Occurrence of illicit drugs in water and wastewater, and their removal during wastewater treatment

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Highlights:

- Levels of illicit drugs are increasing in wastewater, surface and drinking water
- Regional variations in drug consumption are reflected in their detection patterns
- Conventional wastewater treatment shows variable efficacy for drug removal
- Little is known on the removal efficacy of alternative or natural treatment systems
- Almost nothing is known about the environmental fate and toxicity of illicit drugs

Abstract

This review critically evaluates the types and concentrations of key illicit drugs (cocaine, amphetamines, cannabinoids, opioids and their metabolites) found in wastewater, surface water and drinking water sources worldwide and what is known on the effectiveness of wastewater treatment in removing such compounds. It is also important to amass information on the trends in specific drug use as well as the sources of such compounds

that enter the environment and we review current international knowledge on this. There are regional differences in the types and quantities of illicit drug consumption and this is reflected in the quantities detected in water. Generally, the levels of illicit drugs in wastewater effluents are lower than in raw influent, indicating that the majority of compounds can be at least be partially removed by conventional treatment processes such as activated sludge or trickling filters. However, the literature indicates that it is too simplistic to assume non-detection equates to removal, as there is evidence that some compounds may avoid detection via partitioning into the solids fraction (sludge/biosolids), conversion to transformation products, or due to sampling and/or analysis protocols which fail to give a true picture of drug concentration. Generally speaking, activated sludge-type processes appear to offer better removal efficacy across a range of substances, but the lack of detail in many studies makes it difficult to comment on the most effective process configurations and operations. There is also a paucity of information on the removal effectiveness of alternative treatment processes. Research is also required on natural removal processes in both water and sediments that may over time facilitate further removal of these compounds in receiving environments.

Keywords: Illicit drugs; wastewater; surface water; drinking water; drug removal efficacy.

Abbreviations:

6-ACM	6-cetylmorphine
AMPH	Amphetamine
ATS	Amphetamine–type stimulants
BE	Benzoylecgonine
COC	Cocaine
COD	Codeine
DWTP	Drinking Water Treatment Plant
EDDP	2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine
KET	Ketamine
MDA	3,4-methylenedioxyamphetamine
MDEA	3,4-methylenedioxy-N-ethylamphetamine
MDMA	3,4-methylenedioxy-methamphetamine
METH	Methamphetamine

MOR	Morphine
MET	Methadone
THC	Δ9-tetrahydrocannabinol
THC-COOH	11-nor-9-carboxy-THC
THC-OH	11-hydroxy-THC
WWTP	Wastewater Treatment Plant

1. INTRODUCTION

Illicit drugs are recognised as contaminants of emerging concern to the environment. Contaminants of concern are anthropogenic substances, the majority of which do not have established human health or eco-toxicological criteria and associated regulatory guidelines for their monitoring and control. Many contaminants of concern are used in day-to-day life, with examples including pharmaceuticals and personal care products, perfluorochemicals, hormones and steroids, and industrial extracts (Das et al., 2013, Petrovic, 2003, Thomaidis et al., 2012).

Illicit drugs are non-prescribed drugs or psychotropic substances whose production, sale and use are prohibited by national drug control laws or International Drug Control Conventions (Pal et al., 2013, UNODC, 2016a). Illicit drug types include cocaine, cannabis, amphetamine-type stimulants, ecstasy, heroin and other opioids (Degenhardt et al., 2004). Illicit drug usage has a recognised adverse impact on national economies; for example, during the period 2004–2005 AU$8.2 billion was spent in Australia on resolving drug-related crimes, productivity losses and associated healthcare costs (AIHW, 2013). In the USA, a National Drug Intelligence Centre study estimated that illicit drug use negatively impacted the US economy by some US$193 billion in 2007 (National Drug Intelligence Center, 2011). Global production and consumption of illicit drugs has increased notably in recent decades, with the rate of global population drug use increasing disproportionately above that of a normal population growth (Figure 1a). For example, UNODC (2015) estimated that about 246 million people globally aged between 15–64 had consumed an illicit drug at least once in the preceding year (2013), with this number expected to increase in the future if recent use trends continue. Aside from the established adverse economic impacts, increased illicit drug use may have unknown and undesirable diffuse future impacts on both human and environmental health through the constant discharge of wastewater-borne drugs to the environment.

To date, the prevalence of illicit drugs has been assessed through household surveys, consumer interviews, production records, medical records and seizure statistics (AIHW, 2013, Zuccato et al., 2005, EMCDDA, 2015). However, these procedures are time-consuming, expensive and can provide unreliable data. The information provided often relies on effective user or health practitioner communication and, therefore, may not be accurate for reasons such as reporter bias, or targeted/biased sampling. To overcome this, researchers have established a new and alternative way to monitor drugs through raw sewage analysis. This approach was first suggested by Daughton (2001) and later implemented by Zuccato et al. (2005) in their estimation of cocaine use in Italy. Since the majority of administered drugs are ultimately excreted by humans as a primary compound or its metabolite and discharged directly into the sewer network (Pal et al., 2013, Zuccato et al., 2008a, Zuccato et al., 2008b), analysis of the wastewater entering municipal wastewater treatment plants (WWTPs) allows for quantitative, near real-time estimates of illicit drug consumption by populations connected to municipal sewerage systems (Zuccato et al., 2008b, Thomas et al., 2012, Postigo et al., 2008). Accordingly, wastewater analysis offers an efficient means of investigating and profiling population drug consumption (so-called wastewater epidemiology), with wastewater characterisation also useful for studying potential downstream impacts of these substances on the receiving environment. The daily mass loads of illicit drugs (mg drug *used*/day) consumed by local communities can be estimated through back-calculation, by multiplying the concentration of wastewater-measured drug (ng/L) by wastewater flow rate (L/day or m^3/day) which is further divided by the sewer-connected population in 1000's to get final doses/day/1000 people (Van Nuijs et al., 2011b, Zuccato et al., 2011, Postigo et al., 2010, Karolak et al., 2010, Baker et al., 2014, Castiglioni et al., 2013, Tscharke et al., 2015). This approach is not restricted to illicit drugs, but is also used to measure other contaminants like pharmaceuticals and personal care products (Heberer, 2002, Karnjanapiboonwong et al., 2011, Kosma et al., 2014, Ort et al., 2010b) and licit substances like alcohol (Reid et al., 2011), caffeine and nicotine (Senta et al., 2015, Buerge et al., 2003, Bradley et al., 2007).

A number of illicit drugs have so far been detected in raw municipal wastewater (Huerta-Fontela et al., 2008a, Huerta-Fontela et al., 2008b, Huerta-Fontela et al., 2007, Postigo et al., 2008, Postigo et al., 2010, González-Mariño et al., 2012) as well as treated wastewater effluent and receiving surface waters (Zuccato et al., 2008a, Zuccato et al., 2005, Bartelt-Hunt et al., 2009, Bones et al., 2007, Berset et al., 2010, van Nuijs et al., 2009, Boleda et al., 2009) due to incomplete removal of these drugs by conventional WWTP processes. The

concentration of illicit drugs present in treated wastewater depends on the treatment technology incorporated in the WWTP and as such, several studies have even detected these substances in the raw waters of drinking water treatment plants (DWTPs). For example, Huerta-Fontela et al. (2008b) found trace quantities (45–130 ng/L) of the cocaine metabolite benzoylecgonine (BE) in a Spanish DWTP feedwater. Similarly, Rosa Boleda et al. (2011) detected cocaine, BE, methadone and 2-ethylidene-1,5-dimethyl-3,3-diphenylprrrolidine (EDDP) in tap water samples at varying concentrations across several continents; although levels were generally trace (1–10 ng/L) to ultra-trace (<1 ng/L). Even after the prevalence of illicit substances/metabolites in different water sources was established and in light of growing concern about their unknown effects, very few studies have reported on their degradation behaviour and eco-toxicological impacts (Pal et al., 2011, Janusz et al., 2003), with most studies based on detection/analysis, or usage patterns/trends. Rosi-Marshall et al. (2015) emphasised the largely unknown nature of the ecological effects from these substances, stating that while the half-life of some illicit drugs is short, they become more prevalent with continued population usage and environmental release and as such they cannot be ignored. Therefore, these substances are considered ubiquitous contaminants that are continuously discharged from WWTPs into the receiving environment, but with essentially unknown effects on human and environmental health from chronic low-level exposure.

With this in mind, the aim of this review was to present a current synopsis of the types and concentrations of key illicit drugs (cocaine, amphetamine-type stimulants (ATS), cannabinoids, opioids) and their metabolites in wastewater, surface water and drinking water sources worldwide. We also examined the trends in illicit drug usage from recent decades estimated through wastewater analysis and compared these with respective government data from sources such as the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), National Drug Strategy Household Survey (NDSHS) and the United Nations Office on Drugs and Crime (UNODC) (AIHW, 2013, EMCDDA, 2015, UNODC, 2014). To put this in context for the water industry, we also review what is known about the effectiveness of current wastewater treatment process technologies in removing these compounds, and finish with recommendations for further research.

2. TRENDS IN ILLICIT DRUG USAGE

The documented use of illicit drugs has increased globally since the 1990s (UNODCCP, 1999) and importantly, has increased at a rate disproportionately above that attributed to normal population growth (Figure 1(a)) (Bureau, 2017). Clearly, an understanding of the levels of use of the key drug types and their locations should

link to relative quantities to be expected in the connected sewerage and wastewater treatment systems, enabling a defined focus on the key groups. This trend of increased drug consumption will most likely have translated to a concomitant increase in illicit drug loads to WWTPs and their emission to receiving environments globally.

Figure 1: (A) Global overview of illicit drug use growth relative to parallel population growth (rate of increase in drug use was significantly greater than population growth rate from 1998 onwards; ANCOVA, $F_{(1,24)} = 4385$, $p<0.001$); and (B) Category-wise annual prevalence of illicit drug use in percent during the period 1990–2013 (annual prevalence is a measure of the number/percentage of people per year who have consumed an illicit drug at least once) (UNODC, 2015, UNODC, 2014, UNODC, 2008, UNODC, 2003, UNODC, 2000, EMCDDA, 2015, EMCDDA, 2008, EMCDDA, 1995, AIHW, 2013, ACC, 2015)

Figure 1(b) provides a global overview of the changes in different types of illicit drug consumption during the period 1990–2013 as obtained from surveys, reported seizures and worldwide trafficking statistics by the UNODC (EMCDDA, 2015, UNODC, 2000, UNODC, 2003, UNODC, 2014, UNODC, 2015). While illicit drug use is a global phenomenon, the dominant types differ from region to region. For example, according to reports published by the UNODC, cannabis is the most prevalent illicit drug consumed, produced and trafficked globally (Figure 1(b)) (Castiglioni et al., 2008, AIHW, 2013), but is most popular in Africa and Oceania, while cocaine is prevalent in South America. Similarly, opioids are more prevalent in Europe and Asia, with ATS prevalent in Asia, Oceania and Europe (UNODC, 2008, EMCDDA, 2008, UNODC, 2015). Irvine et al. (2011) and Lai et al. (2013a) found that cannabis and methamphetamine (METH) are the most widely used drugs in Australia as compared to cocaine and 3,4-methylenedioxyamphetamine (MDMA), something supported by others (Chen et al., 2011, Tscharke et al., 2015). This difference was ascribed to the fact that the former drugs are relatively inexpensive and can be easily cultivated or produced locally, while cocaine and MDMA are relatively expensive to produce, requiring more specialised production processes (UNODC, 2015). Reports also suggest that the use of cannabis or any other illicit drug in Australia is higher in remote areas than in cities according to wastewater epidemiology data (Tscharke et al., 2015, Irvine et al., 2011, Lai et al., 2013a). Furthermore, the use of cannabis and other drugs is often higher during weekends, as they are often used recreationally (AIHW, 2013, Bijlsma et al., 2012, Lai et al., 2013a, Jiang et al., 2014, Irvine et al., 2011, Thomas et al., 2012). Figure 2 provides global production data for coca bush (hectares), cocaine and opium (tons) during the period 1998–2015.

Figure 2: Global production of illicit drugs; coca bush (ha), cocaine (tons) and opium (tons) from 1998–2015 (UNODC, 2016b)

3. SOURCES OF ILLICIT DRUGS AND THEIR METABOLITES IN WASTEWATER

Considering the global importance and usage rates of illicit drugs in the market, they can be broadly classified into four groups (summarised in Supplementary Table S1) which form the focus of this review. These four groups of commonly used illicit drugs, and their metabolites, include cocaine (BE, norcocaine, norbenzoylecgonine, cocaethylene and ecgonine methyl ester), cannabinoids (Δ9-tetrahydrocannabinol, 11-nor-9-carboxy-Δ9-tetrahydrocannabinol, 11-hydroxy tetrahydrocannabinol), ATS (AMPH, METH, MDMA, 3,4-methylenedioxyethamphetamine (MDEA), 3,4-methylenedioxyamphetamine (MDA), ephedrine) and opioids (heroin, morphine, 6-acetylmorphine, normorphine, morphine-3β-D-glucuronide, codeine, norcodeine, buprenorphine, methadone and EDDP). These drug groups were selected for the review since they are ubiquitous and will, therefore, be present in higher concentrations in wastewater and should thereby carry greater potential risks to human and environmental health.

Previous studies reveal that illicit drugs and their metabolites are directly or indirectly discharged to domestic sewage via pathways including human excretion (urine, faeces, sweat, saliva) or direct dumping/disposal, for example by clandestine laboratories (Boles and Wells, 2010, Janusz et al., 2003, Pal et al., 2013). For example, Janusz et al. (2003) claimed that clandestine laboratories are the major source of sewage-borne illicit drugs in Australia, with Australian law enforcement agencies detecting 190 such laboratories during the period 1990–2000. Depending on the type of drug and synthesis method, enantiomeric profiling may be able to discriminate human drug use versus direct disposal (Emke et al., 2014, Kasprzyk-Hordern and Baker, 2012). Emke et al. (2014), for example, applied enantiomeric profiling to verify sources of AMPH and MDMA in wastewater and found that high mass loads of MDMA are due to direct dumping and not population consumption.

Prior research has shown that a large proportion of administered drugs are excreted unaltered (i.e. as the parent drug) or as their metabolite. Several studies have reported that only 1–9% of cocaine is excreted unaltered, while a large portion is excreted as BE (29–45%) and ecgonine methyl ester (32–49%) (van Nuijs et al., 2011a, Castiglioni et al., 2013, Nefau et al., 2013); although Van Nuijs et al. (2011b) suggest a slightly lower BE

excretion rate (35%) in instances where cocaine and alcohol are taken together. Likewise, several authors have found that for ATS consumption, amphetamine (AMPH) is the major excreted product and about 30% is unchanged in urine. Heroin, however, is excreted as its main metabolite morphine (42.5–55%) (Postigo et al., 2010, Baker et al., 2014, Zuccato et al., 2008b, Van Nuijs et al., 2011b). Helmlin et al. (1996) reported for MDMA that 72% is excreted unaltered and can be recovered within 72 h from urine.

Once excreted and in the sewerage network, illicit drugs are transported to WWTPs where they are subjected to various physical–chemical and biological treatment processes that remove them from the wastewater to varying extents. Any 'untreated' drugs remaining in the wastewater are transferred in the final effluent into receiving aquatic environments (rivers, lakes, oceans and even groundwater) where they can potentially reach drinking water sources (via indirect potable reuse), affect water quality or bioaccumulate (Zuccato and Castiglioni, 2009). Drugs may also enter the receiving environment from leakage or losses along sewer networks, or even through direct environmental dumping. Almost all the compounds present in wastewater undergo degradation at varying rates, with some being more persistent than others (see Section 5). Wastewater contains both solid and liquid phases that can provide opportunities for contaminant chemical dissolution, biological metabolism and physical attachment/adsorption on solid and colloidal particles, with dissolution, metabolism and adsorption kinetics varying depending on the nature of the chemical and the environmental conditions. Increased chemical loads in the raw wastewater and/or insufficient hydraulic retention/contact times along treatment processes may result in reduced removal capacity of such compounds by the WWTP and consequentially they are more likely to appear in the treated effluent and reach receiving environments. Figure 3 provides a conceptual overview of the pathways of illicit drug transfer to the environment via production (and consequent effluent), consumption (and ensuing excretion), through sewage and its pathways of direct environmental contamination or contamination through inadequate treatment.

Figure 3: Conceptual overview of the illicit drug transfer pathway, from production and consumption to the receiving environments

4. OCCURRENCE OF ILLICIT DRUGS IN WATER SOURCES

In recent years, a growing body of literature, especially from Europe, USA and Japan, has emerged on the detection of illicit drugs in various water sources such as wastewater, surface water and drinking water. Figure 4 shows that research interest in this field has been increasing since 2006, with approximately three times as many

studies published in 2016 compared to 2010. During this period the majority of research in this area was carried out in Spain, with 104 publications identified. Comparatively little research in this area has come from Australasia and Southeast Asia; although a number of reports have emerged in recent years (Lai et al., 2015, Lai et al., 2016a, McCall et al., 2016, Lai et al., 2016b, Tscharke et al., 2016). Measurement of these drugs in water using chromatographic methods has proved to be a useful tool for monitoring drug usage. In Australia, illicit drug detection in wastewater using chromatographic methods was first reported by Irvine et al. (2011) and Lai et al. (2011). The report focused on profiling illicit drug use in South Australia and Queensland, respectively, through wastewater analysis. Similarly, Lai et al. (2013b) used this approach to assess drug use in Hong Kong, China. Furthermore, due to the increasing concern and interest in these compounds, studies have been conducted in several other nations in recent years, including Croatia, Colombia, Canada and South Korea (Krizman et al., 2016, Hernández et al., 2015, Kim et al., 2015a, Bijlsma et al., 2016, Li et al., 2016, Palardy et al., 2016).

Figure 4: Number of published articles by year, containing the terms "Illicit drugs in water" (Source: Data from Google Scholar)

Table 1 provides a comprehensive overview of the international body of research, giving details regarding the year and geographical location of the research, the source and nature of water sampled, and the various illicit drugs detected. From Table 1, it is clearly evident that the majority of studies (almost 90%) analysed wastewater samples from WWTPs (influent and/or effluent); the next most common water source analysed was surface water (rivers and lakes) where wastewater discharge occurred. Frequently studied European rivers included the Po (Italy), Llobregat and its tributaries (Spain), Taff and Ely (UK) (Zuccato et al., 2005, Zuccato et al., 2008a, Huerta-Fontela et al., 2008b, Huerta-Fontela et al., 2007, Boleda et al., 2009, Kasprzyk-Hordern et al., 2009, Kasprzyk-Hordern et al., 2008, Kasprzyk-Hordern et al., 2007, Boleda et al., 2007, Mastroianni et al., 2016).

Table 1: Comprehensive overview of illicit drug occurrence including geographical regions, water sources and drugs detected

4.1 Occurrence of illicit drugs in wastewater

According to the literature, groups of illicit drugs and their metabolites found in the untreated sewage and treated effluent wastewater were in the order of a few ng/L up to 10 µg/L. The occurrence of illicit drugs in the raw influent wastewater provides information on community drug use, while assessing their relative

concentration in the treated wastewater reveals information on removal efficacy of WWTP processes. Table 2 presents an overview of the concentrations of key illicit drugs in the raw influent and treated effluent wastewater from WWTPs in a number of countries. As seen in Table 2, cocaine concentrations were reported in both untreated influent and treated effluent wastewater ranging from 0.7–4,700 ng/L and 0.2–530 ng/L respectively, with its main metabolite, BE, ranging from 5–7,500 ng/L and 0.8–1,500 ng/L in the influent and effluent respectively. Interestingly, the concentration of other cocaine metabolites (norcocaine, cocaethylene, norbenzoylecgonine) were quite variable in different parts of the world, with the higher concentrations recorded in European countries relative to other regions. Concentrations of the opioid pharmaceuticals codeine, EDDP and MET in wastewater ranged from 1.3–3,973 ng/L, 2.54–1, 029 ng/L and 1.35–1,531 ng/L respectively. The highest concentration range for codeine (236–3,973 ng/L) was reported in the UK, possibly due to higher rates of therapeutic codeine intake, whereas MET and EDDP were reportedly highest in Spain (Baker et al., 2014, Baker and Kasprzyk-Hordern, 2013, Boleda et al., 2007, Boleda et al., 2009).

Common ATS substances such as AMPH, METH and MDMA were also detected in various wastewaters throughout Europe, USA, UK and some parts of Oceania and Asia. Kasprzyk-Hordern et al. (2009) reported the highest concentration of AMPH (4,310 ng/L) in raw wastewater from South Wales, UK. The next highest AMPH concentrations were reported by Thomas et al. (2012) following wastewater analysis in 19 European cities, with the authors highlighting that the high concentrations may be a result of the direct discharge of the compound into sewerage systems from drug production facilities or from a metabolite of prescribed medicine (e.g. Selegiline). The major metabolites of heroin, including morphine and 6–acetylmorphine, were also detected at several WWTPs in the range of 11–1,007 ng/L and 0.4–756 ng/L respectively. Other detected illicit drugs included cannabis (THC, THC–COOH and THC–OH), ecstasy (MDEA, MDA) ephedrine, heroin and trace amounts of EME, normorphine and norcodeine.

Generally speaking, the levels of illicit drugs measured in wastewater effluents were lower than raw influent levels (Table 2), indicating that the majority of compounds are capable of being removed during wastewater treatment processing (see also Table 5), either by degradation or physical adsorbtion onto solid fractions. For example, active compounds and metabolites of cannabis are concentrated in the sludge fraction during wastewater treatment and then transferred to the treated biosolids, or are biotransformed/biodegraded into some other undetected metabolite (Pal et al., 2013). Average treated effluent drug concentrations were in the order of

tens to hundreds of ng/L for cocaine (80 ng/L), BE (284 ng/L), MDMA (86 ng/L), morphine (210 ng/L), codeine (317 ng/L), MET (74 ng/L) and EDDP (151 ng/L). Some authors actually reported higher concentrations of drugs (EDDP, MOR) in treated effluents relative to untreated influents during their analysis (Table 2), with this discrepancy probably due either the formation of transformation products, or issues with obtaining suitably paired influent and effluent samples as a result of hydraulic residence lag times, something especially problematic in large activated sludge basins. For example, Bones et al. (2007) recorded the presence of EDDP in effluent wastewater and not in influent; they stated that it may be due to the presence of EDDP as a charged species in solution and concentrated in the aqueous phase during the treatment process. In some cases drug metabolites can be reconverted into the parent drug and metabolites (e.g. glucuronides) and transformation products formed during treatment processing not only exist in higher concentrations (e.g. cocaine and its metabolite BE; Table 2, Table 3, Table 4), but are more persistent than the parent drug and exhibit greater toxicity (Farré et al., 2008, Hernández et al., 2005, Kümmerer, 2009, Lambropoulou and Nollet, 2014). Non-detection of parent drug species cannot be assumed to equate to absolute removal of the associated risk with their transformation products and/or metabolites, and given the lack of information on illicit drug transformation products in wastewater and the environment more broadly, more research is needed to quantify and assess the toxicity of key illicit drug degradation products in treated effluents.

As alluded to above, effective sampling is important for any wastewater analyses and uncertainties in sampling processes (collection, preservation and analysis) directly affect the accuracy of the parameters to be measured and the usefulness of associated insights (Cotman and Pintar, 2013). Ort et al. (2010a) and Castiglioni et al. (2013) undertook comprehensive analyses of error and uncertainty surrounding reported drug levels in wastewater and suggested that a short sampling interval should be incorporated to achieve minimal variations. Work by Daelman et al. (2013) assessing the efficacy of different wastewater sampling strategies (varying collection interval and frequency) on data quality (precision and accuracy) showed that the type of sampling strategy had a significant impact data quality, with continuous online monitoring the best approach and short-term weekly grab sampling the least preferred approach due to its inability to adequately capture temporal variability. For illicit drugs where considerable temporal variability exists as a result of dynamic community use, but where online monitoring is not yet feasible, the best sampling strategy for long-term load assessments is likely to consist of time-integrated composite daily sampling (ideally 24-hour composites), with random sampling intervals across the seven day week over a period which provides a relatively large sample size

(ideally $n \geq 50$ according to Daelman and co-authors). McCall et al. (2016) offer useful insights into other sampling considerations for illicit drugs in wastewater, including recommendations for the use of internal controls, sample pre-treatment, preservation and long-term storage, and readers are directed there for further information.

Table 2: Concentrations of illicit drugs (ng/L) reported internationally in WWTP influent (I) and effluent (E)

4.2 Occurrence of illicit drugs in surface water

A considerable body of literature has emerged in recent years describing illicit drugs in surface water (rivers, streams, lakes, and creeks), with this research summarised in Table 3. For the most part, relatively low levels of illicit drugs (i.e. ng/L) are reported in surface waters, with the most commonly detected substances including cocaine, BE, norcocaine, norbenzoylecgonine, cocaethylene, AMPH, METH, MDMA, MDA, morphine, cannabis (THC-COOH), codeine, MET and EDDP (Zuccato et al., 2008a, Postigo et al., 2010, van Nuijs et al., 2009, Baker and Kasprzyk-Hordern, 2013, Li et al., 2016, Mastroianni et al., 2016, Wang et al., 2016, van der Aa et al., 2013).

It is common practice in many countries, particularly throughout Europe and USA, for WWTPs to discharge their treated effluent into nearby rivers. The previous section demonstrated clearly that treated wastewater effluent contains a range of residual drugs, either as primary compounds or their metabolites. Zuccato et al. (2005) reported the first ever assessment of levels of cocaine in Italy's largest river (the Po) and found that the river carried approximately 4 kg of cocaine-equivalents per day. van Nuijs et al. (2009) observed even higher concentrations of cocaine (60 ng/L) and BE (222 ng/L) in the Zenne river and its tributaries in Belgium. The river has an annual average discharge of 4 m^3/s upstream from Brussels, but it receives a similar order of magnitude of wastewater discharge (3.9 m^3/s) from two WWTPs in Brussels (Ouattara et al., 2014). Cocaine concentrations below 0.3 ng/L were also reported in the Taff and Ely rivers in the UK (Kasprzyk-Hordern et al., 2009, Kasprzyk-Hordern et al., 2008, Kasprzyk-Hordern et al., 2007). Studies on the Llobregat River, Spain showed considerable concentrations of cocaine (6–24 ng/L), BE (7–77 ng/L), AMPH (20 ng/L), METH (0.2–0.9 ng/L), MDMA (1.3–14 ng/L), MDA (9.2 ng/L), morphine (1–5.5 ng/L), codeine (14–23 ng/L), THC-COOH (24–27 ng/L), MET (2.3–6.4 ng/L) and EDDP (6.2–12.3 ng/L); concentrations of codeine, EDDP and MET were highest in its tributary rivers the Cardener and Anoia (Boleda et al., 2009). The Llobregat River was found to contain significant concentration of drugs and this was attributed to there being a highly populated catchment,

with more than three million inhabitants, with generated wastewater discharged into the river after treatment (Muñoz et al., 2009b, Rosal et al., 2010, Muñoz et al., 2009a, Mastroianni et al., 2016). Likewise, the prevalence of AMPH, MDMA and MDA were also observed to be higher in Llobregat River, Spain (Huerta-Fontela et al., 2008b). While METH concentrations were higher in downstream samples collected from Big Blue River, Nebraska (maximum 62.6 ng/L) (Bartelt-Hunt et al., 2009). Wang et al. (2016) recently reported on the occurrence of amphetamine-like compounds, cocaine, opioids and ketamine in 36 Chinese rivers, with concentrations ranging from the limit of quantitation (LOQ) to 43.9 ng/L (Table 3).

Opioid pharmaceuticals such as codeine (1.8–342 ng/L), MET (0.5–24.4 ng/L) and EDDP (1–58.8 ng/L) have also been detected in surface waters at various locations across the world (Table 3). Even though surface water opioid concentrations are in the low (ng/L) range, the possible effects of these compounds on humans and aquatic biota remain largely unknown and, therefore, should not be ignored (Pal et al., 2013). Unfortunately, there are almost no studies on the effects of these compounds on freshwater/marine species. One of the few studies reporting on the potential toxicity effects on aquatic organisms (the zebra mussel *Dreissena polymorpha*) when exposed to mixtures of drugs (cocaine, BE, MDMA, AMPH and MOR) observed a significant increase of oxidative damage and variation in the enzymes activities (Parolini et al., 2015). Similar studies from Binelli et al. (2012) and Parolini and Binelli (2014) highlighted DNA damage and decreased the stability of lysosomal membrane when exposed to cocaine and Δ-9-THC respectively. Looking at the data from both Table 2 and Table 3, it can be concluded that many WWTPs do not completely remove many drugs and their metabolites from domestic wastewater (see Section 5 for more detailed on WWTP removal efficacy).

Table 3: Concentrations (ng/L) of illicit drugs detected in surface water in various parts of the world

4.3 Occurrence of illicit drugs in drinking water

While information on the occurrence of illicit drugs in drinking water sources is emerging, there remains a paucity of information on their potential chronic long-term human/environmental health and exposure effects. For example, the levels of illicit drugs were measured in both raw water and treated water in a Spanish DWTP, with Huerta-Fontela et al. (2008b) reporting maximum concentrations of cocaine (60 ng/L), BE (150 ng/L) and AMPH (50 ng/L), whereas Boleda et al. (2009) reported codeine (76 ng/L) and EDDP (31 ng/L) in the same DWTP influent water. Rosa Boleda et al. (2011) also detected very low concentrations (sub-ng levels) of

cocaine, BE, MET and EDDP in tap water samples from Spanish cities. Rodayan et al. (2015) reported cocaine, BE, MDMA and ephedrine in a Canadian DWTP (raw and treated water) which was most likely not using advanced organics removal technologies, such as activated carbon filtration and ozonation. Table 4 presents the concentrations of illicit drugs detected in various drinking water sources and indicates that the highest recorded substance was benzoylecgonine (150 ng/L) followed by cocaine (60 ng/L).

Studies have shown that conventional WWTPs are unable to completely remove illicit drugs from wastewater, such that they are ultimately discharged into receiving waterways including those sourced for drinking water supplies (Watkinson et al., 2007, Petrovic et al., 2009). For this reason, it is important to understand the removal performance of various drinking water treatment processes for these substances. Results obtained by Boleda et al. (2009) showed that common DWTP processes (pre-chlorination, sand filtration, flocculation, ozonation, post-chlorination) can remove morphine, codeine, norcodeine, THC and THC-COOH entirely, with high removal efficacy for MET and EDDP (91% and 87%, respectively). Although concentrations of these compounds in drinking water sources are detected at very low levels as compared to raw wastewater, they cannot be ignored (Pal et al., 2013) since the health effects from chronic low-level exposure are unknown and the concentration of these substances may well continue to increase into the future (Figure 1).

Table 4: Concentrations (ng/L) of illicit drugs detected in drinking water sources internationally

5. ILLICIT DRUG REMOVAL EFFICIENCY DURING WASTEWATER TREATMENT

Since the vast majority of treated wastewater worldwide is discharged into receiving aquatic environments, it is important to understand the removal efficacy of conventional wastewater treatment processes for chemicals of concern. Table 2 shows that treated WWTP effluents generally contain lower concentrations of illicit drugs than does the respective influent; although they are present at varying concentrations depending on location and detection method. Accordingly, such influent and effluent analyses provide qualitative or at best semi-quantitative information regarding the performance of WWTP configurations for removing these drugs (Bartelt-Hunt et al., 2009). Treatment technologies used to treat wastewater vary considerably around the globe, with individual unit processes configured and operated differently depending on site-specific factors, climate, water authority preferences and expertise, and relative cost. As such, the removal efficacy of WWTPs for various

substances, including illicit drugs, will vary considerably depending on the technology used (e.g. low-rate processes like waste stabilisation lagoons or trickling filters, versus high-rate activated sludge) and how the treatment processes are operated (e.g. hydraulic and organic loading rate, sludge retention time (SRT) and mixed liquor suspended solids (MLSS) concentration). It is also likely that any microbially-mediated drug removal will be strongly influenced by process design and operational parameters, as well as environmental factors such as water temperature and dissolved oxygen concentration (Stadler et al., 2012, Jekel et al., 2015). However, hydraulic retention time should be considered while calculating the removals efficacy of treatment plants based on influent and effluent wastewater. Also, the longer the hydraulic retention time of the WWTP the more time for biological degradation (Fernandez-Fontaina et al., 2012).

Different WWTPs may use different secondary treatment process configurations, such as activated sludge treatment, trickling filters, or membrane bioreactors. Several recent studies concluded that activated sludge treatment is more efficient in removing illicit drugs than trickling filters, probably because activated sludge processes allow more efficient reaction of chemical contaminants than trickling filters, with much higher active microbial biomass content and high rates of oxygen input from mechanical aeration that would also enhance volatilization (Kasprzyk-Hordern et al., 2009, Baker and Kasprzyk-Hordern, 2013). Also, solids are continuously removed in the form of waste activated sludge, so this may contribute to drug removal performance via adsorption to the solid phase. Baker and Kasprzyk-Hordern (2013) compared activated sludge treatment with trickling filters for removal of various illicit drugs and found that activated sludge removes 91% cocaine, 99% AMPH and 39% MET, while removal efficiency of trickling filters for cocaine, AMPH, MET was 37%, 89% and 25% respectively. Table 5 compares the removal efficacy of activated sludge and trickling filter treatment process in the removal of selected illicit drugs. Postigo et al. (2010) found that secondary treatment using biological filters and operating with low SRT were less effective compared to activated sludge in removing illicit drugs and their metabolites, reporting high removals (>90%) for cocaine and its metabolite and 49–80% for MDMA through activated sludge. Thus, SRT is another important parameter that should be considered while assessing the removal rate of WWTPs; for example, Clara et al. (2005) concluded in their study that low effluent concentrations could be attained at higher SRTs (>10 days). Bijlsma et al. (2012) reported removals for activated sludge of 100% for both AMPH and METH, 98% for THC-COOH, 90% for BE and 79% for cocaine. Bones et al. (2007), reported the highest removal rate for BE (93%) and the lowest for cocaine (72%) in an Irish WWTP using activated sludge treatment, while Postigo et al. (2008) found average

451 removals of 95% for cocaine and BE. A variant on activated sludge, the membrane bioreactor which uses
452 ultrafiltration membranes submerged in activated sludge, is considered more effective at illicit drug removal
453 than conventional activated sludge (Petrovic et al., 2009), possibly due to some combination of higher operating
454 biomass (MLSS) concentrations, longer SRT and/or improved effluent solids separation. However, clearly more
455 research is needed on the identification of removal pathways, to allow us to distinguish between true drug
456 degradation by biodegradation/biotransformation, volatilization or phase partitioning/sorption of these
457 compounds into the solids fraction (Jekel et al., 2015).
458
459 **Table 5:** Reported illicit drug removal (%) during activated sludge and trickling filter wastewater treatment
460
461 The review has clearly demonstrated that there is relatively little data on illicit drug removal efficacy during
462 'low rate' treatment processes such as waste stabilisation ponds/lagoons, wetlands, reedbeds and other passive
463 filtration processes. Given the prevalence of waste stabilisation pond technology in particular throughout
464 Australia and also internationally, this represents an important knowledge gap. Within activated sludge-based
465 wastewater treatment, differences in the removal rate of these drugs point to potentially important roles for key
466 environmental and operational parameters, such as temperature, dissolved oxygen, MLSS concentration, sludge
467 age/SRT, wastewater C/N ratio, microbial ecology, etc. (Jekel et al., 2015). These could form the basis of future
468 research investigations in order to better understand the removal pathways and performance efficacy for drug
469 removal during activated sludge-type processes. At the same time, more research is also needed on
470 transformation product dynamics during various high- and low-rate wastewater treatment processes.
471

472 ## 6. CONCLUSIONS

473 The review has highlighted the trend of increasing illicit drug use globally and the concomitant increase in drug
474 loads in wastewater and receiving waters. Reports show that illicit drugs were often detected in surface waters,
475 but also that there is a lack of information regarding their fate and potential impact on aquatic ecosystem and
476 human health which should not be neglected. As is the case for many trace organic chemicals of concern,
477 current monitoring methods for illicit drugs are analyte-specific, expensive and labour-intensive, such that
478 simple and rapid detection methods in future would allow for better monitoring data and more informed future
479 health risk assessments and management paradigms.
480

The illicit drugs investigated in this review showed different patterns of removal during the wastewater treatment processes, with some nearly completely removed while others showed effluent concentrations within the range of influent concentrations. Furthermore, there was considerable variability in the removal efficacy of wastewater treatment operations and technologies between studies, making it difficult to draw firm conclusions regarding the removal efficacy of specific compounds via specific wastewater treatment processes. Individual WWTP loading conditions, process configurations and operations are many and varied, so to ensure better comparability between studies reporting on drug concentrations and removal efficacies, researchers should ideally provide detailed information on basic sewage characteristics (pH, temperature, conductivity, suspended solids, chemical oxygen demand, total nitrogen) as well as key WWTP configuration and operating conditions (e.g. engineering process flow schematic, population-equivalent loading rates, SRT, MLSS and dissolved oxygen set-point for activated sludge processes).

Regarding the removal efficacy of activated sludge-type processes versus trickling filters, activated sludge generally performed much better overall across a range of substances; although a lack of detail on WWTP configuration and operation makes it difficult to contrast performance within 'activated sludge' typologies. Future work on drug removal during wastewater treatment could focus on other low-rate processes (e.g. wetlands, reedbeds), different activated sludge-based treatment processes including membrane bioreactors, and other tertiary treatment processes such as membrane filtration, UV irradiation, ozone treatment and advanced oxidation used for water recycling applications. Such information, combined with improved detection methods, will then serve to inform relevant quantitative risk assessments, regulations and water utility operations to better manage any environmental and public health risks associated with these compounds.

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868 Table 1: Comprehensive overview of illicit drug occurrence including geographical regions, water sources and
869 drugs detected

Year	Region, Water sources	Water type	Drugs detected	Reference
2004	USA – 3 WWTPs	WWTP influent/effluent	METH, MDMA	(Jones-Lepp et al., 2004)
2005	Italy – 4 WWTP, River-Po	SW; WWTP influent	COC, BE	(Zuccato et al., 2005)
2006	Nosedo, Switzerland – 2 WWTP	WWTP influent/effluent	BE, NorBE, COC, NorCOC, CE, MOR, 6ACM, M3G, AMPH, METH, MDA, MET, MDMA, MDEA, EDDP, THC-COOH	(Castiglioni et al., 2006)
2006	12 German WWTPs, Rivers, Streams	WWTPs – influent/effluent; SW	BE, COD, MOR	(Hummel et al., 2006)
2007	Ireland – 5 WWTP; River Broad Meadow, Liffey	WWTP influent/effluent, SW	COC, BE, EDDP, MOR	(Bones et al., 2007)
2007	Spain – 16 WWTP, Llobregat River	WWTP influent/effluents; SW	COC, BE, AMPH, MDMA, MDEA, KET	(Huerta-Fontela et al., 2007)
2007	Belgium – 5 WWTP, Rivers	Influent WWTP, SW	COC, BE	(Gheorghe et al., 2008)
2007	River Taff (UK), Warta (Poland)	SW	BE, COC, AMPH	(Kasprzyk-Hordern et al., 2007)
2007	Spain – 5 WWTP; Llobregat River	Influent/effluent WW, SW	MOR, NorMOR, COD, MET, NorCOD, 6ACM, HER, EDDP, THC-COOH, THC	(Boleda et al., 2007)
2008	Spain – DWTP, Rivers	SW, DWTP	APMH, METH, MDMA, MDA, COC, BE	(Huerta-Fontela et al., 2008b)
2008	Spain – 42 WWTP	WWTPs influent/effluent	APMH, METH, MDMA, MDA, MDEA, COC, BE, KET	(Huerta-Fontela et al., 2008a)
2008	3 WWTPs: Milan; Switzerland; London	Untreated WW–WWTPs	COC, BE, MOR, THC-COOH, AMPH, METH, MDMA	(Zuccato et al., 2008b)
2008	Rivers, Lakes	SW	BE, NorBE, COC, NorCOC, CE, MOR, 6ACM, AMPH, METH, MDA, MDMA, MET, EDDP, THC-COOH, COD, 6AC	(Zuccato et al., 2008a)
2008	Spain – 4 WWTP	Influent/effluent sewage water	BE, COC, CE, MOR, 6ACM, AMPH, METH, MDMA, HER, THC-COOH, THC, EPH	(Postigo et al., 2008)
2008	USA – 7 WWTP	Raw influent	APMH, METH, EPH, MDMA, MDA, KET, MDEA, COC, BE, MET, NorCOC, NorBE	(Chiaia et al., 2008)
2008	South Wales, UK River Taff, Ely	SW	AMPH, COC, BE	(Kasprzyk-Hordern et al., 2008)
2009	UK – 2 WWT, Rivers - Taff, Ely	WWTP influent/effluent; SW	AMPH, COC, BE	(Kasprzyk-Hordern et al., 2009)
2009	USA – WWTP, Rivers	SW, Effluent–Omaha WWTP	METH, AMPH	(Bartelt-Hunt et al., 2009)
2009	Belgium – 30 WWTP**,** 10 Rivers	WWTP influent/effluent, SW	COC, BE	(van Nuijs et al., 2009)
2009	Spain – 15 WWTP, River Llobregat and its tributaries	WWTP influent/effluent, SW; DWTPs	HER, 6ACM, MOR, COD, MET, THC, NorMOR, NorCOD, FEN, EDDP, THC-COOH	(Boleda et al., 2009)
2009	Florence – 2 WWTP	WWTP influent	COC, BE, MOR	(Mari et al., 2009)

Year	Region, Water sources	Water type	Drugs detected	Reference
2010	Switzerland– WWTP; Rivers/ creeks/ lakes	WWTP influent /effluent, 22 rivers or creeks water samples	BE, COC, MOR, 6ACM, COD, 6ACOD, AMPH, METH, MDMA, MET, THC-COOH, EDDP	(Berset et al., 2010)
2010	Spain –7 WWTP	WWTP influent/effluent, Ebro river Basin (15 SW samples)	BE, COC, CE, MOR, 6ACM, AMPH, METH, MDMA, HER, THC-COOH, THC, EPH	(Postigo et al., 2010)
2010	France–4 WWTP	Influent/effluent WW	COC, AMPH, MDMA, BUPN	(Karolak et al., 2010)
2010	Canada –3 WWTP	Treated/untreated WW	COC, BE, AMPH, METH, MDMA	(Metcalfe et al., 2010)
2011	Brussels–WWTP	Influent WW	COC, AMPH, METH, MDMA, HER, METD	(Van Nuijs et al., 2011b)
2011	South Australia – 13 WWTP	WWTP influent	BE, METH, MDMA	(Irvine et al., 2011)
2011	2 WWTPs – Milan and Como	WWTP Influent	COC, HER, METH	(Zuccato et al., 2011)
2011	Queensland – WWTP	WWTP influent	BE, COC, AMPH, METH, MDA, MDMA, MET, MOR,COD EDDP, THC-COOH,	(Lai et al., 2011)
2012	19 European Cities – 21 WWTPs	WWTP inlets	COC, AMPH, METH, MDMA, THC-COOH	(Thomas et al., 2012)
2012	Netherlands – 5 WWTP	Influent/effluent sewage water	AMPH, BE,COC, METH, MDMA	(Bijlsma et al., 2012)
2012	Spain – WWTP	Treated/raw WW	COC, BE, CE, AMPH, MET, COD MDMA, THC-COOH, MOR, EDDP	(González-Mariño et al., 2012)
2013	Queensland – WWTP	Influent WWTP	Cannabis, COC, MDMA, METH	(Lai et al., 2013a)
2013	25 WWTPs (23 WWTPs –France, 1 WWTP–Paris, 1 WWTP – Réunion Island)	WWTPs influents/ effluents	COC, BE, EME, NorCOC, CE, AMPH, MDMA, MDEA, MDA, HER, 6ACM, MOR, MET, EDDP, BUPN, THC-COOH	(Nefau et al., 2013)
2013	England – 7 WWTP, River	WWTP influent/effluent; SW	BE, NorBE, COC, NorCOC, CE, AMPH, METH, MDA, MDMA, MDEA, HER, MET, MOR, 6ACM, COD, NorMOR, EDDP, NorCOD, BUPN, EPH, NorEPH	(Baker and Kasprzyk-Hordern, 2013)
2013	Croatia – 3 WWTP	Raw influent, activated sludge, secondary effluent from WWTPs	M3G, MOR, AMPH, COD, METH, MDMA, 6ACM, BE, COC, EDDP, MTD, THC-OH, THC-COOH	(Senta et al., 2013)
2013	Hong Kong – WWTP	WWTP Influent	BE,COC, KET,METH, Nor KET	(Lai et al., 2013b)
2014	Taiwan – 2 WWTP, River.	SW; WWTP influent/effluent	COD, KET, MDMA	(Jiang et al., 2014)
2014	Slovakia – 8 WWTP	WWTP influent	AMPH, BE,COC, METH, MDMA, THC-COOH	(Mackuľak et al., 2014)
2014	England – WWTP	WWTP influent	BE, NorBE, COC, CE, NorCOC, AMPH, MDA, METH, MDMA, MDEA, MOR, 6ACM, COD, MET, NorMOR, EPH, NorCOD, EDDP, KET, BUPN, NorEPH	(Baker et al., 2014)
2014	Beijing – 13 WWTP	WWTP influent/effluent	AMPH, METH	(Li et al., 2014)

Continued

Year	Region, Water sources	Water type	Drugs detected	Reference
2014	Finland – 10 WWTP	WWTP influent	AMPH, BE, MDMA, METH	(Kankaanpää et al., 2014)
2015	South Korea – 15 WWTP	Raw WW	AMPH, COD,BMETH, MDA	(Kim et al., 2015b)
2015	China – 36 WWTP	Influent/effluent Water from WWTP	AMPH, KET, METH	(Du et al., 2015)
2016	Canada – WWTP	WWTP influent/effluent	BE, COD, METH, MET, MOR, THC-COOH,	(Palardy et al., 2016)

AMPH: Amphetamine, BE: Benzoylecgonine, BUPN: Buprenorphine, CE: Cocaethylene, COC: Cocaine, COD: Codeine, EDDP:2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine, EPH: Ephedrine, FEN: Fentanyl, HER: Heroin, KET: Ketamine, METH: Methamphetamine, MDA:3,4-methylenedioxyamphetamine, MDMA:3,4-methylenedioxy-methamphetamine, MDEA:3,4Methylenedioxyethylamphetamine, MET: Methadone, MOR: Morphine, NorBE: Benzoylecgonine, NorCOC: Norcocaine, NorCOD: Norcodeine, NorEPH: Norephedrine, NorKET: Norketamine, NorMOR: Normorphine, THC-OH:11-Hydroxy-tetrahydrocannabinol, THC-COOH:11-nor-9-carboxy-Δ9-tetrahydrocannabinol, 6ACM:6-Acetylmorphine

DWTP: Drinking water treatment plant, SW: Surface water, WW: Wastewater, WWTP: Wastewater treatment plant

881 **Table 2:** Concentrations of illicit drugs (ng/L) reported internationally in WWTP influent (I) and effluent (E)

Country	COCAINE												Reference
	Cocaine		Benzoylecgonine		Nor BE		Nor cocaine		Cocaethylene		EME		
	I–WW	E–WW	I–WW	E–WW	I–WW	E–WW	I–WW	E–WW	I–WW	E–WW	I–WW	E–WW	
Australia	3.96–200[b]		14–72.3										(Lai et al., 2013a, Irvine et al., 2011, Lai et al., 2011)
Beijing	32–562		80–1190										(van Nuijs et al., 2009)
Belgium	22–678		82–1898										(Van Nuijs et al., 2011b, Gheorghe et al., 2008, van Nuijs et al., 2009)
Canada	209–823	<LOQ–530	287–2624	62–775									(Metcalfe et al., 2010)
Croatia	0.7–53		5–100										(Senta et al., 2013)
Europe	2–1998[a]												(Thomas et al., 2012)
France	<LOQ–1532	<LOQ–335	21–3050	<LOQ–910			25	<LOQ	10–167	5–25	40–761	50–137	(Karolak et al., 2010, Nefau et al., 2013)
Germany			78	49									(Hummel et al., 2006)
Hong Kong	60.8[b]		101[b]										(Lai et al., 2013b)
Ireland	489	47–138	290	22–31									(Bones et al., 2007)
Italy	42–421		117–1132		37		13.7		11.5				(Zuccato et al., 2008b, Zuccato et al., 2005, Castiglioni et al., 2006, Mari et al., 2009)
London	140 [a]		296 [a]										(Zuccato et al., 2008b)
Netherlands	87–957	10–235	260–3701	10–351									(Bijlsma et al., 2012)
Slovakia	40–96		24–219										(Mackuľak et al., 2014)
Spain	4–4700	1–105	9–7500	1–1500					18–97	1.5–6.8			(Huerta-Fontela et al., 2008a, Huerta-Fontela et al., 2008b, Huerta-Fontela et al., 2007, Postigo et al., 2008, Postigo et al., 2010, González-Mariño et al., 2012)
Switzerland	218–248	10.7–15	267–604	96–100	19	7.5	4.3	0.7	5.9	0.2			(Zuccato et al., 2008b, Castiglioni et al., 2006, Berset et al., 2010)
UK	5.1–521	0.6–128	15.8–1544	0.8–1091	1.8–54	0.5–14.6							(Kasprzyk-Hordern et al., 2009, Baker et al., 2014, Baker and Kasprzyk-Hordern, 2013)

USA	10–860		110–2800		14–170	4–50	0.9–44.7	0.5–7.9	(Chiaia et al., 2008, Baker et al., 2014, Baker and Kasprzyk-Hordern, 2013)

Country	**CANNABINOIDS**					**References**
	THC-COOH		**THC**		**THC-OH**	
Australia	1.2–2.7					(Lai et al., 2011)
Croatia	ND–111				ND–66	(Senta et al., 2013)
Europe	14–192[a]					(Thomas et al., 2012)
France	44–1196	6–161				(Nefau et al., 2013)
Italy	20–63					(Zuccato et al., 2008b, Castiglioni et al., 2006)
London	50[a]					(Zuccato et al., 2008b)
Netherlands	73–489	11–22				(Bijlsma et al., 2012)
Slovakia	42–140					(Mackuľak et al., 2014)
Spain	4.3–402	1.8–71.7	11.3–127	13–20.5	7.6[d]	(Postigo et al., 2008, Postigo et al., 2010, Boleda et al., 2007, González-Mariño et al., 2012, Boleda et al., 2009)
Switzerland	43–91	7.2				(Zuccato et al., 2008b, Castiglioni et al., 2006)

	Amphetamine type stimulants										
	Amphetamine		**METH**		**MDMA**		**MDEA**		**MDA**	**Ephedrine**	
Australia	2.4–4.66[b]		17.45–833		108–281				0.65–4.6[b]		(Lai et al., 2013a, Irvine et al., 2011, Lai et al., 2011)
Beijing	2–101	0.9–2.8	21.2–304	0.4–12.2							(Mackuľak et al., 2014, Li et al., 2014)
Belgium	76[a]		2[a]		13[a]						(Van Nuijs et al., 2011b)
Canada	<LOQ–25	<LOD–14	5–65	3–95	9–35	<LOD–32					(Metcalfe et al., 2010)
China	38.3		229.3								(Du et al., 2015)
Croatia	<1.6–22		<1.2		-						(Senta et al., 2013)
Europe	33–3040[a]		3–376[a]		32–615[a]						(Thomas et al., 2012)
France	52–82	ND	51	24	2.6–136	<0.7–165			71–1637	16–902	(Karolak et al., 2010, Nefau et al., 2013)
Hong Kong			97.8[b]								(Lai et al., 2013b)
Italy	2.7–14.7	ND	4.5–16.2	3.5	4.2–14.2	4.4	1.5	ND	4.6	1.1	(Zuccato et al., 2008b, Castiglioni et al., 2006)
London	24[a]		2.4[a]		3.4[a]						(Zuccato et al., 2008b)

Netherlands	40–1779	4.5–12	16–17	<5 [M]	12–241	19–222							(Bijlsma et al., 2012)
Slovakia	98–257		79–658		<0.5–35								(Senta et al., 2013, Mackuľak et al., 2014)
S. Korea	<LOQ–17		<LOQ–50						ND–9.44				(Kim et al., 2015b)
Spain	3–688	0.5–210	3–277	1.3–90	2–598	2–376	6–114	12	3–266	1–200	360–592	91.6–266	(Huerta-Fontela et al., 2008a, Huerta-Fontela et al., 2007, Postigo et al., 2008, Postigo et al., 2010, González-Mariño et al., 2012)
Switzerland	7	<LOQ	<LOQ	<7	13.6–26	5.1–<11			<LOQ	0.9			(Zuccato et al., 2008b, Castiglioni et al., 2006, Berset et al., 2010)
UK	77.2–4310	2–201[M]	18–39.8	0.4–1.3	0.7–455	0.6–178	1.4	ND	7.2–32.4	6.3–24.5			(Kasprzyk-Hordern et al., 2009, Baker et al., 2014, Baker and Kasprzyk-Hordern, 2013)
USA	80–550	ND	10–2000	2–350	3–70	0.5			2–7	ND	580–6900	ND	(Bartelt-Hunt et al., 2009, Jones-Lepp et al., 2004, Chiaia et al., 2008)

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Country	Opioids																References
	Heroin		Morphine		Nor Morphine		6-Acetylmorphine		Codeine		Nor Codeine		Methadone		EDDP		
	I–WW	E–WW	I–WW	E–WW	I–WW	E–WW	I–WW	E–WW	I–WW	E–WW	I–WW	E–WW	I–WW	E–WW	I–WW	E–WW	
Australia			39.2–75[b]						116–185[b]				1.4–2.4[b]		2.54–5.1[b]		(Lai et al., 2011)
Belgium	415[a]												138				(Van Nuijs et al., 2011b)
Croatia			45–164				<0.4–3.1		146–350				12–100		27–232		(Senta et al., 2013)
France	25–194	31	28–83	29–152			49–756	30–352					11–234	10–118	6–260	10–246	(Nefau et al., 2013)
Germany			820	110													(Hummel et al., 2006)
Italy			11–83				11.8						11.6	9.1	19.8	22.6	(Zuccato et al., 2008b, Castiglioni et al., 2006, Mari et al., 2009)

Ireland				452–874											ND	9–206	(Bones et al., 2007)
England			173[a]														(Zuccato et al., 2008b)
Netherlands							27–73	7.3–30	73–894	89–599			<45[M]	6–58			(Bijlsma et al., 2012)
Spain	2.3–2.4	1.2	17–278	12–81.1	12.5–30	30.7–107	2.7–13	2–3.6	5.7–120	3–397	5–46.1	5–40.3	3.4–1531	3.4–732	3.3–1029	2.7–1150	(Postigo et al., 2008, Postigo et al., 2010, Boleda et al., 2007, González-Mariño et al., 2012, Boleda et al., 2009)
S. Korea									1.3–20.6								(Kim et al., 2015b)
Switzerland			102–1007	55.4–929			10.4–38	<5	228	204			49.7–112	36.2–46	91.3–315	72.1–294	(Zuccato et al., 2008b, Castiglioni et al., 2006, Berset et al., 2010)
UK			65.6–985.6	13–266.6	38–300	11.6–47	3–224	0.6–7.7	236–3973	9.7–1502	10.2–161	7.2–72.1	2.6–171.1	1.4–91	3.7–342.2	2.6–162	(Baker et al., 2014, Baker and Kasprzyk-Hordern, 2013)
USA													5–62				(Chiaia et al., 2008)

I–WW: Influent wastewater; E–WW: Effluent wastewater; a: mg/day/1000 inhabitants; b: g/day; d: Median; M: Mean, ND: Not Detected, LOQ: Limit of quantitation, LOD: Limit of detection

885 **Table 3:** Concentrations (ng/L) of illicit drugs detected in surface water in various parts of the world

River name, origin	BE	COC	AMPH	METH	MDA	MDMA	MOR	6ACM	THC–COOH	COD	MET	EDDP	References
Po, Italy	25	1.2											(Zuccato et al., 2005)
	3.7	0.5	<0.65	<0.41	<1.18	0.2	<0.55	<0.93	0.3	1.8	0.5	1.0	
Olona, Italy	183	44	<0.65	1.7	<1.18	1.7	38.0	<0.93	<0.48	51.0	8.6	18.0	(Zuccato et al.,
Lambro, Italy	50	15	<0.65	2.1	<1.18	1.1	3.5	<0.93	3.7	12.0	3.4	9.9	2008a)
Arno, Italy	21.8	1.7	<0.65	<0.41	1.2	1.0	3.0	<0.93	0.5	6.2	4.8	4.3	
Thames, UK	11.2	4.7	<0.65	<0.41	2.6	3.6	12.7		<0.58				
Broad meadow, Ireland		25											(Bones et al., 2007)
Liffey, Ireland		33											
Llobregat, Spain	77	6				3							(Huerta-Fontela et al., 2007)
	64	23.8	20	0.9	9.2	14.1							(Huerta-Fontela et al., 2008b)
							5.5	3.4	24	23.0	6.4	12.3	(Boleda et al., 2007)
	7-11.6[M]	2.1-3.7[M]	<LOQ	0.2-1.6[M]		1.3-2.8[M]	1-1.6[M]				1.1-2.3[M]	3.3-3.7[M]	(Mastroianni et al., 2016)
							4		27	14	2.3	6.2	
Cardener, Spain									17.8	8.9	1.9	5.3	(Boleda et al., 2009)
Anoia, Spain							10.7		3.4	26.8	9.3	30.7	
Rubi creek, Spain							29		5.7	231.8	15	58.8	
Ebro river basin[m],	11.4	1.4	6.8	0.4		1.0	9.8		5.5				(Postigo et al., 2010)
Spain	3.2-3.6	3.2-3	4.2	0.3-2.5		0.4-0.6	1.9-2.1				0.9-0.8	0.5-1.1	(Mastroianni et al., 2016)
Taff, South	<1–92	<0.3–4	<1–13										(Kasprzyk-Hordern
Wales, UK	<1	<0.3	7.7							29.0			et al., 2009, Kasprzyk-Hordern et al., 2007)
	<1–123	<0.3–7	<1–14										(Kasprzyk-Hordern et al., 2008, Jones-Lepp et al., 2004)

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River name, origin	BE	COC	AMPH	METH	MDA	MDMA	MOR	6ACM	THC–COOH	COD	MET	EDDP	Reference
Ely, South Wales, UK	<1–84 <1–54	<0.3 <0.3	<1–21 <1–3										(Kasprzyk-Hordern et al., 2009, Kasprzyk-Hordern et al., 2008)
Loup, Us/Ds, USA				1.3/2.3									
Big blue, Us/Ds, USA				ND/ 62.6									(Bartelt-Hunt et al., 2009)
Wood, Us/Ds, USA				1.4/6.6									
Salt creek, Us/Ds, USA				ND/25.2									
Grote Molenbeek, Belgium	191	26											(Gheorghe et al., 2008, van Nuijs et al., 2009)
Demer, Belgium	41–44	13–14.3											
Senette, Belgium	53	7											(Gheorghe et al., 2008)
11 rivers, Germany	3	-					30			35.8			(Hummel et al., 2006)
Warta, Poland	<1	<0.3	<1							12			(Kasprzyk-Hordern et al., 2007)
Rivers, Switzerland	16	0.4					2.2			2.9	1.7	4.9	
Lakes, Switzerland	0.4									2.8	1.3	2.6	(Berset et al., 2010)
Hain, Belgium	110	24											
Dijle, Belgium	38.5	6.8											
Grote Nete, Belgium	8.5	4.5											(van Nuijs et al., 2009)
Zenne, Belgium	222.3	59.8											
Bellebeek, Belgium	76.5	19											
River–Us/Ds^{max}, England	32.4/72.4	5.6/17.4	3.8/4.3	0.1/0.4	ND/1.9	7.4/24.8	9.7/32.3			171/341	18/24	28/41	(Baker and Kasprzyk-Hordern, 2013)
Rivers – Meuse, Rhine, Netherlands	5	2		1		2	7			7	2		(van der Aa et al., 2013)
SARNO river, Italy	91	13											(Maddaloni et al., 2014)

887 M: Median; Max: Maximum; Us/Ds: Upstream/downstream, ND: Not Detected, LOQ: Limit of Quantitation

Table 4: Concentrations (ng/L) of illicit drugs detected in drinking water sources internationally

Drugs reported	Region	Year	Concentration (ng/L)	Reference
Cocaine	DWTP Intake, Llobregat River, Spain	2008	0.1–60	(Huerta-Fontela et al., 2008b)
	Cazalegas Reservoir, Spain	2010	2.11	(Valcárcel et al., 2012)
	43 Spanish Cities	2008-09	0.4	(Rosa Boleda et al., 2011)
	Europe [a]		0.1	
	Latin America [b]		0.6	
Benzoylecgonine	DWTP Intake, Llobregat River, Spain	2008	15–150	(Huerta-Fontela et al., 2008b)
	Cazalegas Reservoir, Spain	2010	2.47	(Valcárcel et al., 2012)
	43 Spanish Cities	2008-09	0.4	(Rosa Boleda et al., 2011)
	Europe [a]		0.2	
	Latin America [b]		4.5	
Cocaethylene	43 Spanish Cities		0.2	
Amphetamine	DWTP Intake, Llobregat River, Spain	2008	0.4–50	(Huerta-Fontela et al., 2008b)
Methamphetamine			<0.2–2	
MDMA			1–40	
MDA			0.4–20	
Morphine	DWTP Intake, Llobregat River, Spain	2009	12	(Boleda et al., 2009)
Codeine			76	
THC-COOH			4.8	
EDDP	DWTP Intake, Llobregat River, Spain	2009	31	(Boleda et al., 2009)
	Cazalegas Reservoir, Spain	2010	0.34	(Valcárcel et al., 2012)
	43 Spanish Cities	2008-09	0.4	(Rosa Boleda et al., 2011)
	Europe [a]		0.4	
	Latin America [b]		0.4	
	Japan [c]		0.1	
Methadone	DWTP Intake, Llobregat River, Spain	2009	9.0	(Boleda et al., 2009)
	Cazalegas Reservoir, Spain	2010	0.47	(Valcárcel et al., 2012)
	DWTP (tap water), Toledo city		0.99	
	Europe [a]	2008-09	0.1	(Rosa Boleda et al., 2011)
	Latin America [b]		0.2	
	43 Spanish Cities		0.2	

[a]: Include 15 samples from Europe, tap water; [b] : 9 Samples from Latin America, tap water; [c]:3 Samples from Japan, tap water

DWTP: Drinking water treatment plant, EDDP: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine, MDA: 3,4-methylenedioxyamphetamine, MDMA: 3,4-methylenedioxy-methamphetamine, THC-COOH: 11-nor-9-carboxy-Δ9-tetrahydrocannabinol

Table 5: Reported illicit drug removal (%) during activated sludge and trickling filter wastewater treatment

Drugs	Secondary Treatments		Reference
	Activated Sludge	Trickling Filters	
Benzoylecgonine	81	27	Baker and Kasprzyk-Hordern (2013)
	100	No removal	Kasprzyk-Hordern et al. (2009)
	88		Postigo et al. (2010)
	90		Bijlsma et al. (2012)
	93		Bones et al. (2007)
	33-57 (46)		Chiavola et al. (2017)
Cocaine	91	37	Baker and Kasprzyk-Hordern (2013)
	100	25	Kasprzyk-Hordern et al. (2009)
	96		Postigo et al. (2010)
	79		Bijlsma et al. (2012)
	72		Bones et al. (2007)
Nor Benzoylecgonine	42	21	Baker and Kasprzyk-Hordern (2013)
Cocaethylene	68	25	Baker and Kasprzyk-Hordern (2013)

	95		Postigo et al. (2010)
Amphetamine	99	89	Baker and Kasprzyk-Hordern (2013)
	100	95	Kasprzyk-Hordern et al. (2009)
	95		Postigo et al. (2010)
	100		Bijlsma et al. (2012)
	33-84 (59)		Chiavola et al. (2017)
Methamphetamine	ND	60	Baker and Kasprzyk-Hordern (2013)
	54.5		Loganathan et al. (2009)
	100		Bijlsma et al. (2012)
	33-97 (63)		Chiavola et al. (2017)
MDMA	19	13	Baker and Kasprzyk-Hordern (2013)
	36		Postigo et al. (2010)
Methadone	39	25	Baker and Kasprzyk-Hordern (2013)
	37		Boleda et al. (2009)
EDDP	61	46	Baker and Kasprzyk-Hordern (2013)
Codeine	81	50	Baker and Kasprzyk-Hordern (2013)
	<50		Boleda et al. (2009)
Morphine	73		Boleda et al. (2009)
	89		Baker and Kasprzyk-Hordern (2013)
THC	97		Boleda et al. (2009)
	90		Postigo et al. (2010)
THC-COOH	98		Bijlsma et al. (2012)
	48		Postigo et al. (2010)
	31		Boleda et al. (2009)
	29-86 (46)		Chiavola et al. (2017)

EDDP: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine, MDMA: 3,4-methylenedioxy-methamphetamine, THC: Tetrahydrocannabinol, THC-COOH: 11-nor-9-carboxy-Δ9-tetrahydrocannabinol, ND: Not detected