach has limitations as it only yields a snap shot of EC concentration for a specific point in time. Time and volume/flow proportional composite samplers are also used (Plósz et al., 2010; Coutu et al., 2013; López-Serna et al., 2013), but to a lesser extent. The latter being preferred as it accounts for fluctuations in flow. The relatively high cost and logistical issues associated with this sampling mode has resulted in very few studies applying flow proportional sampling. Also, a major uncertainty of 24 h composite sampling is chemical stability. This is not often investigated but is known to be significant for some chemicals (Baker and Kasprzyk-Hordern, 2013). Due to uncertainties of existing sampling methods, there is lack of understanding on spatial and temporal variations in EC concentrations.

3.1.2. *Spatial distribution*

Assessing spatial distribution of EC contamination is notoriously difficult. The collation and interpretation of literature data from a variety of sources has obvious limitations. On the other hand, studies have been able to tentatively assess spatial distribution within a single catchment (Vazquez-Roig et al., 2012; Baker and Kasprzyk-Hordern, 2013). Such studies have to rely heavily on discrete grab sampling due to the large number of sites which are monitored at approximately the same time. Despite the uncertainties associated with grab

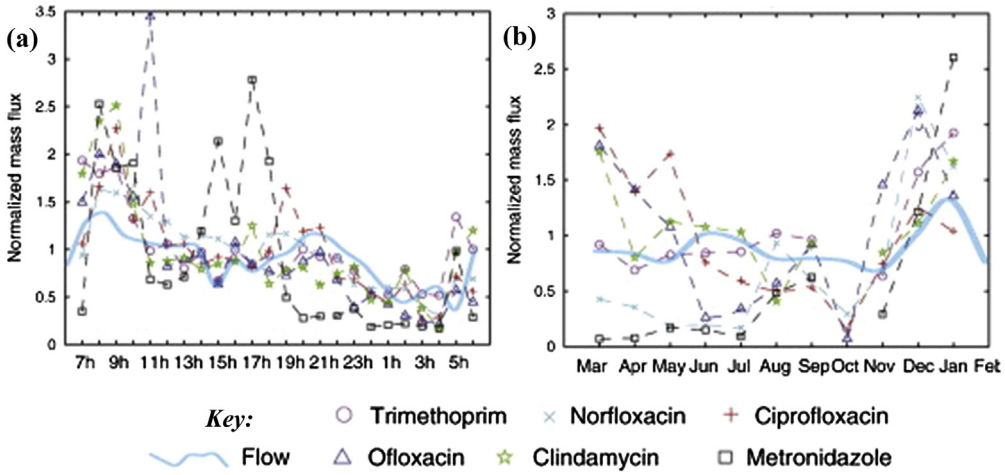

Fig. 1 – Fluctuations of mass flux for selected antibiotics in wastewater throughout a one day period (a) and during the course of a year (b) – adapted from Coutu et al. (2013).

sampling, information attained from such studies is extremely valuable. It can be used as a primary indicator of sites within the catchment that require more detailed study. These can then be subject to more robust sampling protocols to facilitate greater understanding of EC fate and occurrence during wastewater treatment and in the environment at these predetermined sites of interest.

3.1.3. *Intra-day variation*

It is anticipated that concentrations of ECs in receiving wastewater vary throughout the day. Coutu et al. (2013) collected hourly composite samples (i.e., one sample every 15 min to create an hourly composite) for influent wastewater over 24 h sampling periods. This was used to investigate within day variability of antibiotic concentrations. Samples were chilled upon collection but their stability at 4 °C was not investigated or referenced to. However, significant degradation (>15%) has been observed for some ECs stored at 4 °C for only 12 h (Baker and Kasprzyk-Hordern, 2013). Despite this uncertainty, the six antibiotics studied (trimethoprim, norfloxacin, ciprofloxacin, ofloxacin, clindamycin, metronidazole) showed variation in concentration throughout the day (Coutu et al., 2013). A peak in receiving load was observed between 07:00 and 9:00 h (Fig. 1a). This is explainable by posology and the accumulation of administered drugs within urine during sleep (Plósz et al., 2010; Coutu et al., 2013). Therefore following the first toilet flush of the day an increase in load of antibiotics is observed. Other urine derived ECs are expected to behave in the same way. Yet it is unknown how the performance of WwTWs responds to this daily spike in receiving concentration and volumetric load. Collection of corresponding final effluent samples would help address this.

3.1.4. *Inter-day variability*

A European wide study of 19 European countries using a variety of time, flow and volume proportional sampling attempted to investigate inter-day variability (i.e., over a one week period) of illicit drugs in influent wastewater (Thomas et al., 2012). Collated data revealed a trend of recreational use for some compounds (Fig. 2). Both benzoylecgonine (the major metabolite of cocaine) and MDMA showed elevated levels at weekends. In contrast, it is anticipated that hospital dispensed chemicals such as X-ray contrast media and anticancer drugs will be observed at higher concentrations

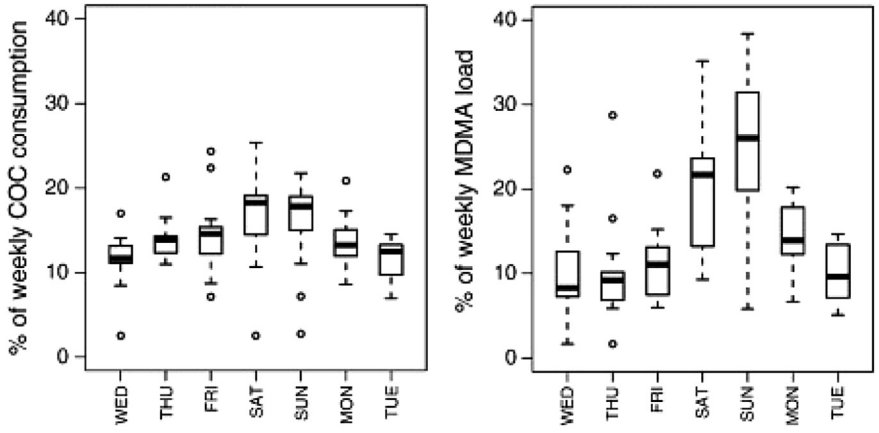

Fig. 2 – Inter-day variation in cocaine (COC) and MDMA consumption calculated from a European wide study profiling wastewater of 19 cities – adapted from Thomas et al. (2012).

during weekdays when hospital appointments are greatest. Inter-day variability of EC concentration is difficult to fully appreciate without conducting flow proportional sampling. This is most significant when comparing weekday and weekend periods where wastewater flows can vary notably. Differences in weekday/weekend flow will be specific for the catchment in question. For example, a residential (commuter) or tourist area will see increased flow during weekends. On the other hand, a catchment containing industrial works may observe a reduction in flow and dilution during weekends. Rainfall will also result in changes to wastewater flow between days. This illustrates that reporting load (mass per day) over the traditional approach of concentration (mass per litre) to overcome temporal variations in flow is more suited to describe findings.

3.1.5. *Seasonality*

Some ECs have seasonal uses indicating that their influent load will vary throughout the year. For example, monthly prescription information for the UK showed antihistamines used to treat allergies (e.g., hay fever) peaked from May to August when pollen production is greatest (Fig. 3) (National Health Service, 2012). Generally, quantities prescribed were 100% greater in summer compared to winter months. This relationship has been established for the antihistamine cetirizine in Norwegian wastewater (Harman et al., 2011). Prescription information also showed a similar trend for the number of prescribed sunscreens and sunscreening preparations (Fig. 3). This indicates that personal care products associated with these preparations such as UV filters will also be more prevalent in wastewater during summer. In contrast, pseudoephedrine (used in nasal decongestants) and pholcodine (used in cough preparations) showed an opposite trend in their usage with highest prescription observed during winter months (Fig. 1) (National Health Service, 2012). Cumulative concentration of ephedrines has been reported at higher concentrations during winter months (Kasprzyk-Hordern and Baker, 2012a). Furthermore, a high contribution of the enantiomer 1*S*,2*S*(+)-pseudoephedrine during winter is consistent with increased usage of over-the-counter-medication used to treat symptoms of cold (Kasprzyk-Hordern and Baker, 2012b). A study by Veach and Bernot (2011) attempted to determine temporal variations of 15 ECs within two rivers over a one year period. However, the sampling protocol consisted of a single monthly grab sample which severely restricts understanding of seasonal variation. A more robust approach which undertook weekly 24 h flow proportional sampling every month for a one year period, investigated temporal variations of antibiotics within influent wastewater (Coutu et al., 2013). Seasonality was reported for both ciprofloxacin and norfloxacin in receiving wastewater for a WwTW in Switzerland (Fig. 1b). Mass fluxes were higher in winter and spring months,

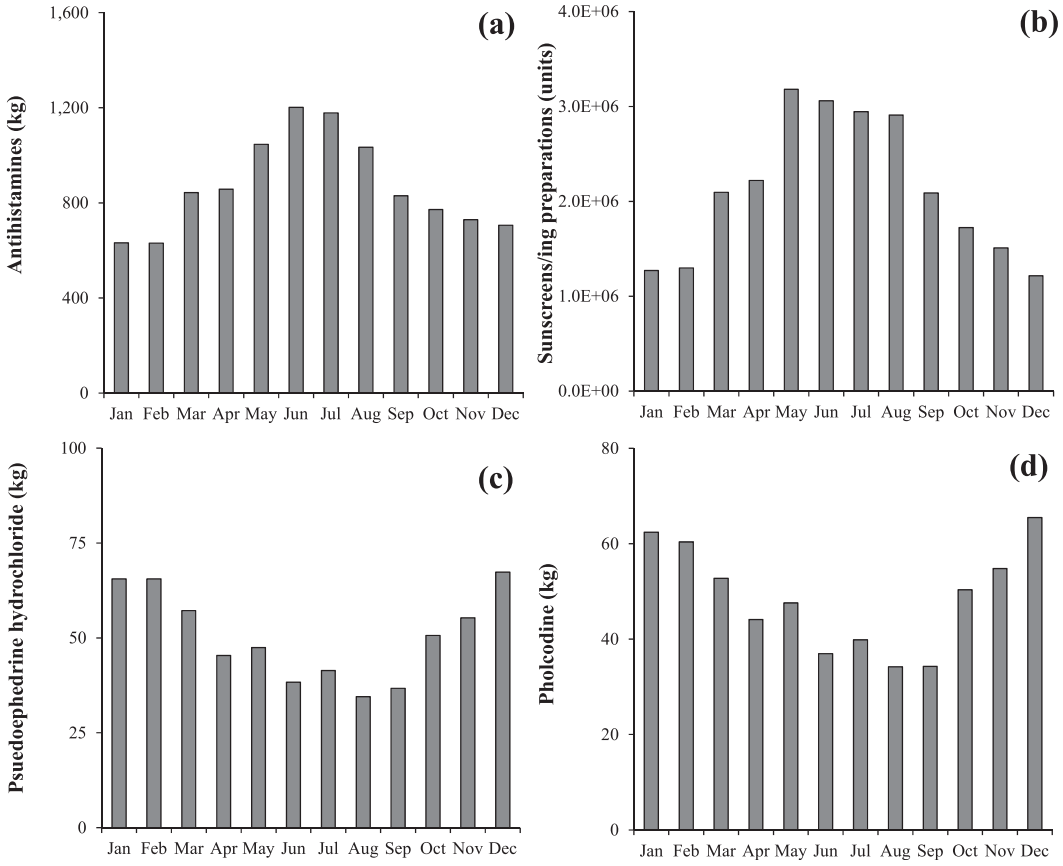

Fig. 3 – Monthly National Health Service Prescription Cost Analysis information (items dispensed by pharmacy and appliance contractors in England) for antihistamines (loratadine, cetirizine hydrochloride and fexofenadine hydrochloride) (a), sunscreen and sunscreening preparations (b), pseudoephedrine hydrochloride (c) and pholcodine (d) in 2012 (National Health Service, 2012).

explained by seasonal therapeutic use. For example, ciprofloxacin is used to treat airway infections and infections affecting the throat, nose and ear (Coutu et al., 2013). This relationship could not be established for UK Prescription Cost Analysis data (National Health Service, 2012).

3.1.6. Occasional events

There is a lack of knowledge on the impact of occasional events to the loading of ECs in wastewater, or their impact to wastewater treatment performance and to biota of the receiving environment. An increase in drug use may be anticipated during music festivals (Lai et al., 2013a), public holidays (Lai et al., 2013b), major sporting events (Gerrity et al., 2011) and by students during exam periods for improved concentration (Dennhardt and Murphy, 2013). A less predictive source of increased drug load can be observed during the direct disposal of a large quantity of illicit drug during a police raid of an illegal production factory. To demonstrate, Emke et al. (2014) observed a load of MDMA 20 times higher than normal during a weekly sampling campaign at a WwTW in Utrecht. Direct disposal was considered to be the source of this spike based on findings of enantiomeric profiling (i.e., no metabolism) (Fig. 4). This irregularly high load coincided with a police raid within the catchment two days earlier. However, such events are difficult to monitor due to their unpredictable occurrence. A further scenario which could result in a sharp increased load of a drug within the environment is in the event of a pandemic. A UK outbreak of influenza in 2009 resulted in a high number of people treated with antivirals and antibiotics (Singer et al., 2011; Slater et al., 2011; Singer et al., 2013). There is limited knowledge of the resilience of WwTWs to maintain normal performance and achieve antibiotic removal in such events. Nevertheless, laboratory scale investigation showed that typically reported concentrations of oseltamivir carboxylate (the active metabolite of Tamiflu®, the medicine used in response to the influenza outbreak) reduced activated sludge performance with respect to nutrient removal (Slater et al., 2011).

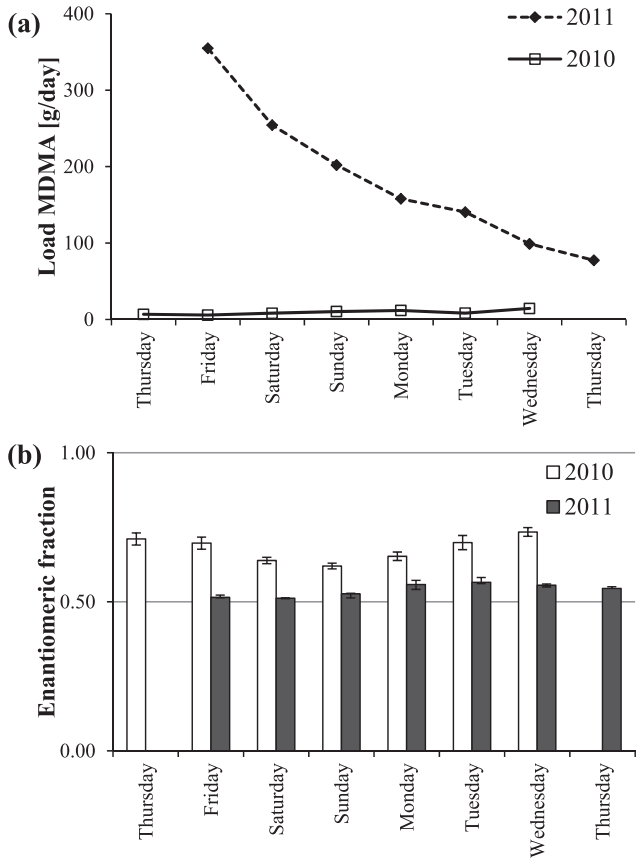

Fig. 4 – Load of MDMA in wastewater collected during week long sampling campaigns conducted in 2010 and 2011 (a) and their corresponding enantiomeric fraction (b) – adapted from Emke et al. (2014). Note: Enantiomeric fraction = (+)/[(+)+(−)] − 0.5 denotes a racemic distribution.

3.2. Partitioning of ECs to solid matter during wastewater treatment

3.2.1. Influent wastewater and final effluent

Emerging contaminant analysis in wastewaters tends to be undertaken on the aqueous phase only (i.e., a pre-filtered sample) (Table 1). Particulate phase analysis is not routinely undertaken because up to one gram of dry solids is often required for each analysis and additional sample extraction is needed (Radjenović et al., 2009a; Baker and Kasprzyk-Hordern, 2011b). However, analysis here is essential as some chemicals have a high affinity to particulate matter. Numerous chemicals including amitriptyline, EMDP, dosulepin, fluoxetine, norfluoxetine, triclosan, ofloxacin and ciprofloxacin have been found to be within the particulate phase of influent wastewater at significant concentrations (>20% of the total concentration) (Baker and Kasprzyk-Hordern, 2011a,b; Petrie et al., 2014c). Consequently, particulate phase determination is necessary to correctly report influent concentration for some chemicals. This is also essential for back calculations of population usage by wastewater-based epidemiology (Baker et al., 2012). Partitioning of ECs to suspended matter in final effluents is even less studied due to the very low solids concentrations encountered (typically 10–30 mg l^{-1} for secondary processes). Nevertheless, Petrie et al. (2014c) found that final effluent of secondary processes had >20% of the total triclosan, ofloxacin and ciprofloxacin concentration to be within the particulate phase, despite very low suspended solids concentrations. Particulate phase concentrations were equivalent to, and in the range 26–296 ng l^{-1}, respectively. This provides a route for their release into the environment which goes unmonitored and the environmental fate of these particulate bound chemicals is unknown.

3.2.2. Diagnosis of EC removal during wastewater treatment

Common sampling approaches to measure wastewater treatment performance with respect to EC removal monitor aqueous phase of influent and effluent samples only (Table 1). To better understand their pathways of removal during wastewater treatment, particulate phase analysis is needed as well as analysis of the biomass (either suspended or attached) of the process (Petrie et al., 2014a,c). Ideally, corresponding aqueous and particulate determinations should be undertaken for each sampling point such that a complete process mass balance is attained. This can give valuable information

on the dominant mechanisms which govern removal (Petrie et al., 2014a,c). Removal can vary greatly between ECs from a physically driven process (adsorption) to biologically mediated enzymatic reactions (biodegradation) (Helbling et al., 2010; Petrie et al., 2014a). Their identification also needs to be supported with information of process conditions and operation, nutrient removal and complimentary analysis of the physical/biological characterisation of biomass (Petrie et al., 2014a). With this knowledge, the operation of the process could be adjusted to favour their removal (Petrie et al., 2014b). Such information can also be used to identify where further research efforts may be needed. For example, those chemicals removed by biodegradation suggest further investigation of possible biotransformation products in final effluents is needed, and those removed by adsorption require further understanding of their fate during and following sludge treatment.

3.2.3. *Biosolids and amended soils*

During anaerobic digestion, biosolids (or treated sludge) are generated. These are often applied to agricultural land as a fertiliser in some countries. Despite lengthy digestion (20–30 days) and outdoor storage for up to six months following treatment, some ECs have shown to persist (Cortés et al., 2013). No legislation currently controls the use of biosolids on agricultural land with respect to concentration of ECs. Consequently, a lack of analysis has been observed here (Table 2). The majority of chemicals previously investigated in biosolids were found at <1 mg kg^{-1}. On the other hand bisphenol A, triclosan, triclocarban and the antibiotics ciprofloxacin, ofloxacin and norfloxacin have all been reported at >1 mg kg^{-1} (Table 2) (Golet et al., 2002; McAvoy et al., 2002; Lindberg et al., 2005; Morales et al., 2005; Heidler et al., 2006; Chu and Metcalfe, 2007; Ying and Kookana, 2007; Stasinakis et al., 2008; Cha and Cupples, 2009; Langdon et al., 2011; Gottschall et al., 2012; Sabourin et al., 2012; Guerra et al., 2014). These chemicals have very different physicochemical properties (hydrophobicity, water solubility etc) (Table 2), suggesting their fate and transport in amended soils will vary (Morais et al., 2013). Triclosan and triclocarban exhibit greater hydrophobicity (log K_{ow} 4.2–4.8) indicative of retention within the soil matrix. In contrast, those which are relatively water soluble ($\geq 3.0 \times 10^4$ mg l^{-1} – ciprofloxacin, norfloxacin and ofloxacin) suggest hydrophilic mobility which may result in their transport to surrounding surface waters. However, Tolls (2001) demonstrated that antibiotics show a wide range of mobility in soil. This implies other mechanisms are likely to be important, particularly for charged ECs. Partitioning behaviour of charged ECs is likely to be governed by other mechanisms such as electrostatic attractions (Hyland et al., 2012). If charge interactions play a role in sorption, then the K_{ow} concept is not meaningful here and cannot be applied. Therefore the acid-dissociation constant (p*Ka*) of the EC in question and pH of the matrix are critical for better understanding partitioning behaviour. For those ECs which are ionisable, the pH dependant octanol–water coefficient (log D_{ow}) should be applied to account for different behaviour.

To better appreciate the fate of ECs in soils, long term field studies at real environmental conditions are needed. These require sampling of biosolids, soil (pre- and post-application, and at various depths), surrounding surface waters and uptake by plants over an extended time period. Supporting information of pH, rainfall, temperature, sunlight and soil type/characteristics would help understand their fate. An excellent study by Butler et al. (2012) found that following biosolids application, triclosan (~0.8–1.0 mg kg^{-1}) showed little change in concentration over the initial eight months for three different soil types. However, after 12 months less than 20% of the initial concentration was recovered. A large fraction of this was attributed to the biological transformation of triclosan to methyl triclosan. Methyl triclosan was observed up to 0.4 mg kg^{-1}, demonstrating that transformation products need to be investigated here.

3.3. *Fate of ECs in environmental waters*

3.3.1. *Human metabolites*

Parent chemicals are often excreted from the human body with a number of associated metabolites. As an example, ibuprofen is excreted as the unchanged drug (1%) and several metabolites: (+)-2-4′-(2-Hydroxy-2-methylpropyl)-phenyl-propionic acid (25%), (+)-2-40-(2-carboxypropyl)-phenyl-propionic acid (37%) and conjugated ibuprofen (14%) (Kasprzyk-Hordern et al., 2008b). However, only ~20% of ECs previously reported in UK waters were metabolites (Table 1), and this is mirrored in international studies (Gros et al., 2012; Hughes et al., 2013; López-Serna et al., 2013). Admittedly their determination has been restricted by a lack of available analytical reference standards. Despite this, their determination is essential as free parent ECs are often cleaved from human metabolites and in particular, glucuronide conjugates when exposed to environmental conditions (Ternes et al., 1999). This has been observed in crude sewage and activated sludge batch studies for steroid estrogens (17α-EE2 3-glucuronide, estriol 16α-glucuronide, and estrone 3-glucuronide) (Gomes et al., 2009) and suggested to occur specifically for carbamazepine during full-scale activated sludge treatment (Vieno et al., 2007). Furthermore, analysis of metabolites is necessary as they can be found at concentrations much greater than the corresponding parent chemical and can themselves be pharmacologically active (Kasprzyk-Hordern et al., 2008b). To demonstrate, a major metabolite of carbamazepine (carbamazepine epoxide) has been found in influent wastewater at concentrations ranging from 880 to 4026 ng l^{-1} whereas the parent compound was found at <1.5–113 ng l^{-1} (Huerta-Fontela et al., 2010). Metabolites can also be persistent during secondary wastewater treatment (Lajeunesse et al., 2012; Petrie et al., 2013b). Their release into the environment and the possibility of subsequent biotransformation/deconjugation in environmental compartments to the parent EC makes their determination essential to better assess ecological risk.

3.3.2. *Microbial transformation*

Many ECs undergo microbially mediated reactions during secondary wastewater treatment (Helbling et al., 2010), and in the environment. Biodegradation is often referred to as the dominant fate pathway for the removal of some ECs from the aqueous phase of wastewaters and surface waters (Andersen et al., 2005; Bagnall et al., 2012a,b). However, this can result in

Table 2 – Concentration and physicochemical properties (ChemicalBook, 2014; ChemSpider, 2014; DrugBank, 2014) of ECs found in biosolids ($n \geq 3$).

Emerging contaminant	Log K_{ow}	pK_a	Water solubility (mg l^{-1})	Country	Mean biosolid conc. (mg kg^{-1} dry weight)	Reference
Estrone	3.13	10.3	30.0	Germany	<MQL-0.02	Ternes et al., 2002
				Canada	0.06	Sabourin et al., 2012
				Australia	<MQL-0.28	Langdon et al., 2011
Ibuprofen	3.97	4.91	21.0	Spain	0.30	Radjenović et al., 2009a
				Canada	0.15[a]	Guerra et al., 2014
				Spain	0.02–0.44	Albero et al., 2014
				Canada	0.17	Sabourin et al., 2012
				Canada	0.06	Gottschall et al., 2012
				Spain	0.09	Morais et al., 2013
Naproxen	3.18	4.15	15.9	Canada	0.02[a]	Guerra et al., 2014
				Spain	<MQL-0.02	Albero et al., 2014
				Canada	0.01	Sabourin et al., 2012
Diclofenac	4.51	4.15	2.37	Spain	0.19	Radjenović et al., 2009a
				Spain	<MQL-0.63	Albero et al., 2014
				Spain	0.06	Morais et al., 2013
				Canada	<MQL-0.02	Spongberg and Witter, 2008
Acetaminophen	0.460	9.38	1.40×10^4	Spain	0.03	Radjenović et al., 2009a
				USA	<MQL-0.37	Ding et al., 2011
				Canada	0.02[a]	Guerra et al., 2014
				Spain	0.02–0.29	Albero et al., 2014
Gemfibrozil	3.40	4.75	–	Spain	0.12	Radjenović et al., 2009a
				Spain	<MQL-0.07	Albero et al., 2014
				Canada	0.008	Sabourin et al., 2012
				Canada	<MQL-0.003	Spongberg and Witter, 2008
Carbamazepine	2.45	13.9	17.7	Spain	0.08	Radjenović et al., 2009a
				USA	<MQL-0.02	Ding et al., 2011
				Canada	0.26	Miao et al., 2005
				Canada	0.18	Gottschall et al., 2012
				Canada	0.09	Sabourin et al., 2012
				Spain	0.03	Morais et al., 2013
				Canada	0.01	Spongberg and Witter, 2008
Fluoxetine	4.05	3.95	5.00×10^4	Spain	0.12	Radjenović et al., 2009a,b
				Canada	0.09	Sabourin et al., 2012
				Canada	0.11	Gottschall et al., 2012
Propranolol	3.48	9.42	61.7	Spain	0.03	Radjenović et al., 2009a
				Canada	0.04	Sabourin et al., 2012
				Canada	0.12	Gottschall et al., 2012
				Canada	0.36[a]	Guerra et al., 2014
				Canada	0.23	Gottschall et al., 2012
Ciprofloxacin	0.280	6.09	3.00×10^4	Switzerland	2.27–2.42	Golet et al., 2002
				Sweden	0.50–4.80	Lindberg et al., 2005
				Canada	6.50[a]	Guerra et al., 2014
				Canada	5.87	Sabourin et al., 2012
				Canada	3.26	Gottschall et al., 2012
				Canada	<MQL-0.05	Spongberg and Witter, 2008
Norfloxacin	−1.03	2.75	1.78×10^5	Switzerland	2.13–2.37	Golet et al., 2002
				Sweden	0.10–4.20	Lindberg et al., 2005
				Canada	1.75	Sabourin et al., 2012
				Canada	1.01	Gottschall et al., 2012
Ofloxacin	−0.390	5.23	2.83×10^4	Sweden	<MQL-2.00	Lindberg et al., 2005
				Spain	0.07	Radjenović et al., 2009a,b
				Canada	0.69[a]	Guerra et al., 2014
				Canada	1.07	Sabourin et al., 2012
				Canada	1.40	Gottschall et al., 2012
Tetracycline	−1.30	3.30	5.00×10^4	USA	<MQL-0.56	Ding et al., 2011
				Canada	0.24[a]	Guerra et al., 2014
				Canada	0.34	Sabourin et al., 2012
				Canada	0.51	Gottschall et al., 2012
				Canada	<MQL-0.01	Spongberg and Witter, 2008

Table 2 – (continued)

Emerging contaminant	Log K_{ow}	pK_a	Water solubility (mg l^{-1})	Country	Mean biosolid conc. (mg kg^{-1} dry weight)	Reference
Triclosan	4.80	7.90	10.0	Greece	3.21	Stasinakis et al., 2008
				USA	0.53–15.6	McAvoy et al., 2002
				Spain	1.51	Morales et al., 2005
				Canada	0.68–11.55	Chu and Metcalfe, 2007
				Australia	5.58	Ying and Kookana, 2007
				USA	4.89–9.28	Cha and Cupples, 2009
				Canada	6.80[a]	Guerra et al., 2014
				Canada	4.68	Sabourin et al., 2012
				Canada	10.9	Gottschall et al., 2012
				Australia	0.22–9.89	Langdon et al., 2011
Triclocarban	4.20	12.7	0.110	Canada	3.05–5.97	Chu and Metcalfe, 2007
				USA	0.09–7.06	Cha and Cupples, 2009
				USA	51.0	Heidler et al., 2006
				Canada	2.90[a]	Guerra et al., 2014
				Canada	6.03	Sabourin et al., 2012
				Canada	4.94	Gottschall et al., 2012
Bisphenol A	3.43	10.3	120	Greece	0.53	Stasinakis et al., 2008
				China	0.01	Song et al., 2014
				Australia	0.06–1.37	Langdon et al., 2011

Key: Log K_{ow}, octanol–water coefficient; pK_a, acid dissociation co-efficient; MQL, method quantitation limit.
[a] Reported as median.

the formation of numerous degradation or transformation products. These are not well studied as typical targeted screening approaches for known compounds (low resolution mass spectrometry utilising triple quadrupoles technology) are not capable of their identification. Also, as biotransformation pathways are not often known, there are very few standards available for these transformation products. Helbling et al. (2010) successfully identified previously unreported biological transformation products for the pharmaceuticals bezafibrate, diazepam (Fig. 5a), levetiracetam, oseltamivir and valsartan using high resolution mass spectrometry (linear ion trap-orbitrap technology) during laboratory scale investigation of activated sludge. Transformation products have also been reported at indigenous concentrations in final effluents of activated sludge WwTWs (Gómez et al., 2010). Gómez et al. (2010) identified transformation products of acetaminophen (P-aminophenol) and azithromycin (unnamed compound) by non-targeted screening using quadrupole time of flight (QTOF) mass spectrometry. Their identification is essential as these can be more toxic than the parent compound as is the case with P-aminophenol (Bloomfield, 2002; Gómez et al., 2010). Therefore removal of the parent EC does not necessarily translate into removal of toxicity. Considering the high number of parent

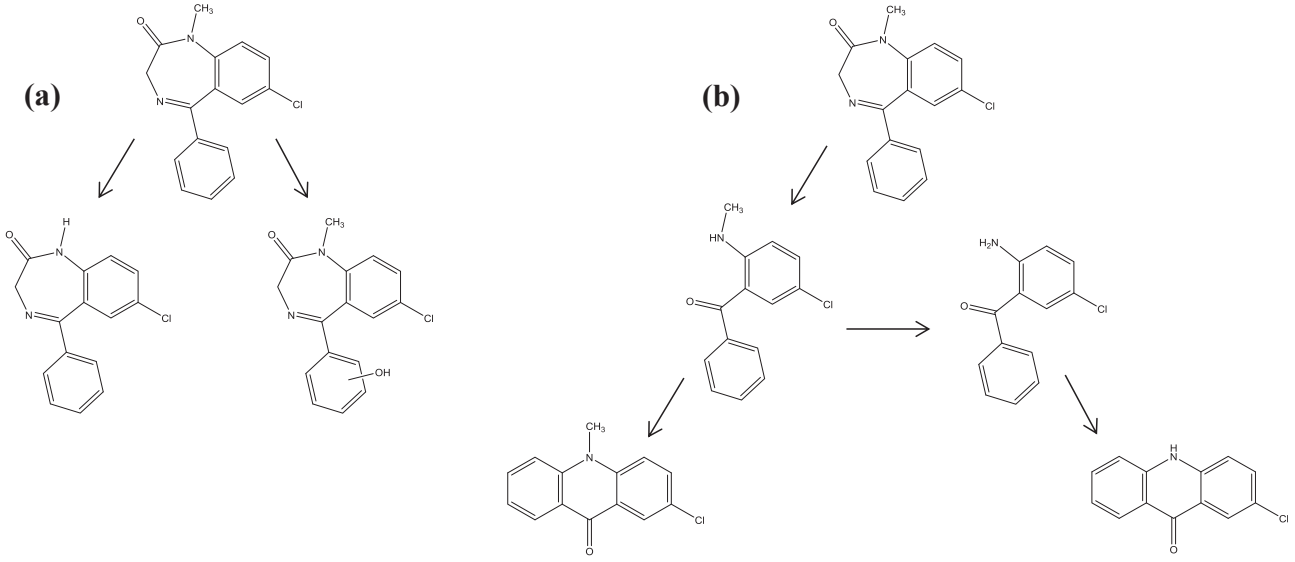

Fig. 5 – Transformation pathways of diazepam during activated sludge treatment (a) – adapted from Helbling et al. (2010) and when exposed to simulated sunlight (b) – adapted from West and Rowland (2012).

ECs in wastewater (Table 1) (Hughes et al., 2013), it is expected that a great number of transformation products (of unknown toxicity and persistence) exist in final effluent and receiving surface waters.

3.3.3. *Physicochemical processes*

Physicochemical mechanisms can also contribute to EC removal from wastewaters and surface waters. Sorption onto biomass during wastewater treatment, or into sediments when present in the riverine environment will result in removal from the aqueous phase. However, this is only likely to hold true for some ECs. For example, if equilibrium is established between the biomass or sediment and the aqueous medium for a specific EC, the net exchange between the two phases (and removal from the aqueous phase) will be zero (Schwarzenbach et al., 2003). Therefore sorption will not contribute to their removal. This has been observed across activated sludge WwTWs for some ECs such as steroid estrogens (Andersen et al., 2005; Petrie et al., 2014a). On the other hand, the antibiotics ofloxacin and ciprofloxacin were shown to be removed by sorption during wastewater treatment due to their high affinity to solid organic matter (Petrie et al., 2014c). Therefore understanding the role of physicochemical properties to the sorption of these ECs is essential. Consideration must also be given to the impact of dissolved organic matter to the fate of ECs in the environment. Binding of ECs to dissolved organic matter could help retain ECs in the aqueous phase of environmental matrices. Furthermore, formation of EC-dissolved organic matter complexes may lead to the EC going undetected during analysis.

When present in the aqueous environment, ECs are susceptible to breakdown by photolysis. Photolysis has been shown to successfully degrade several ECs such as ketoprofen, propranolol, naproxen, E2, EE2, gemfibrozil and ibuprofen in river water (Lin and Reinhard, 2005). Half-lives ranged broadly from four minutes for ketoprofen to 15 h for gemfibrozil and ibuprofen. This range of susceptibility to breakdown by photolysis observed is attributed to differences in their chemical structure. For example, the carbonyl moiety of ketoprofen is in conjugation with two aromatic rings which results in a very reactive triple state and a high susceptibility to breakdown by photolysis (Lin and Reinhard, 2005). Therefore photolysis can contribute notably to the removal of a number of ECs from surface waters. As with biological degradation, removal of the parent compound by photolysis is not indicative of complete mineralisation and several transformation products can be observed (Fig. 5b). Therefore a reduction in toxicity may not be observed with removal of the parent compound. It can be postulated that the presence of dissolved organic matter of comparatively high concentration, as well as particulates in environmental waters will reduce EC degradation kinetics by clouding sunlight intensity. However, West and Rowland (2012) found that humic acid (a small molecular weight charged species) slowed or increased degradation rate, dependant on the specific EC investigated. Increased degradation in the presence of humic acid or nitrates can be attributed to indirect photolysis (Andreozzi et al., 2003). Wastewater effluents contain hydroxyl radicals and triplet excited state organic matter which facilitates indirect photolysis of some ECs (Ryan et al., 2011). Other environmental factors such as depth of river, shading from bankside vegetation, presence of particulate matter and season also require further investigation to assess their impact to EC photolysis in environmental conditions.

3.4. *Toxicological impact of ECs within the environment*

3.4.1. *Collated acute toxicity information*

Testing aquatic ecotoxicity of ECs is usually undertaken at controlled laboratory conditions. This often involves determining acute toxicity of a single compound to a specific indicator species. The most common taxon is the crustacean *Daphnia magna*, with standard methods available to measure EC_{50} based on their mobility (OECD, 2004). These methods are conducted in an exposure medium consisting of clean laboratory water. Such tests are an excellent indicator of the potential risks posed by individual chemicals. The general approach is to classify those with an EC_{50} between 10 and 100 mg l^{-1} as harmful, from 1 to 10 mg l^{-1} as toxic, and those <1 mg l^{-1} as very toxic to aquatic organisms (Commission of the European Communities, 1996; Cleuvers, 2003). Collation of EC_{50}data from different literature sources has limitations due to the range of test species used, as well as the variety of toxicological endpoints studied. Effect concentrations will be dependent on the test species studied as ECs can cause different toxicological responses between different species. Despite this, collated data can give an indication of toxicity for the most well studied ECs (Fig. 6). Non-steroidal anti-inflammatory drugs (acetaminophen, ibuprofen, diclofenac and naproxen), lipid regulators (bezafibrate, clofibric acid – metabolite), carbamazepine and trimethoprim are generally classified as harmful to aquatic organisms. Other antibiotics (ofloxacin, sulfamethoxazole, oxytetracycline, erythromycin) mostly fall within the toxic range. However, there is also a lack of information on the synergistic impact of these chemicals, particularly at low concentration over longer exposure times.

3.4.2. *Impact of mixtures and chronic impact*

Aquatic biota within the receiving environment is continually exposed to a complex mixture of ECs. Studies have shown that mixtures of pharmaceuticals exhibit greater effect than the compounds individually. To demonstrate, the antiepileptic carbamazepine and the lipid lowering agent clofibric acid (which belong to very different therapeutic classes and expectant modes of action), exhibited stronger effects to *D. magna* during immobilization tests than the single compounds at the same concentration (Cleuvers, 2003). Furthermore, Cleuvers (2004) reported considerable acute toxicity for a mixture of NSAIDs (diclofenac, ibuprofen, naproxen and aspirin) at the same concentration where little or no effect was observed for the chemicals individually. This underpins the need to assess chronic impact of EC mixtures at environmentally relevant concentrations, as well as undertaking whole life cycle determinations. However, this is very difficult to ascertain over long time periods where relatively subtle toxicological responses are observed in comparison to acute effects such as death or mobility which are easily measurable. Nevertheless, increasing numbers of studies assessing the chronic impact of EC mixtures have found significant effects. For example, female *Danio rerio* exposed to a pharmaceutical

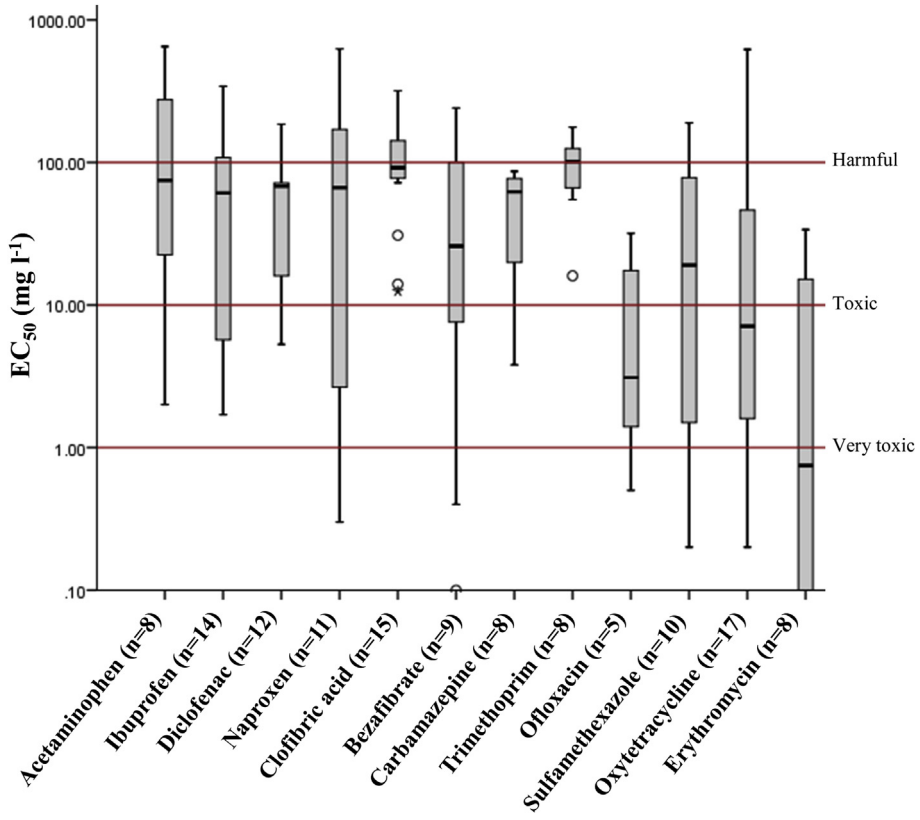

Fig. 6 – Ecotoxicity EC_{50} information ($n \geq 5$) available in the literature for ECs reported for a minimum of three different species types with boxes showing interquartile range and median, and whiskers showing range, outliers also shown. It should be noted that collated toxicological response information only gives a subjective insight into toxicity as this is highly dependent on the test species studied as ECs can cause varying toxicological responses between species type. Data obtained from: (Henschel et al., 1997; Holten Lützhøft et al., 1999; Wollenberger et al., 2000; Cleuvers, 2003; Ferrari et al., 2003; Pro et al., 2003; Cleuvers, 2004; Eguchi et al., 2004; Pomati et al., 2004; Cleuvers, 2005; Isidori et al., 2005a,b; Heckmann et al., 2007; Isidori et al., 2007; Kim et al., 2007; DeLorenzo and Fleming, 2008; Park and Choi, 2008; Quinn et al., 2008b; De Liguoro et al., 2009; Rosal et al., 2010; Han et al., 2010; Van den Brandhof and Montforts, 2010; Dave and Herger, 2012). EC_{50}'s classified as <1 mg l^{-1} = very toxic to aquatic organisms, 1–10 mg l^{-1} = toxic to aquatic organisms, 10–100 mg l^{-1} = harmful to aquatic organisms and >100 mg l^{-1} = not classified (Commission of the European Communities, 1996; Cleuvers, 2003).

mixture (acetaminophen, carbamazepine, gemfibrozil and venlafaxine) as well as WwTW effluent showed significant reductions in embryo production over a six week period (Galus et al., 2013). Also, Dietrich et al. (2010) investigated single compound and mixture toxicity of carbamazepine (500 ng l^{-1}), diclofenac (360 ng l^{-1}), EE2 (0.1 ng l^{-1}) and metoprolol (1200 ng l^{-1}) to *D. magna* over six generations. These concentrations were selected to represent environmentally relevant concentrations for river waters in Germany (Dietrich et al., 2010). However, the influence of the pharmaceutical mixture was inconsistent and unpredictable. This is in disagreement to acute toxicity testing of pharmaceutical mixtures conducted at greater concentrations (Cleuvers, 2003, 2004). Also, no relationship in toxicological effect was observed for successive generations of *D. magna*. It was postulated that this may be due to the development of resistance towards the pharmaceuticals (Dietrich et al., 2010). It is clear that further studies are needed to confirm the chronic impact of multiple ECs synergistically, whilst at low concentration. Furthermore, these studies need to assess ecological impact to organisms of different trophic levels. Consideration must also be given to the exposure medium used. Surface waters contain dissolved organic matter which could potentially reduce compound bioavailability. This is not currently considered in existing laboratory toxicity testing protocols.

3.4.3. *Illicit drugs*

Despite numerous illicit drugs being reported in surface waters (Table 1) and the possibility of shock loads which can be encountered (Emke et al., 2014), there are only a few experimental studies which have investigated toxicity to aquatic organisms. Illicit drugs are potent in nature therefore a high toxicity to exposed aquatic organisms is inferred. Parolini and Binelli (2014) investigated oxidative and genetic responses induced by Δ-9-tetrahydrocannabinol (main psychoactive compound of cannabis) to the mollusc *Dreissena polymorpha*

Table 3 – Toxicological response of chiral enantiomers and their enantiomeric distribution in the environment.

Emerging contaminant	Enantiomer	Toxicological response of chiral enantiomers		Distribution of chiral enantiomers within the environment			
		Potency within the human body	Toxicity to aquatic organisms	Country	Surface water	Enantiomeric fraction	Reference
Ibuprofen	S(−); R(+)	S > 100 times more potent[a]	–	Switzerland	Lakes and rivers	0.41–0.47	Buser et al., 1999
				Spain	Rivers	0.30–0.50	López-Serna et al., 2013
				Australia	River	0.60–0.80	Khan et al., 2013
				China	Canal and river	0.13–0.33	Wang et al., 2013
Naproxen	S(−); R(−)	S more potent[k]	–	Australia	River	1.00	Khan et al., 2013
Propranolol	S(−); R(+)	S 100 times more active[a]	Similar acute response to *P. promelas* and *D. magna*[c]	USA	Rivers	0.21–0.53	Fono and Sedlak, 2005
			S higher chronic toxicity to *P. promelas*[c]	UK	River	0.45	Bagnall et al., 2012a,b
			S and R chronic toxicity similar to *D. magna*[c]	Spain	Rivers	0.38–0.60	López-Serna et al., 2013
Atenolol	S(−); R(+)	S more potent[f]	S ~4 times more toxic to *T. thermophila*[d]	UK	River	0.38–0.56	Kasprzyk-Hordern and Baker, 2012b
			R ~2 times more toxic to *D. magna*[d]	UK	River	0.47	Bagnall et al., 2012a,b
			S and R toxic effects similar to *P. subcapita*[d]	Spain	Rivers	0.38–0.50	López-Serna et al., 2013
Sotalol	R/S(±)	R possesses majority of β-blocking activity[h]	–	Spain	Rivers	0.41–0.65	López-Serna et al., 2013
Metoprolol	R/S(±)	S 35 times more potent[g]	–	Spain	Rivers	0.42–0.51	López-Serna et al., 2013
				Germany	River	0.43–0.46	Kunkel and Radke et al., 2012
Fluoxetine	S(+); R(−)	S and R have different pharmacological activity[e,i]	S ~10 times more toxic to *P. promelas*[b]	Spain	Rivers	0.64–0.68	López-Serna et al., 2013
			S and R toxic effects similar to *D. magna*[b,d]				
			S ~10 times more toxic to *T. thermophila*[d]				
Norfluoxetine	R/S(±)	Enantiomers have different potency[i]	–	Spain	Rivers	0.76	López-Serna et al., 2013
Venlafaxine	R/S(±)	R more potent[j]	–	UK	River	0.40–0.65	Kasprzyk-Hordern and Baker, 2012b
				UK	River	0.58	Bagnall et al., 2012a,b
				France	River	0.46–0.74	Li et al., 2013
Ephedrine	1R,2S(−); 1S,2R(+)	–	–	UK	River	0.79–1.00	Kasprzyk-Hordern and Baker, 2012b
MDMA	S(+); R(−)	S more potent[l]	–	UK	River	0.56–0.81	Kasprzyk-Hordern and Baker, 2012b
MDA	R/S(±)	S more potent[l]	–	UK	River	0.56–0.58	Kasprzyk-Hordern and Baker, 2012b
Amphetamine	S(+); R(−)	Dextro enantiomer more potent[o]	–	UK	River	0.81–0.86	Kasprzyk-Hordern and Baker, 2012b

Note: *Enantiomeric fraction* = (+)/[(+)+(−)] − 0.5 denotes a racemic distribution.
[a] Kasprzyk-Hordern, 2010.
[b] Stanley et al., 2007.
[c] Stanley et al., 2006.
[d] De Andrés et al., 2009.
[e] Steiner et al., 1998.
[f] Pearson et al., 1989.
[g] Spahn et al., 1989.
[h] Mehvar and Brocks, 2001.
[i] Stevens and Wrighton, 1993.
[j] Lerer, 2002.
[k] Honjo et al., 2011.
[l] National Highway Traffic Safety Administration, 2014.
[o] Heal et al., 2013.

(zebra mussel). Concentrations of 500 ng l^{-1} over a 14 day exposure period led to notable changes in oxidative status. This could lead to increased lipid peroxidation, protein carbonylation and DNA damage (Parolini and Binelli, 2014). The possible effects of cocaine and its metabolites to aquatic organisms have been given more attention (Binelli et al., 2012; Parolini et al., 2013; Parolini and Binelli, 2013). An initial study investigated cyto-genetoxic effects of cocaine to *D. polymorpha* at concentrations of 40, 220 and 10,000 ng l^{-1} (Binelli et al., 2012). Primary DNA damage, increased micro-nucleated cells and apoptosis were all observed after an exposure time of 96 h, even at the lowest exposure concentration (40 ng l^{-1}). An investigation of sub-lethal effects of benzoylecgonine showed enzyme defence chain imbalances of *D. polymorpha* at 500 ng l^{-1} for a 14 day time period (Parolini et al., 2013). Finally, a study of ecognine methyl ester (another cocaine metabolite) found 14 days exposure to 500 ng l^{-1} induced destabilization of lysosome membranes, inactivation of defence enzymes, increased lipid peroxidation, protein carbonylation and DNA fragmentation of *D. polymorpha* (Parolini and Binelli, 2013). These studies have given an excellent insight into the toxicity of illicit drugs to aquatic organisms. Toxicity testing of illicit drugs should be expanded to include compounds such as MDMA, which have not been investigated previously. Additionally, these findings need to be supported with standard toxicity testing protocols for a variety of accepted indicator species types. Coupled with environmental occurrence information, this would help prioritise those chemicals which require immediate in-depth investigation of their fate and ecological impact.

3.4.4. *River sediments and amended soils*

Emerging contaminants have also been reported in riverine sediments (Da Silva et al., 2011; Azzouz and Ballesteros, 2012; Chen and Zhou, 2014). Determining toxicological impact here is essential as sediments can act as a sink for their accumulation. However, this is notoriously difficult to ascertain due to the complexity of the system. Benthic organisms can be exposed to ECs within the sediment itself, in interstitial water and in overlying water (Gilroy et al., 2012). This makes experimental design and set-up critical for reproducing representative conditions. A study investigating toxicity of diclofenac to the crustacean *Hyalella azteca*, prepared synthetic sediment at a 1:3 ratio with water (Oviedo-Gómez et al., 2010). The authors failed to report or investigate aqueous/liquid partitioning of diclofenac, whether equilibrium conditions were present or if desorption occurred throughout the test. Consequently, reporting toxicological effect concentrations for sediments can have considerable uncertainties. An improved study by Gilroy et al. (2012) supported biological response information with chemical analysis for both aqueous and particulate phases. Findings suggested that sorption to sediments resulted in a reduction of bioavailability and toxicity. On the other hand, the accumulation (and increased concentration) of readily sorbed compounds in sediments within the environment could compensate for this reduction in toxicity. Interestingly, the activity of benthic invertebrate also resulted in increased desorption, leading to improved bioavailability (Gilroy et al., 2012). Numerous mechanisms take place, illustrating the complexity of

ascertaining sediment toxicity. Studies over long time periods which simulate representative steady-state riverine sediment conditions are required for a range of indicator species. These firstly need to be supported with chemical analysis to assess the behaviour of the EC(s) in question. Such studies would help assess chronic and multi-generation impact of sediment contamination to benthic organisms. Similarly (and as discussed previously – Section 3.2.3), amended soils can also contain significant concentrations of some municipal derived ECs. The resulting toxicity to terrestrial organisms is poorly understood due to the lack of knowledge on their occurrence to drive investigation of their toxicological impact. Also, no standard methods are available which can easily measure toxicity to exposed terrestrial organisms. Nevertheless, indirect methods such as soil respiration rate can be used to measure possible impact to the soil community (Butler et al., 2011). These need to be supported with controlled single (and multi) compound toxicity testing with predetermined indicator species to help understand the ecological impact of applying biosolids to agricultural soils.

3.4.5. *Chirality*

Pharmaceuticals are often prepared and dispensed as racemic mixtures (i.e., a 50:50 mixture of two enantiomers). Metabolism within the human body and exposure to biological mediated reactions during wastewater treatment can result in the enrichment of one specific enantiomer. On the other hand, some pharmaceuticals such as NSAIDs are marketed as a single enantiomer. Chiral inversion can lead to the distribution of two enantiomers. This has been observed for naproxen during biological wastewater treatment (Hashim et al., 2011). However, conventional analytical approaches are not able to distinguish between enantiomers of the same compound (Evans and Kasprzyk-Hordern, 2014). As a result there is a paucity of information on the enantiomeric distribution of chiral compounds within the environment. Nevertheless, available information in the literature show chiral ECs to be mostly non-racemic when present in surface waters (Table 3). Enantiomeric fractions range broadly from 0.1 for ibuprofen (Wang et al., 2013) to 1.0 for naproxen and ephedrine (Kasprzyk-Hordern and Baker, 2012b; Khan et al., 2013) (an enantiomeric fraction of 0.5 denotes a racemic mixture). Concern arises from the large amount of toxicity testing being undertaken with racemic mixtures (or unknown/not reported enantiomeric composition) of the chemical under investigation (Fig. 6) (Henschel et al., 1997; Holten Lützhøft et al., 1999; Wollenberger et al., 2000; Cleuvers, 2003; Ferrari et al., 2003; Pro et al., 2003; Cleuvers, 2004; Eguchi et al., 2004; Pomati et al., 2004; Cleuvers, 2005; Isidori et al., 2005a,b; Heckmann et al., 2007; Isidori et al., 2007; Kim et al., 2007; DeLorenzo and Fleming, 2008; Park and Choi, 2008; Quinn et al., 2008b; De Liguoro et al., 2009; Rosal et al., 2010; Han et al., 2010; Van den Brandhof and Montforts, 2010; Dave and Herger, 2012). However, the toxicological response and potency of pharmaceuticals in the human body is known to differ between enantiomers of the same chemical (Table 3). For example, the *S*-enantiomer of ibuprofen is 100 times more active than *R*-enantiomer (Kasprzyk-Hordern, 2010). This suggests that their toxicity to organisms within the environment will also differ. The few studies which have been undertaken at the enantiomeric level showed significantly different toxic responses for some aquatic taxa (Table 3) (Stanley et al., 2006, 2007; De Andrés et al., 2009). To demonstrate, *S*-fluoxetine was found to be ~10 times more toxic to *P. promelas* and *T. thermophila* than *R*-fluoxetine (Stanley et al., 2007; De Andrés et al., 2009). Toxiclogical effect information gained from current ecotoxicity testing which use racemic mixtures may therefore underestimate the risk actually posed in the environment. Findings from racemic toxicity testing have been used to recommend predicted effect/no effect concentrations (Ferrari et al., 2004; Quinn et al., 2008a; Martins et al., 2012) and can be seen as a precursor for environmental legislation and the proposal of quality standards. Although environmental legislation has safety buffers incorporated into their derivation, failure to recognise the enantiomeric distribution of chiral compounds in the environment and a lack of information on the toxicological differences between enantiomers is concerning.

4. Future recommendations for environmental monitoring of ECs

4.1. *Sampling mode and strategy*

Arguably, the most important step in monitoring for ECs in wastewaters and in the environment is sampling. This is fundamental to obtaining representative data. To monitor treatment process performance for the removal of ECs, corresponding grab samples can be used to compensate for hydraulic retention time (HRT) (Petrie et al., 2013b,c; 2014c). This approach can monitor performance of processes such as trickling filters which operate at comparatively short HRTs (<2 h). However, this is not practical for systems such as activated sludge which often operate at HRTs ≥6 h. Corresponding grab samples are also typically taken once daily and do not enable the performance of the process to be fully understood. For example, pollutant removal at daily peak flows (between 7:00 and 9:00 h) and during low flow spells (3:00 to 5:00 h) are not appreciated. Therefore a sampling approach is needed which can: (i) obtain a composite sample representative of a system over a longer period of time (e.g., a 24 h time period and flow or volume proportional) and, (ii) can ensure the stability of analytes by using a suitable preservation technique (i.e., acidification or addition of sodium azide (Hillebrand et al., 2013)). Although collecting flow proportional samples has logistical issues for the deployment of sampling equipment (samplers and flow measurement devices) at suitable locations across WwTWs or on rivers, their use is paramount to attaining representative measurements during environmental monitoring. Alternatively, passive samplers could be considered but these require further investigation to establish their suitability for the uptake of more polar chemicals such as ECs (Mills et al., 2014). Ideally, *in situ* real-time sensors would be used. In any case sampling campaigns should be at least one week in length to incorporate weekends where substantial variations in flow and EC load are likely. Furthermore, the frequency of repeat sampling campaigns throughout the year needs consideration. A minimum of two sampling events per year (summer/winter) to reflect the

dynamics of seasonal change is recommended. This will enable seasonal usage patterns of EC to be established, as well as the impact of temperature on WwTW performance. The sampling strategy itself must consider attaining complete mass balances for the WwTW or stretch of river system in question. Analysis of waste/recycled sludge and river sediment are essential to determine fate of ECs across such systems. This includes particulate phase analysis of all sampling positions (Petrie et al., 2014c). Admittedly this will be problematic to obtain for final effluents over a complete sampling campaign. However, determination of final effluent particulate phase concentrations at least once during the sampling campaign is valuable, considering the lack of analysis previously undertaken here.

4.2. *Analysis methods*

Analytical methods which can determine ECs at the enantiomeric level are recommended. However, achieving multi-residue separations with chiral stationary phases is difficult due to their highly specific nature and a poor understanding of the separation mechanism. Also, the maximum back pressure of chiral columns is generally ~2000 psi which limits their operation to high-performance liquid chromatography mode. Consequently, run times are often ≥60 min (Kasprzyk-Hordern et al., 2010; Bagnall et al., 2012a,b; López-Serna et al., 2013), restricting sample throughput and turnover. Stationary phases comprised of smaller particle sizes (i.e., <2 μm) which can achieve the performance of ultra-performance liquid chromatography (UPLC) in terms of run time and column efficiency (Evans and Kasprzyk-Hordern, 2014) whilst attaining multi-residue enantiomeric separations would be advantageous. Until their development, the use of comparatively fast achiral UPLC methods supported with chiral separations to determine enantiomeric fraction for as many chemicals as possible is suggested. Targeted UPLC methods are capable of the simultaneous determination of up to 100 ECs in various environmental matrices at relatively short analysis times (~10 min) (Gracia-Lor et al., 2011; López-Serna et al., 2011; Gros et al., 2012). Ideally, these multi-residue methods used for the analysis of ECs should be dynamic such that they can perform non-targeted (qualitative) screening whilst undertaking targeted (quantitative) determinations. The use of high resolution mass spectrometers such as QTOF or Orbitrap technology which can undertake both targeted and non-targeted screening and allow for retrospective analysis is beneficial (Radjenović et al., 2009b). Such technology enables chemicals not originally included in targeted screening but identified as of interest, to be easily added for subsequent quantitative determination. The success of non-targeted screening is reliant on good chromatographic separation. Therefore the chromatography method should be optimised for the separation of a broad range of target ECs representing extremities of physicochemical composition (hydrophobicity, molecular weight etc). Coupled with screening in both negative and positive ionisation modes will help identify unknown chemicals of notable concentration. However, non-targeted screening has several limitations as the chemistry of the ECs in question is unknown. Therefore they may not be recovered during sample preparation or may not be ionised during analysis. Chemical analysis also needs to be supported with novel bioanalytical techniques (e.g., metabolomics). Using a metabolomics approach can yield information on organism function and health at the molecular level (Bundy et al., 2009). Such information would otherwise be missed by traditional toxicological tests which rely on endpoints such as growth, death and reproduction for a limited number of indicator species. Long term multi-generational studies at different trophic levels which can simulate environmental conditions and EC concentrations are needed. This would help establish the ecological impact of observed EC concentrations within the environment.

4.3. *Conclusions and future outlook*

It is anticipated that environmental legislation will be widened to cover a range of municipal derived ECs. However, sound knowledge of their fate during wastewater treatment and within the environment is currently lacking. Due to the limitations of previously used sampling methods, reported removals of ECs by WwTWs have uncertainties. Therefore, removal performance of different WwTW process types at various operational conditions needs re-evaluated with suitable sampling protocols. This will help establish steps required for EC amelioration. The growing trend of improving sustainability and reducing energy demand of wastewater treatment will see an increase in the application of novel treatment methods. For example, algae ponds for secondary effluent polishing are a promising treatment method which can indirectly produce energy through the production of biogas. However, there are very few studies which have monitored their performance for EC removal (De Godos et al., 2012). Further studies of these process types are needed to determine fate and removal of ECs during treatment, considering their likely implementation into the conventional WwTW flow sheet. Environmental monitoring must also now apply a holistic approach. This involves determining fate and impact of ECs across their complete life cycle which includes the terrestrial environment. For example, measuring biosolids and amended soils for their occurrence is needed as well as supporting analysis. Detailed case studies of amended soils in field conditions which investigate leaching and runoff, impact to surrounding surface water quality, in soil degradation, toxicity to terrestrial organisms and the potential uptake by plants and entry into the human food chain are needed. A similar approach can be taken for monitoring other contaminated environmental compartments such as river sediments. Finally, the combined use of chemical and biological analysis to better assess environmental impact from ECs will enable the revision and development of more accurate environmental risk assessment.

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