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**Review**

# Neuropsychiatric pharmaceuticals and illicit drugs in wastewater treatment plants: a review

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**Environmental context.** Neuropsychiatric pharmaceuticals and illicit drugs in wastewaters are of increasing environmental concern. We compile the recent literature and evaluate the concentrations and profiles of various drugs and their removal efficiencies in wastewater treatment plants. The sewage epidemiology approach, used in the estimation of drug usage in communities, is discussed, and we make recommendations for future research in this area.

**Abstract.** Neuropsychiatric pharmaceuticals and illicit drugs encompass a broad range of compounds including opioids, amphetamine-type stimulants, cannabinoids, benzodiazepines, barbiturates, antipsychotics, anaesthetics, anti-epileptics and mood stabilisers, lysergic compounds, sympathomimetic amines and cocaine derivatives. In this article, we review studies on the occurrence and fate of these drugs in wastewater treatment plants. In general, among various drugs studied, the concentrations and detection frequencies of opioids and cocaine derivatives were the highest in wastewaters. The forensic analysis of wastewaters suggests that cocaine and opioids usage has increased. Given the fact that data on drug usage can be used for making regulatory decisions and policies, this review focuses on understanding the sources and environmental dynamics of neuropsychiatric and illicit drugs. There is a pressing need for more research on the magnitude and extent of illicit drug consumption. The 'sewage epidemiology' approach, currently applied in the estimation of illicit drug consumption in communities, is reviewed. The field of wastewater research has been advancing in multipronged paths, incorporating concepts in analytical chemistry, organic chemistry, environmental chemistry, biochemistry, sewage engineering, drug epidemiology and statistics. Future prospects with regard to the occurrence and environmental fate of illicit and psychoactive drugs are recommended.

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## Introduction

Licit neuropsychiatric pharmaceuticals and illicit drugs (both parent compounds and their metabolites) are emerging environmental contaminants.[1–6] Owing to their high production and consumption volumes, many of these drugs are widely distributed in the aquatic environment.[1–6] Approximately 8% of the USA population has been prescribed neuro-active medications,[2] and in 2007, 12 of the 100 most prescribed drugs in the USA were neuro-active and psychoactive.[4] The United Nations Office on Drugs and Crime reported in 2011 that, globally, 167–315 million people of 15–64 years of age were estimated to have used an illicit drug in the previous

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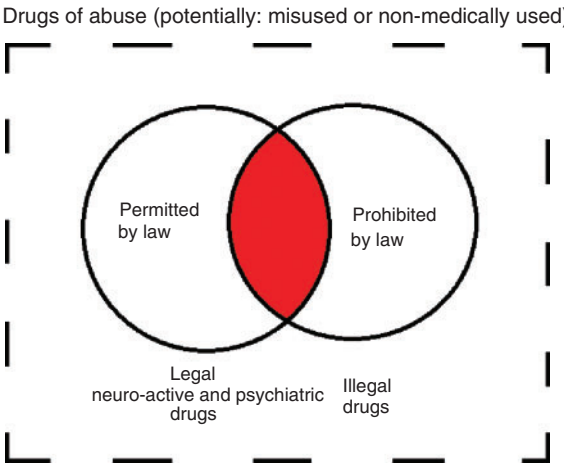



**Fig. 1.** Distinction between licit neuro-active and psychoactive pharmaceuticals, illegal drugs, and drugs of abuse.

year (http://www.unodc.org/unodc/secured/wdr/wdr2013/World_Drug_Report_2013.pdf, accessed 16 February 2016). Moreover, the total global spending on drugs is expected to increase in the near future.[7]

Licit drugs are those for which the prescription for medical use is permitted by law, and in the present review, we consider neuro and psychoactive pharmaceuticals that fall under the classes of amphetamine-type stimulants, benzodiazepines, barbiturates, antipsychotics, anaesthetics, anti-epileptics and mood stabilisers, opioids and cannabinoids.[2–4,8–15] Illicit drugs are those for which non-medical use is prohibited by law[5]; here, we group opioids, amphetamine-type stimulants, cannabinoids, sympathomimetic amines, hallucinogens and cocaine compounds under illicit drugs.[5,6] Misuse or non-medical use of substances, legal or illegal, is referred to as 'drug abuse' when it entails excessive or repeated use of chemical substances to achieve certain biochemical and physiological effects.[6] Drug abuse is common among 'poly-drug' users in order to enhance the effects of other simultaneously consumed drugs (or other drugs of abuse). In some cases, a drug may fall under two or more categories of licit drug, drug of abuse or illicit drug, depending on its usage (Fig. 1). Scientific and legal ambiguity still exists in the classification of licit and illicit drugs to a certain extent.

The presence of drugs in the environment has attracted a lot of recent attention; these compounds are designed to deliver a pharmacological effect, and therefore can have a detrimental effect on non-target organisms.[15] Although drugs are usually detected in surface waters at only trace levels (ng $L^{-1}$ to μg $L^{-1}$), they are of increasing concern owing to their continual introduction into the environment, development of drug resistance in pathogenic organisms, and chronic toxicity including potential for synergistic effects in non-target organisms.[13,16–23]

Wastewater treatment plants are an important source for the introduction of pharmaceuticals into the environment. Drugs enter the treatment plants directly through disposal into the sewage system and, indirectly, as human excretion products where they are present both as free and conjugated forms (e.g. glucuronides, sulfates). Because many of the drugs are enantiomeric, and enantiomers of a particular drug can, owing to their unique stereoselectivity, differ markedly in their biological or toxicological properties, the environmental fate of a drug (i.e. degradation, bioaccumulation, persistence and toxicity) can be considerably affected by the chirality.[19,20] However, the effect of chirality has been often overlooked in studies of environmental impacts, even though over 50 % of illicit drugs possess at least one chiral centre.[19,20]

Because the use of illicit drugs can instigate economic and social damage and can seriously affect users' health, information regarding usage patterns of illicit drugs in a community is important to take targeted actions against illicit drug consumption. Such information is generally obtained by means of population surveys, consumer interviews, medical records, crime statistics and seizure data. These indirect measures have several disadvantages, such as low objectivity, long study times and high costs. In recent years, analysis of wastewater has been shown to provide significant information with regard to trends and patterns of drug consumption in a population. The key concept is that the excreted drugs are rapidly pooled through the centralised sewage systems and reach the wastewater treatment plants. Valuable information can be obtained through calculation methodologies concerning the amount and type of drug consumed by a specific population. The innovative concept known as 'sewage epidemiology' was introduced in the early 2000s by Christian Daughton.[24]

The aims of the present review are to compile available data on the occurrence of 50 selected psychoactive pharmaceuticals and illicit drugs, both as parent compounds and their metabolites, in wastewater treatment plants and to demonstrate the application of the sewage epidemiology approach in the determination of illicit drug usage in communities. Furthermore, we discuss the significance of considering chirality of drugs for a more accurate elucidation of sources and pathways in the environment.

## Chemicals of concern

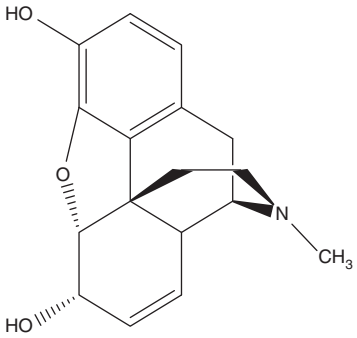
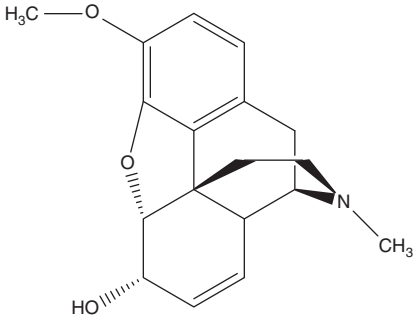
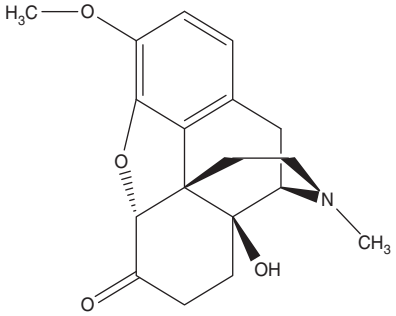
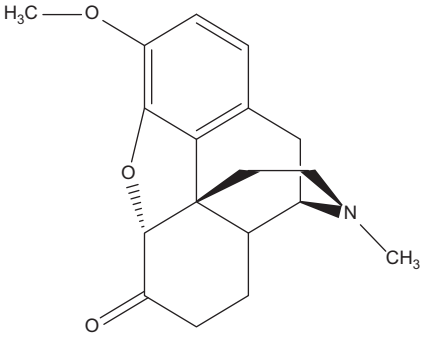
A brief introduction to target drugs and their metabolites is presented in the following section. The structure, chemical formula, molecular weight (g $mol^{-1}$), octanol–water partition coefficients (log P), and Chemical Abstracts Service (CAS) numbers are presented in Tables 1 to 11.

### *Opioids*

Opium and its derivatives have been known to relieve pain and alter mood.[21] Opioids can be classified into two categories: natural and synthetic. Natural opioids (opiates) are the naturally occurring alkaloids found in opium poppy plants (*Papaver somniferum*).[22] Popular natural opioids are morphine and codeine (Table 1).[22–24] Oxycodone, hydrocodone and buprenorphine are synthetic opioids that are synthesised from the (non-narcotic) alkaloid thebaine found in opium (Table 1).[23–27] Other known synthetic opioids are heroin (diacetylmorphine or diamorphine) and oxymorphone (Table 1).[22,26] Heroin is metabolised in human bodies into 6-monoacetylmorphine and morphine among others[23,28] (Table 1). Morphine, the major constituent of opium, can also be derived from codeine, heroin and 6-monoacetylmorphine.[10,29]

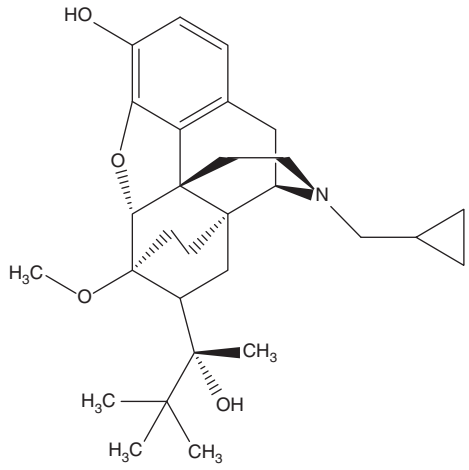
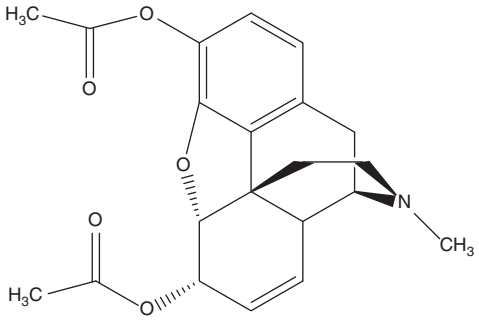
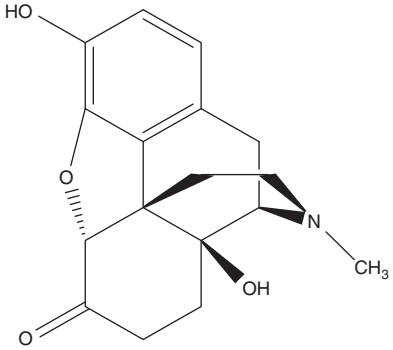
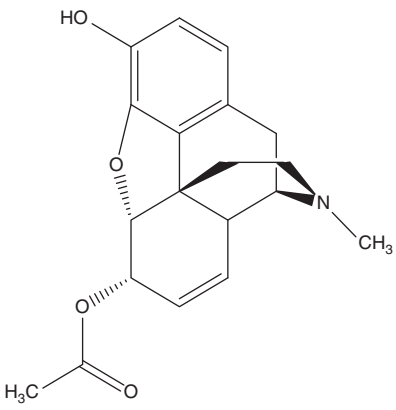
Synthetic opioids are designed to mimic the action of opiates. Methadone is an extensively abused opioid (Table 1). Methadone is also prescribed for patients in substance-abuse programs and has a readily quantifiable metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) (Table 1).[23,28,30,31] Morphine is excreted in urine as morphine-3β-D-glucuronide and morphine-6β-D-glucuronide or as free morphine.[10] Codeine is excreted in urine mainly (~70 %) as codeine-6-glucuronide.[10] However, these glucuronides are readily hydrolysed to their parent

**Table 1. Structure and some properties of target opioids**

| Chemical | Molecular structure | Molecular formula | Molecular weight (g $mol^{-1}$) | log P[149,150] (octanol–water) | CAS number |
|---|---|---|---|---|---|
| Morphine (MOR) |  | $C_{17}H_{19}NO_3$ | 285.34 | 1.07 | 57-27-2 |
| Codeine (COD) |  | $C_{18}H_{21}NO_3$ | 299.36 | 1.35 | 76-57-3 |
| Oxycodone (OC) |  | $C_{18}H_{21}NO_4$ | 315.36 | 0.91 | 76-42-6 |
| Hydrocodone (HC) |  | $C_{18}H_{21}NO_3$ | 299.36 | 1.83 | 125-29-1 |

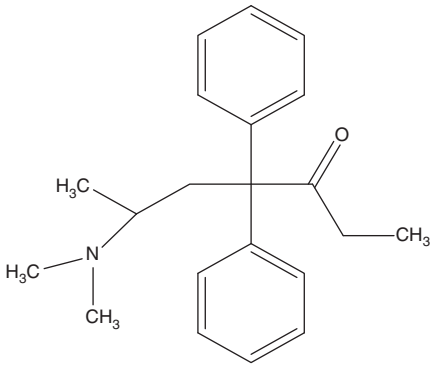
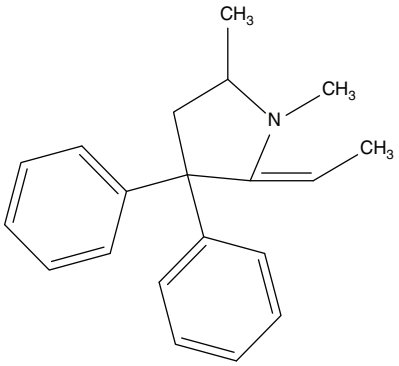
(*Continued*)

**Table 1. (Continued)**

| Chemical | Molecular structure | Molecular formula | Molecular weight (g mol$^{-1}$) | log P[149,150] (octanol–water) | CAS number |
|---|---|---|---|---|---|
| Buprenorphine (BN) |  | $C_{29}H_{41}NO_4$ | 467.64 | 3.43 | 52485-79-7 |
| Heroin (HER) |  | $C_{21}H_{23}NO_5$ | 369.41 | 1.88 | 561-27-3 |
| Oxymorphone (OXM) |  | $C_{17}H_{19}NO_4$ | 301.33 | 0.90 | 76-41-5 |
| 6-Mono-acetylmorphine (6-MAM) |  | $C_{19}H_{21}NO_4$ | 327.37 | 0.42 | 2784-73-8 |

(*Continued*)

**Table 1. (Continued)**

| Chemical | Molecular structure | Molecular formula | Molecular weight (g mol$^{-1}$) | log P[149,150] (octanol–water) | CAS number |
|---|---|---|---|---|---|
| Methadone (METH) |  | $C_{21}H_{27}NO$ | 309.45 | 4.77 | 76-99-3 |
| 2-Ethylidene-1, 5-dimethyl-3, 3-diphenylpyrrolidine (EDDP) |  | $C_{20}H_{23}N$ | 277.41 | 5.36 | 30223-73-5 |

compounds in untreated wastewater and during wastewater treatment.[10] Glucuronidated morphine has been detected in wastewater influent at low concentrations (2–18 ng L$^{-1}$), demonstrating the cleavage of the glucuronide bond in wastewater treatment processes.[29]

### *Cocaine and metabolites*

Cocaine is a naturally occurring alkaloid that is extracted from the leaves of *Erythroxylon coca*.[32] Cocaine consumption has increased during the last decade, reaching the second highest among the illicit drugs in Europe, after cannabis, with 4.3–4.75 million cocaine users in 2009.[33,34] Cocaine is excreted by humans partly unchanged but mainly as its metabolites, benzoylecgonine (BE) and ecgonine methyl ester (EME) (Table 2).[34] Following ingestion of cocaine, the unchanged drug and its metabolite benzoylecgonine are excreted in urine at 1–9 and 35–54 % of the initial dose respectively.[3] Based on the respective excretion rates and the molar masses of the two compounds, the cocaine/benzoylecgonine ratio in wastewater influents was expected to range between 0.02 and 0.27[3]; a ratio exceeding 0.27 can suggest cocaine sources originating from direct disposal of this drug into the sewage system.[3] However, it should be noted that cocaine and benzoylecgonine can also be excreted in human urine from the consumption of 'Health Inca Tea', a tea traditionally consumed in some countries, which has an average cocaine content of 4.8 mg per tea bag.[35]

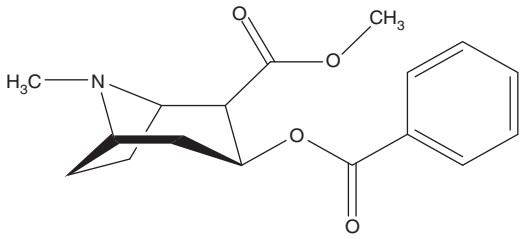
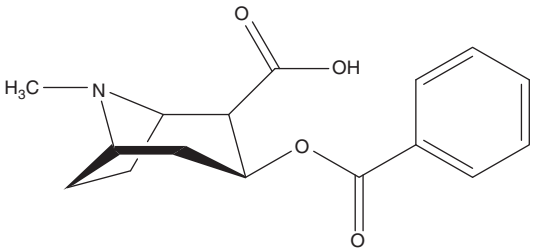
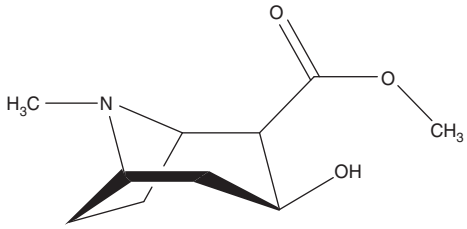
### *Amphetamine-type stimulants*

Amphetamine-type stimulants are a group of synthetic stimulants including amphetamine, methamphetamine, 3,4-methylenedioxy amphetamine (MDA or 'Love pills'), 3,4-methylenedioxy-*N*-methylamphetamine (MDMA or 'Ecstasy') and 3,4-methylenedioxy-N-ethyl-amphetamine (MDEA or 'Eve') (Table 3).[28,36,37] Amphetamine and methamphetamine are released into the environment through human excretion and discharges from clandestine laboratories.[38] As legal medications, amphetamine and methamphetamine are commonly prescribed for attention-deficit hyperactivity disorder, obesity and Parkinson's disease.[38,39] Amphetamine is also a metabolite of methamphetamine and of many other drugs (e.g. selegiline, amphetaminil and prenylamine).[40,41] The consumption rates of amphetamine and methamphetamine, as drugs of abuse, have exceeded those of heroin and cocaine.[5] The common abusive dose for MDA, MDMA and MDEA is 125–150 mg.[28]

### *Cannabinoids*

The most active cannabinoid in common use is $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC), which is the psychoactive constituent of cannabis (herbal cannabis or hashish), and it is one of the two cannabinoids licenced for medical use (the other one is nabilone, a synthetic analogue of $\Delta^9$-THC).[8,9,42] $\Delta^9$-THC is also used for the treatment of nausea caused by cancer chemotherapy and human immunodeficiency virus (HIV) therapy, neuropathic pain associated with multiple sclerosis, and suppression of spasticity.[9] $\Delta^9$-THC is the most widely used illicit drug (cannabis) followed by amphetamine, methamphetamine and MDMA.[5,34] In *Cannabis sativa*, $\Delta^9$-tetrahydrocannabinolic acid ($\Delta^9$-THCA) is the non-psychoactive precursor of $\Delta^9$-THC (Table 4).[9] It is found in fresh plant material, and ~90 % of the total $\Delta^9$-THC is available as $\Delta^9$-THCA.[9] When heated,

**Table 2. Structure and some properties of target cocaine and metabolites**

| Chemical | Molecular structure | Molecular formula | Molecular weight (g mol$^{-1}$) | log P[150] (octanol–water) | CAS number |
|---|---|---|---|---|---|
| Cocaine (COC) |  | $C_{17}H_{21}NO_4$ | 303.35 | 3.08 | 50-36-2 |
| Benzoylecgonine (BE) |  | $C_{16}H_{19}NO_4$ | 289.33 | 2.26 | 519-09-5 |
| Ecgonine methyl ester (EME) |  | $C_{10}H_{17}NO_3$ | 199.25 | –0.23 | 7143-09-1 |

metabolised, smoked or baked, $\Delta^9$-THCA is partially converted to $\Delta^9$-THC. Thus, $\Delta^9$-THCA can also be detected in the urine of cannabis consumers.[8,9] $\Delta^9$-THCA is also excreted as a glucuronide conjugate, but the conjugate is readily hydrolysed in untreated wastewater and in wastewater treatment processes.[43]

### *Lysergic compounds*

Lysergic acid diethylamide (LSD) is a highly potent hallucinogen and a well-known drug of abuse (Table 5).[44] The typical dose used by an abuser ranges from 25 to 150 mg, with doses above 20 mg necessary to produce psychotropic effects.[44] LSD is extensively metabolised in humans (unchanged LSD represents $<1$ % of the ingested dose)[44]; its main urinary metabolite is 2-oxo-3-hydroxy-lysergic acid diethylamide (OH-LSD) (Table 5).[45]

### *Benzodiazepines*

Benzodiazepines are the most frequently prescribed drugs (all drugs including psychoactive), and are widely used as tranquilisers, hypnotics, anaesthetics, anticonvulsants or muscle relaxants.[46] Major benzodiazepines that are in commerce are alprazolam (brand name: Xanax; Pfizer), bromazepam (brand name: Lexotan; Roche), chlordiazepoxide (brand name: Librium; Roche), diazepam (brand name: Valium; Roche), nordiazepam, flunitrazepam (brand name: Rohypnol; Roche), lorazepam, nitrazepam, oxazepam and temazepam (Table 6).[47–56] The presence of flunitrazepam in environmental and biological samples is commonly confirmed by measuring 7-aminoflunitrazepam, a pharmacologically active in vivo metabolite and in vitro degradation product (Table 6).[52,53] Nordiazepam and oxazepam are used as drugs, but they are also formed as metabolites of diazepam.[57]

### *Barbiturates: phenobarbital and pentobarbital*

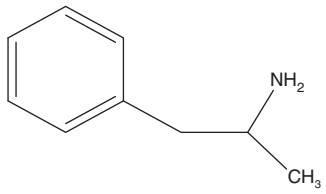
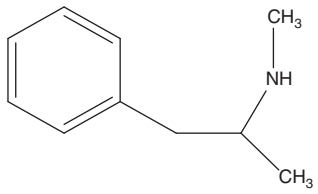
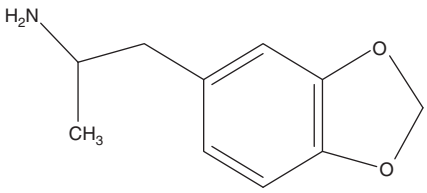
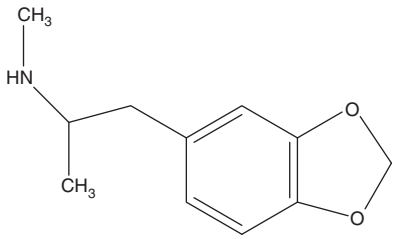
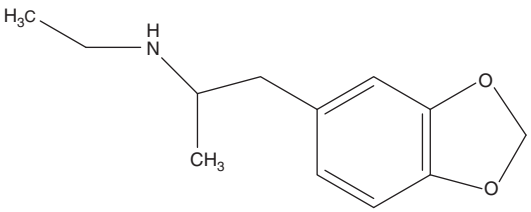
Barbiturates are occasionally used to treat patients suffering from seizures such as epilepsy.[11,58] Known barbiturate derivatives are phenobarbital (brand name: Luminal; Novelis) and pentobarbital (brand name: Nembutal; Lundbeck) (Table 7).[11,58] Phenobarbital belongs also to the class of antiepileptics and mood stabilisers. When used at their prescribed dosage, barbiturates produce their intended medical effect, but when used at higher doses, they elicit depression of the nervous system with several side-effects.[58] In recent years, barbiturates have been replaced by benzodiazepines.[58]

### *Antipsychotics and antischizophrenia pharmaceuticals*

Antipsychotic and antischizophrenia pharmaceuticals are used in the treatment of disorders such as schizophrenia, mania and delusional disorder.[59] The antipsychotic and antischizophrenia compounds are classified as ‘typical’ (or classic) or ‘atypical’ based on their main mechanism of action and the manifestation of side-effects associated with their pharmacological actions.[60]

Typical antipsychotics, such as chlorpromazine, maintain a precise pharmacological mechanism of action as potent dopamine D2 receptor (D2R protein) antagonists [60] (Table 8).

**Table 3. Structure and some properties of target amphetamine-type stimulants**

| Chemical | Molecular structure | Molecular formula | Molecular weight (g mol$^{-1}$) | log P[150] (octanol–water) | CAS number |
|---|---|---|---|---|---|
| Amphetamine (Amp) |  | $C_9H_{13}N$ | 135.21 | 1.81 | 300-62-9 |
| Methamphetamine (MAmp) |  | $C_{10}H_{15}N$ | 149.23 | 2.20 | 537-46-2 |
| 3,4-Methylenedioxy-amphetamine (MDA or 'Love pills') |  | $C_{10}H_{13}NO_2$ | 179.22 | 1.67 | 4764-17-4 |
| 3,4-Methylenedioxy-N-methylamphetamine (MDMA or 'Ecstasy') |  | $C_{11}H_{15}NO_2$ | 193.24 | 1.81 | 42542-10-9 |
| 3,4-Methylenedioxy-N-ethyl-amphetamine (MDEA or 'Eve') |  | $C_{12}H_{17}NO_2$ | 207.27 | 2.34 | 82801-81-8 |

Atypical antipsychotics maintain multiple modes of pharmacological action and elicit various therapeutic and toxic side-effects.[60] Clozapine, norclozapine and risperidone (brand name: Belivon; Janssen-Cilag GmbH) are known 'atypical' antipsychotics (Table 8).[60] Risperidone is extensively metabolised in the liver by hydroxylation to its main pharmacoactive metabolite, 9-hydroxyrisperidone, which has been investigated for the treatment of schizophrenia (brand name: Paliperidone; Janssen-Cilag GmbH) (Table 8).[60]

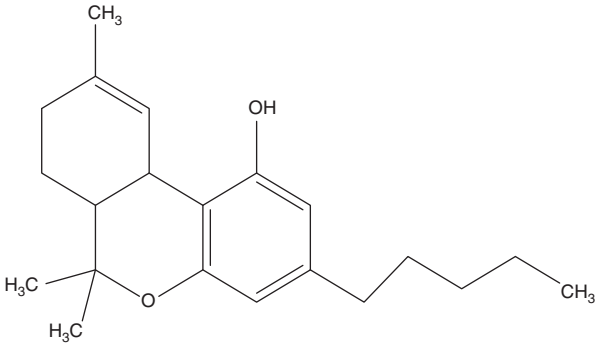
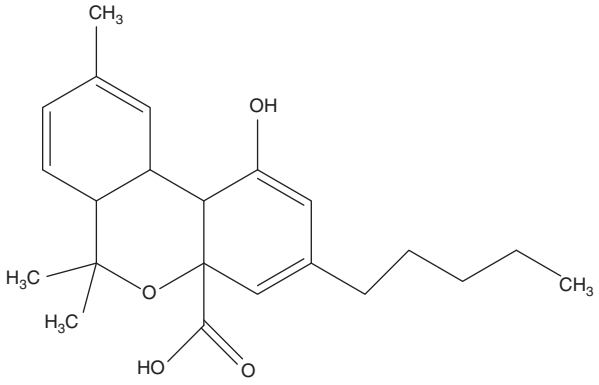
### *Anaesthetics*

In addition to producing the desired anaesthesia, anaesthetics also can induce various side effects.[61] Known anaesthetics include lidocaine (brand name: Xylocaine; AstraZeneca), fentanyl, thiopental and ketamine (Table 9). Lidocaine is widely used as a local anaesthetic and anti-arrhythmic agent for cardiac disorders.[62] Fentanyl, an opioid, is a narcotic analgesic used as a surgical anaesthetic and for the treatment of pain in cancer patients.[58,61,63] The main metabolite of fentanyl is norfentanyl (Table 9).[63] Thiopental is a general anaesthetic and is also a barbiturate.[58] Ketamine is used for premedication, sedation, post-operative analgesia, and induction or maintenance of general anaesthesia[61]; it is also used in trauma victims, patients with hypovolemic and septic shock, and pulmonary diseases.[61] Norketamine is the main metabolite of ketamine (Table 9).[61]

### *Anti-epileptics and mood stabilisers: carbamazepine and primidone*

There is an overlap between anti-epileptics in the neurological literature and mood stabilisers in the psychiatric literature.[64] Well-known drugs in this broader category (anti-epileptics and mood stabilisers) are carbamazepine and primidone (Table 10).[64]

**Table 4. Structure and some properties of target cannabinoids**

| Chemical | Molecular structure | Molecular formula | Molecular weight (g mol$^{-1}$) | log P[150] (octanol–water) | CAS number |
|---|---|---|---|---|---|
| Tetrahydrocannabinol ($\Delta^9$-THC) |  | $C_{21}H_{30}O_2$ | 314.46 | 7.68 | 1972-08-3 |
| Tetra-hydrocannabinolic acid ($\Delta^9$-THCA) |  | $C_{22}H_{30}O_4$ | 358.47 | Not available | 23978-85-0 |

Carbamazepine is a classic anti-epileptic that maintains an antimanic activity,[64] whereas primidone is mainly used for epilepsy.[64] Phenobarbital, oxazepam and diazepam (see *Benzodiazepines* and *Barbiturates: phenobarbital and pentobarbital* sections) are some of the metabolites of primidone.[65]

### *Sympathomimetic amines: ephedrine and phenylpropanolamine*

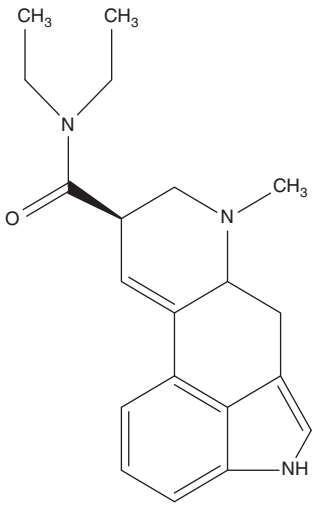
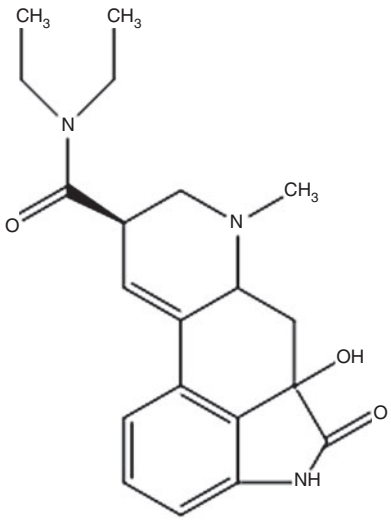
Ephedra ('ma huang') is a herbal source of ephedrine, a natural sympathomimetic amine mainly used as a stimulant, appetite suppressant and decongestant (Table 11).[66] Even though primidone is efficacious in the treatment of numerous ailments, it is a potentially harmful stimulant.[66] Phenylpropanolamine (norephedrine or pseudoephedrine; PPA) is a synthetic sympathomimetic amine that is mainly used as a decongestant and anorectic agent (Table 11).[67] Ephedrine and pseudoephedrine are other amphetamine-type stimulant derivatives.[66–68]

## Occurrence of drugs in wastewater treatment processes

Studies on the environmental occurrence of pharmaceuticals and drugs have greatly increased over the past decade.[69–148] Analysis of wastewater for drugs was first introduced in 1998 by Ternes and coworkers to assess the effectiveness of treatment plants to remove pharmaceuticals.[69] A large number of studies have been published and several reviews have appeared on this regard. In the present review, we compiled recent studies on the occurrence of the aforementioned drugs in wastewater treatment plants. Some of the target compounds mentioned above have been extensively studied, whereas for other compounds, the data available are still sparse. Very few studies have reported on the occurrence of drugs in sludge and particulate fraction of wastewater. This is because of the presumption that drugs are highly water-soluble and that the dissolved fraction contains the majority, if not all, of the pharmaceutical load. Nevertheless, a few recent studies have shown that particulate matter does contain a significant proportion of drugs that have high log P values. It must be noted that if there were partitioning or retention of drugs onto particulate matter or sludge, estimates of community drug consumption on the basis of the sewage epidemiology approach could be grossly underestimated.[70] The US National Research Council pointed out the lack of information on pharmaceuticals in sludge and biosolids, and highlighted the need for further research on bioactive chemicals in sludge.[57,71]

The fate (including the removal mechanisms) of drugs in wastewater treatment plants depends on the substances' physiochemical properties and biodegradability.[72,73] These treatment plants were originally designed to reduce conventional pollution parameters such as biochemical oxygen demand. They incorporate a secondary treatment step, the biological treatment, with the aim to degrade pollutants through contact with 'activated sludge'.[73] Activated sludge is a process for treating wastewaters using air and cultivated microorganisms; chemicals not biodegraded, desorbed or volatilised through this process are eventually discharged through effluents

**Table 5. Structure and some properties of target lysergic compounds**

| Chemical | Molecular structure | Molecular formula | Molecular weight (g $mol^{-1}$) | log P[150] (octanol–water) | CAS number |
|---|---|---|---|---|---|
| Lysergic acid diethylamide (LSD) |  | $C_{20}H_{25}N_3O$ | 323.43 | 2.74 | 50-37-3 |
| 2-Oxo-3-hydroxy-lysergic acid diethylamide (OH-LSD) |  | $C_{20}H_{25}N_3O_3$ | 355.43 | Not available | 111295-09-1 |

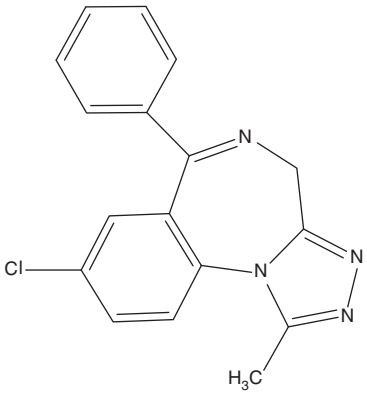
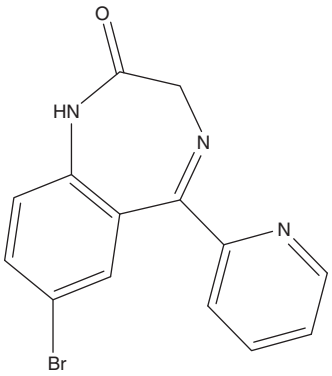
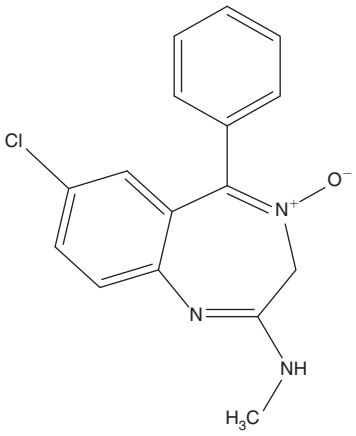
into the surface waters.[73] Contamination of soil and surface water can still occur through the disposal of sludge for agricultural purposes.[74] Modern treatment plants are equipped with advanced processes (e.g. ozonation, $O_3$/UV, $O_3/H_2O_2$, ultrafiltration, reverse osmosis, granular activated carbon and membrane biological reactors) to facilitate the removal of organic pollutants from influents.[75–81] In addition, the removal of pharmaceuticals in wastewater is being examined through the application of other technologies such as constructed wetlands, surface flow systems (lagoons or anaerobic or facultative ponds), horizontal subsurface flow systems, and vertical subsurface flow systems.[76,80]

### *Opioids*

Occurrence of opioids in wastewater treatment plants has been reported extensively, with most reports originating from the European countries (Table 12). Among opioids, morphine, 6-monoacetylmorphine, methadone, codeine and EDDP are the most studied compounds (Table 12). The reported concentration ranges in effluents were usually only 20–70 % of the levels found in influents (Table 12). Opioids were found in 84–100 % of influent and effluent samples from Switzerland,[82] and in 75–100 % samples from the UK.[84] Based on our meta-analysis, the rank order of wastewater concentrations of opioids was: codeine > morphine > EDDP > methadone > 6-monoacetylmorphine > heroin. The high morphine concentrations can be attributed to several factors including high abuse of heroin, use of morphine in pain management and cough suppression formulations, and use of poppy seeds in bakery products.[82] The high detection rates and concentrations of 6-monoacetylmorphine and EDDP in wastewaters indicate that future studies need to focus on these metabolites to assess the mass loads of the respective precursor compounds, heroin and methadone.

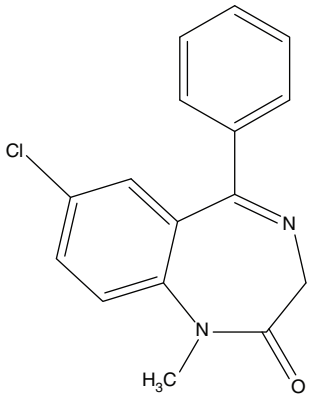
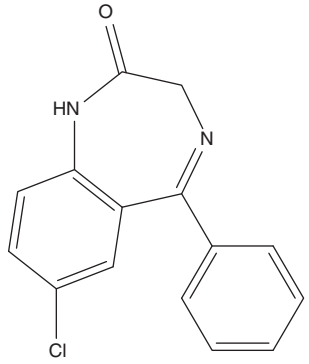
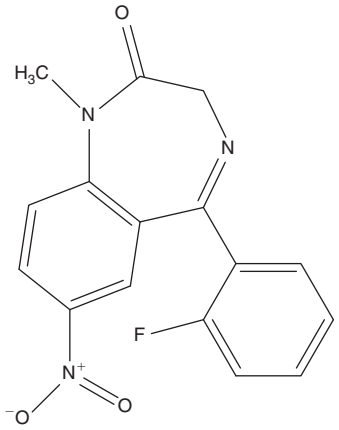
Oxycodone, hydrocodone, buprenorphine and oxymorphone are the less-studied opioids in wastewater treatment plants, and very few studies have reported their concentrations. Hydrocodone and oxycodone were found in influents and in effluents from 12 German treatment plants; the median concentrations of hydrocodone and oxycodone were $<50$ and $<20$ ng $L^{-1}$

**Table 6. Structure and some properties of target benzodiazepines**

| Chemical | Molecular structure | Molecular formula | Molecular weight (g $mol^{-1}$) | log P[150] (octanol–water) | CAS number |
|---|---|---|---|---|---|
| Alprazolam (Xanax) (ALPZ) |  | $C_{17}H_{13}ClN_4$ | 308.76 | 2.50 | 28981-97-7 |
| Bromazepam (Lexotan) (BROZ) |  | $C_{14}H_{10}BrN_3O$ | 316.15 | 1.65 | 1812-30-2 |
| Chlordiazepoxide (Librium) (CHDIAZ) |  | $C_{16}H_{14}ClN_3O$ | 299.75 | 2.16 | 58-25-3 |

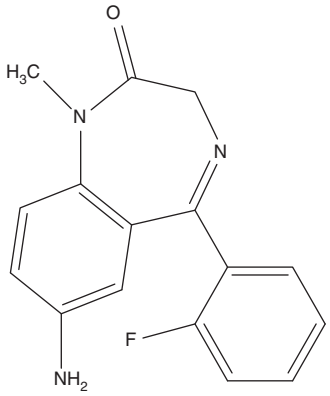
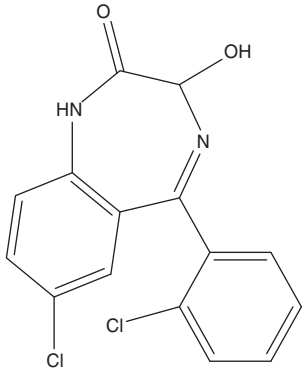
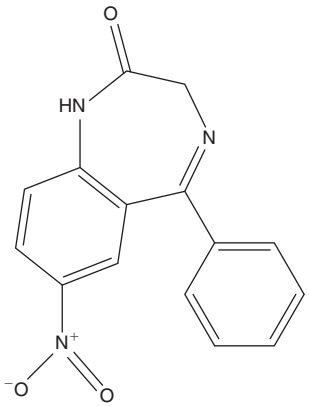
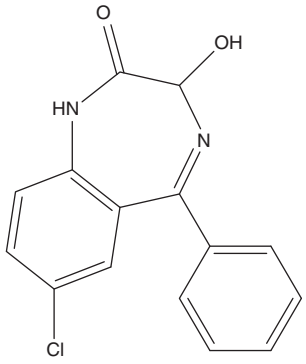
(*Continued*)

**Table 6. (Continued)**

| Chemical | Molecular structure | Molecular formula | Molecular weight (g mol$^{-1}$) | log P[150] (octanol–water) | CAS number |
|---|---|---|---|---|---|
| Diazepam (Valium) (DIAZ) |  | $C_{16}H_{13}ClN_2O$ | 284.74 | 2.91 | 439-14-5 |
| Nordiazepam (Nordazepam) (NORDZ) |  | $C_{15}H_{11}ClN_2O$ | 270.71 | 3.15 | 1088-11-5 |
| Flunitrazepam (Rohypnol) (FLUZ) |  | $C_{16}H_{12}FN_3O_3$ | 313.28 | 1.44 | 1622-62-4 |

(*Continued*)

**Table 6. (Continued)**

| Chemical | Molecular structure | Molecular formula | Molecular weight (g $mol^{-1}$) | log P[150] (octanol–water) | CAS number |
|---|---|---|---|---|---|
| 7-Amino-flunitrazepam (AFLUZ) |  | $C_{16}H_{14}FN_3O$ | 283.30 | 0.80 | 34084-50-9 |
| Lorazepam (LORZ) |  | $C_{15}H_{10}Cl_2N_2O_2$ | 321.16 | 2.47 | 846-49-1 |
| Nitrazepam (NITZ) |  | $C_{15}H_{11}N_3O_3$ | 281.27 | 2.18 | 146-22-5 |
| Oxazepam (OXAZ) |  | $C_{15}H_{11}ClN_2O_2$ | 286.71 | 2.31 | 604-75-1 |

(*Continued*)

**Table 6. (Continued)**

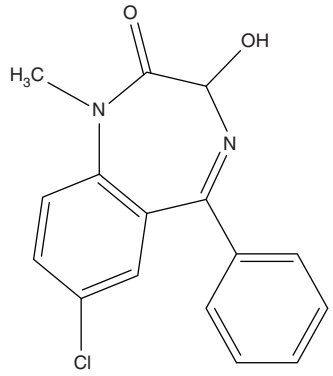
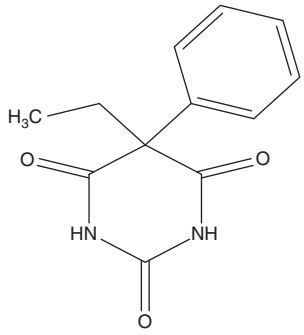
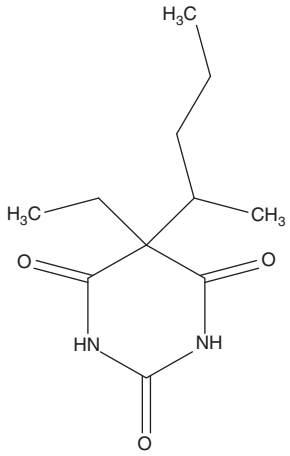
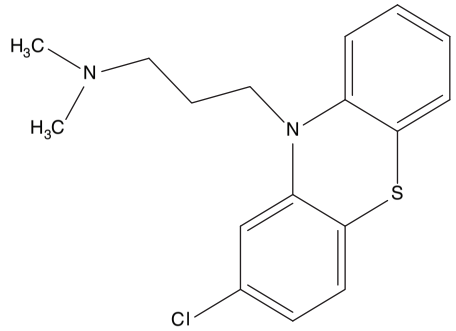
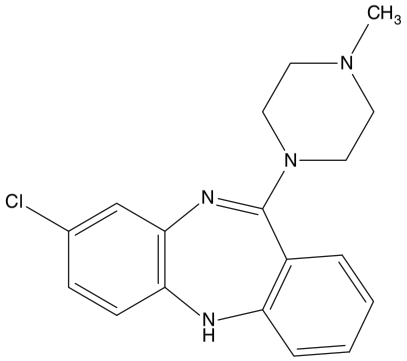
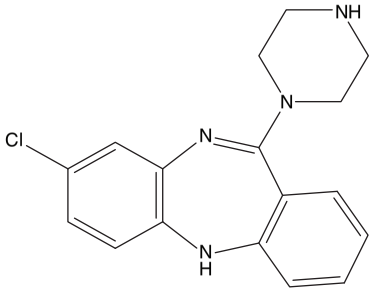
| Chemical | Molecular structure | Molecular formula | Molecular weight (g mol$^{-1}$) | log P[150] (octanol–water) | CAS number |
|---|---|---|---|---|---|
| Temazepam (TEMZ) |  | $C_{16}H_{13}ClN_2O_2$ | 300.74 | 2.15 | 846-50-4 |

**Table 7. Structure and some properties of target barbiturates**

| Chemical | Molecular structure | Molecular formula | Molecular weight (g mol$^{-1}$) | log P[150] (octanol–water) | CAS number |
|---|---|---|---|---|---|
| Phenobarbital (Luminal) (PHBAR) |  | $C_{12}H_{12}N_2O_3$ | 232.24 | 1.67 | 50-06-6 |
| Pentobarbital (Nembutal) (PEBAR) |  | $C_{11}H_{18}N_2O_3$ | 226.27 | 2.05 | 76-74-4 |

respectively.[83] Buprenorphine was reported in 25 treatment plants in France, and was detected in influents at concentrations ranging from 40 to 195 ng L$^{-1}$ and occasionally in effluents (<40 ng L$^{-1}$).[30] A study from the UK reported oxycodone and oxymorphone at a detection rate of 61 and 38 % in influent samples respectively, and at 58 and 10 % in effluent samples respectively.[84] Buprenorphine was less frequently detected in influents and effluents at a concentration range of 4–112 ng L$^{-1}$.[84] These data indicate that opioids are not removed efficiently in treatment plants, and there is also

**Table 8. Structure and some properties of target antipsychotics and antischizophrenia pharmaceuticals**

| Chemical | Molecular structure | Molecular formula | Molecular weight (g $mol^{-1}$) | log P[150] (octanol–water) | CAS number |
|---|---|---|---|---|---|
| Chlorpromazine (CHZN) |  | $C_{17}H_{19}ClN_2S$ | 318.86 | 5.20 | 50-53-3 |
| Clozapine (CLOZN) |  | $C_{18}H_{19}ClN_4$ | 326.82 | 2.36 | 5786-21-0 |
| Norclozapine (NORZN) |  | $C_{17}H_{17}ClN_4$ | 312.80 | 1.97 | 6104-71-8 |

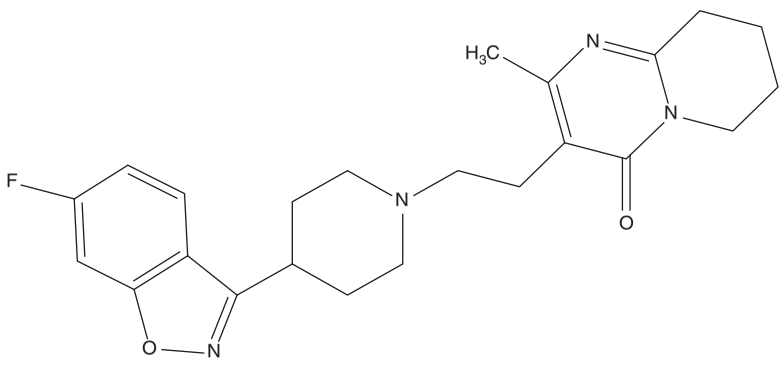
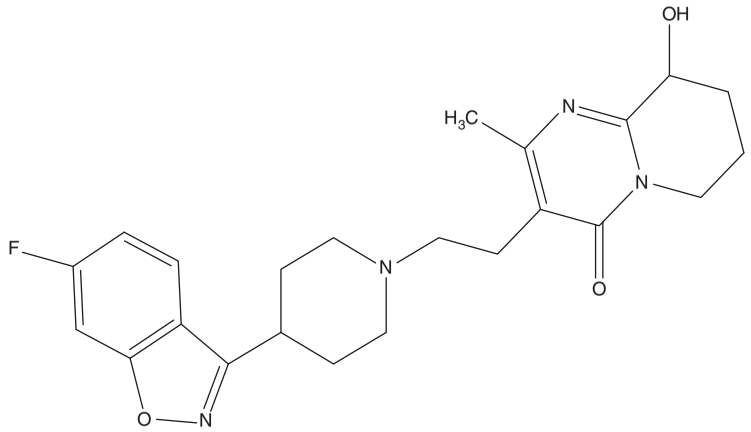
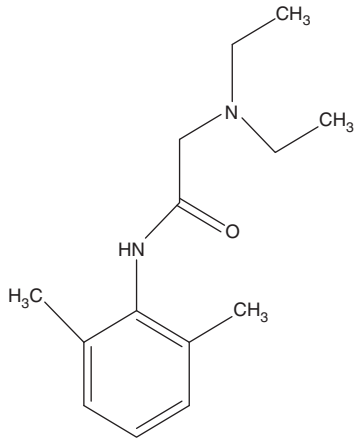
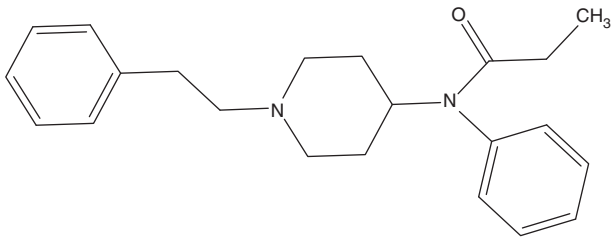
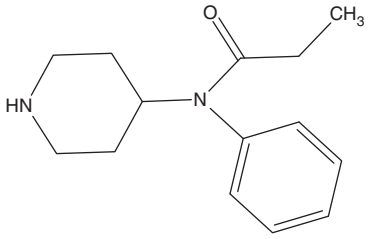
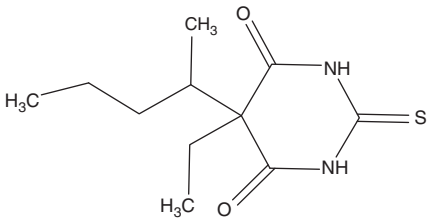
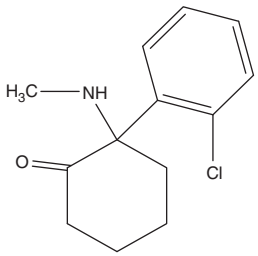
| | | | | | |
|---|---|---|---|---|---|
| Risperidone (Belivon) (RISP) |  | $C_{23}H_{27}FN_4O_2$ | 410.48 | 2.88 | 106266-06-2 |
| 9-OH-Risperidone or Paliperidone (OH-RISP) |  | $C_{23}H_{27}FN_4O_3$ | 426.48 | 1.52 | 147687-18-1 |

**Table 9. Structure and some properties of target anaesthetics**

| Chemical | Molecular structure | Molecular formula | Molecular weight (g mol$^{-1}$) | log P[150] (octanol–water) | CAS number |
|---|---|---|---|---|---|
| Lidocaine (Xylocaine) (LIDC) |  | $C_{14}H_{22}N_2O$ | 234.34 | 2.36 | 137-58-6 |
| Fentanyl (FENL) |  | $C_{22}H_{28}N_2O$ | 336.47 | 3.89 | 437-38-7 |
| Norfentanyl (NORL) |  | $C_{14}H_{20}N_2O$ | 232.32 | 1.59 | 1609-66-1 |
| Thiopental (THIL) |  | $C_{11}H_{18}N_2O_2S$ | 242.34 | 2.99 | 76-75-5 |
| Ketamine (KETN) |  | $C_{13}H_{16}ClNO$ | 237.73 | 2.18 | 1867-66-9 |

(*Continued*)

**Table 9. (Continued)**

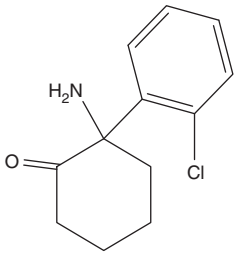
| Chemical | Molecular structure | Molecular formula | Molecular weight (g mol$^{-1}$) | log P[150] (octanol–water) | CAS number |
|---|---|---|---|---|---|
| Norketamine (NORT) |  | $C_{12}H_{14}ClNO$ | 223.70 | 1.96 | 35211-10-0 |

**Table 10. Structure and some properties of target anti-epileptics and mood stabilisers**

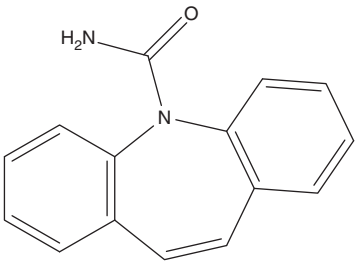
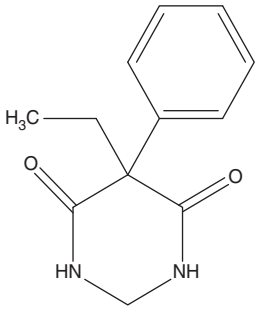
| Chemical | Molecular structure | Molecular formula | Molecular weight (g mol$^{-1}$) | log P[150] (octanol–water) | CAS number |
|---|---|---|---|---|---|
| Carbamazepine (CBZ) |  | $C_{15}H_{12}N_2O$ | 236.27 | 2.67 | 298-46-4 |
| Primidone (PRD) |  | $C_{12}H_{14}N_2O_2$ | 218.25 | 0.40 | 125-33-7 |

**Table 11. Structure and some properties of target sympathomimetic amines**

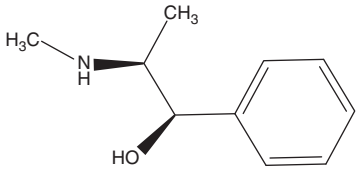
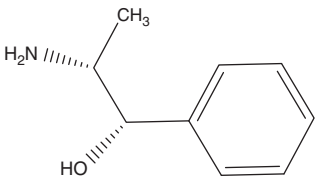
| Chemical | Molecular structure | Molecular formula | Molecular weight (g mol$^{-1}$) | log P[150] (octanol–water) | CAS number |
|---|---|---|---|---|---|
| Ephedrine (EPH) |  | $C_{10}H_{15}NO$ | 165.23 | 1.05 | 299-42-3 |
| Phenylpropanolamine (norephedrine or pseudoephedrine; PPA) |  | $C_9H_{13}NO$ | 151.21 | 0.81 | 700-65-2 |

**Table 12. Concentrations of opioids reported in wastewater treatment plants ($WWTP_A$ and $WWTP_B$) from several countries**
EDDP, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; –, not available

| Samples | Country | Range (or single value) (ng $L^{-1}$, unless stated otherwise) | Mean, geometrical mean or median (ng $L^{-1}$, unless stated otherwise) | References |
|---|---|---|---|---|
| Influents | Switzerland | Morphine: <20–1970 | Mean: 1007 | [82] |
| | | 6-Monoacetylmorphine: <20–82 | Mean: 38 | |
| | | Codeine: <20–389 | Mean: 228 | |
| | | Methadone: 42–202 | Mean: 112 | |
| | | EDDP: 153–634 | Mean: 315 | |
| Effluents | | Morphine: 84–1270 | Mean: 929 | |
| | | 6-Monoacetylmorphine: <20 | Mean: 5 | |
| | | Codeine: 94–274 | Mean: 204 | |
| | | Methadone: 44–128 | Mean: 65 | |
| | | EDDP: 151–442 | Mean: 294 | |
| Influents | Italy, Switzerland | Morphine: – | Mean: 83 (Italy); 204 (Switzerland) | [29] |
| | | 6-Monoacetylmorphine: – | Mean: 12 (Italy); 10 (Switzerland) | |
| | | Methadone: – | Mean: 12 (Italy); 50 (Switzerland) | |
| | | EDDP: – | Mean: 20 (Italy); 91 (Switzerland) | |
| Effluents | | Morphine: not quantified | – | |
| | | 6-Monoacetylmorphine: not quantified | – | |
| | | Methadone: – | Mean: 9 (Italy); 36 (Switzerland) | |
| | | EDDP: – | Mean: 23 (Italy); 72 (Switzerland) | |
| Influents (5 treatment plants) | Spain (Catalonia) | Morphine: <7–97 | – | [8] |
| | | 6-Monoacetylmorphine: not quantified | – | |
| | | Codeine: 18–120 | – | |
| | | Methadone: 4–24 | – | |
| | | EDDP: 5–41 | – | |
| | | Heroin: not quantified | – | |
| Effluents (5 treatment plants) | | Morphine: <7–81 | – | |
| | | 6-Monoacetylmorphine: not quantified | – | |
| | | Codeine: 3–397 | – | |
| | | Methadone: 4–25 | – | |
| | | EDDP: 5–57 | – | |
| | | Heroin: not quantified | – | |
| Primary effluents | Spain | Morphine: 104–166 | – | [75] |
| | | Codeine: 243–337 | – | |
| | | EDDP: 14–29 | – | |
| Secondary effluents | | Morphine: 79–138 | – | |
| | | Codeine: 152–189 | – | |
| | | EDDP: 33–75 | – | |
| Tertiary effluents | | Morphine: 2–53 | – | |
| | | Codeine: 4–17 | – | |
| | | EDDP: <8 | – | |
| Influents (12 treatment plants) | Germany | Morphine: max. 820 | Median: 310 | [83] |
| | | Codeine: max. 540 | Median: 220 | |
| | | Hydrocodone: max. 95 | Median: <50 | |
| | | Oxycodone: max. 70 | Median: <20 | |
| Effluents (12 treatment plants) | | Morphine: max. 110 | Median: 40 | |
| | | Codeine: max. 260 | Median: 85 | |
| | | Hydrocodone: max. 50 | Median: <50 | |
| | | Oxycodone: max. <20 | Median: <20 | |
| Influents (25 treatment plants) | France | Morphine: 71–1637 | – | [30] |
| | | Methadone: <40–234 | – | |
| | | EDDP: 6–260 | – | |
| | | Heroin: 52–82 | – | |
| | | 6-Monoacetylmorphine: <40–136 | – | |
| | | Buprenorphine: 40–195 | – | |
| Effluents (25 treatment plants) | | Morphine: <40–902 | – | |
| | | Methadone: <40–145 | – | |
| | | EDDP: 10–246 | – | |
| | | Heroin: not detected | – | |
| | | 6-Monoacetylmorphine: – | – | |
| | | Buprenorphine: <40 | – | |

(*Continued*)

**Table 12. (Continued)**

| Samples | Country | Range (or single value) (ng $L^{-1}$, unless stated otherwise) | Mean, geometrical mean or median (ng $L^{-1}$, unless stated otherwise) | References |
|---|---|---|---|---|
| Influents (7 treatment plants) | UK | Morphine: 66–986 | Median: 371 | [84] |
| | | Codeine: 236–3973 | Median: 1256 | |
| | | Methadone: 3–171 | Median: 66 | |
| | | EDDP: 4–342 | Median: 81 | |
| | | Heroin: not detected | – | |
| | | 6-Monoacetylmorphine: 3–224 | Median: 9 | |
| | | Oxycodone: 5–49 | Median: 9 | |
| | | Buprenorphine: 20–73 | Median: 47 | |
| | | Oxymorphone: 11–31 | Median: 15 | |
| Effluents (7 treatment plants) | | Morphine: 13–267 | Median: 59 | |
| | | Codeine: 10–1502 | Median: 372 | |
| | | Methadone: 1–91 | Median: 42 | |
| | | EDDP: 3–162 | Median: 32 | |
| | | Heroin: not detected | – | |
| | | 6-Monoacetylmorphine:1–8 | Median: 2 | |
| | | Oxycodone: 2–35 | Median: 7 | |
| | | Buprenorphine: 4–112 | Median: 15 | |
| | | Oxymorphone: 2–11 | Median: 8 | |
| Particulate matter of influents | UK | Morphine: 19–116 ng $g^{-1}$ | – | [85] |
| | | Codeine: 59–240 ng $g^{-1}$ | – | |
| | | Methadone: 19–58 ng $g^{-1}$ | – | |
| | | EDDP: 30–194 ng $g^{-1}$ | – | |
| | | Heroin: not detected | – | |
| | | 6-Monoacetylmorphine: – | – | |
| | | Buprenorphine: max. 3 ng $g^{-1}$ (rarely detected) | – | |
| Influents (2 treatment plants) | Taiwan | Morphine: $WWTP_A$: 40 | – | [86] |
| | | $WWTP_B$: 71 | – | |
| | | Codeine: $WWTP_A$: 26 | – | |
| | | $WWTP_B$: 67 | – | |
| | | 6-Monoacetylmorphine: $WWTP_A$: not quantified | – | |
| | | $WWTP_B$: not quantified | – | |
| Effluents (2 treatment plants) | | Morphine: $WWTP_A$: not quantified | – | |
| | | $WWTP_B$: not quantified | – | |
| | | Codeine: $WWTP_A$: 29 | – | |
| | | $WWTP_B$: 59 | – | |
| | | 6-Monoacetylmorphine: $WWTP_A$: not quantified | – | |
| | | $WWTP_B$: not quantified | – | |
| Influents (2 treatment plants) | Canada | Morphine: $WWTP_A$: max. 24 | Mean: 18 | [123] |
| | | $WWTP_B$: max. 4 | Mean: 2 | |
| | | Codeine: $WWTP_A$: max. 234 | Mean: 177 | |
| | | $WWTP_B$: max. 31 | Mean: 22 | |
| | | Oxycodone: $WWTP_A$: max. 93 | Mean: 66 | |
| | | $WWTP_B$: max. 10 | Mean: 1 | |
| | | Methadone: $WWTP_A$: not detected | – | |
| | | $WWTP_B$: max. 3 | Mean: 2 | |
| | | EDDP: $WWTP_A$: not detected | – | |
| | | $WWTP_B$: max. 15 | Mean: 15 | |
| Effluents (2 treatment plants) | | Morphine: $WWTP_A$: max. 18 | Mean: 13 | |
| | | $WWTP_B$: max. 4 | Mean: 4 | |
| | | Codeine: $WWTP_A$: max. 1139 | Mean: 893 | |
| | | $WWTP_B$: max. 18 | Mean: 15 | |
| | | Oxycodone: $WWTP_A$: max. 235 | Mean: 220 | |
| | | $WWTP_B$: max. 10 | Mean: 9 | |
| | | Methadone: $WWTP_A$: max.171 | Mean: 128 | |
| | | $WWTP_B$: max. 9 | Mean: 9 | |
| | | EDDP: $WWTP_A$: max. 254 | Mean: 193 | |
| | | $WWTP_B$: max. 12 | Mean: 11 | |

**Table 13. Concentrations of cocaine and metabolites reported in wastewater treatment plants from several countries**
EME, ecgonine methyl ester

| Samples | Country | Range (or single value) (ng $L^{-1}$, unless stated otherwise) | Mean, geometrical mean or median (ng $L^{-1}$, unless stated otherwise) | References |
|---|---|---|---|---|
| Influents (5 treatment plants) | Netherlands | Cocaine: 99–957<br>Benzoylecgonine: 260–3701 | –<br>– | [87] |
| Effluents (5 treatment plants) | | Cocaine: <6–235<br>Benzoylecgonine: <2–351 | –<br>– | |
| Influents (2 treatment plants) | Belgium | Cocaine: –<br>Benzoylecgonine: –<br>EME: – | Mean (monthly range): 243–409<br>Mean (monthly range): 519–846<br>Mean (monthly range): 115–180 | [90] |
| Influents (7 treatment plants) | Spain | Cocaine: 195–961<br>Benzoylecgonine: 545–3790 | Median: 384<br>Median: 1310 | [3] |
| Effluents (7 treatment plants) | | Cocaine: 2–31<br>Benzoylecgonine: 4–510 | Median: 17<br>Median: 115 | |
| Influents (4 treatment plants) | Spain | Cocaine: 316–861<br>Benzoylecgonine: 1020–4226 | –<br>– | [88] |
| Effluents (4 treatment plants) | | Cocaine: 6–105<br>Benzoylecgonine: 30–220 | –<br>– | |
| Primary effluents (1 treatment plant) | Spain | Cocaine: 160–2486<br>Benzoylecgonine: 1169–3336 | –<br>– | [75] |
| Secondary effluents (1 treatment plants) | | Cocaine: <10<br>Benzoylecgonine:14–47 | –<br>– | |
| Tertiary effluents (1 treatment plant) | | Cocaine: <9<br>Benzoylecgonine: 1–42 | –<br>– | |
| Influents (Castellón treatment plant) | Spain | Cocaine: –<br>Benzoylecgonine: – | Mean (weekly concentrations) for 2011 and 2012: 400 and 450 respectively<br>Mean (weekly concentrations) for 2011 and 2012: 1000 and 1400 respectively | [89] |
| Influents (37 treatment plants) | Belgium | Cocaine: 10–753<br>Benzoylecgonine: 33–2258<br>EME: <20 | –<br>–<br>– | [91] |
| Influents (25 treatment plants) | France | Cocaine: max. 1532<br>Benzoylecgonine: max. 3050<br>EME: max. 761 | –<br>–<br>– | [30] |
| Effluents (25 treatment plants) | | Cocaine: max. 335<br>Benzoylecgonine: max. 910<br>EME: max. 137 | –<br>–<br>– | |
| Influents | Italy, Switzerland | Cocaine:–<br>Benzoylecgonine: – | Mean: 421 (Italy); 218 (Switzerland)<br>Mean: 547 (Italy); 1132 (Switzerland) | [29] |
| Effluents | | Cocaine: –<br>Benzoylecgonine: – | Mean: not quantified (Italy); 11 (Switzerland)<br>Mean: not quantified (Italy); 100 (Switzerland) | |
| Particulate matter of wastewater influents | UK | Cocaine: 1.8–2.1 ng $g^{-1}$<br>Benzoylecgonine: 0.1–1.1 ng $g^{-1}$<br>EME: not detected | –<br>–<br>– | [85] |

evidence that at least some of these compounds are not removed completely even after tertiary treatment. For example, effluent from a wastewater treatment plant in Spain contained morphine (2–53 ng $L^{-1}$) and codeine (4–17 ng $L^{-1}$) even after tertiary treatment involving chlorination, coagulation and flocculation, laminar clarification and sand filtration (Table 12).[75]

Sorption of opioids on particulate matter has been reported in wastewater influents; the proportion of the total associated with particulate material varied with the compound from low sorption for codeine (1.9–5.2 %) and morphine (2.0–5.6 %) to higher sorption for methadone (8.1–18.6 %) and EDDP (12.1–34.5 %) (Table 12).[85] These differences in particulate matter sorption can be explained by the high log $K_{OC}$ (partition coefficient) and low water solubilities of opioids.[130] These data suggest that calculations of mass loadings of methadone and EDDP based only on the concentration in the aqueous fraction can significantly underestimate the total load in wastewater influents.

### *Cocaine and metabolites*

Occurrence of cocaine and its metabolites (benzoylecgonine and EME) in wastewater treatment plants has been reported extensively in Switzerland, Italy, Spain, Belgium, France and the UK (Table 13). High concentrations, at hundreds of nanograms to micrograms per litre, of cocaine and benzoylecgonine have been reported in wastewaters (Table 13).[26] A meta-analysis of all reported concentrations (for all countries) for cocaine and benzoylecgonine showed that they are generally found in the highest concentrations out of all illicit drugs in wastewaters. The overall abundance of cocaine derivatives in wastewaters was in the following order: benzoylecgonine > cocaine >> EME. Influent samples collected daily from the largest wastewater

treatment plant in Belgium for 8 months (during 2009–10) showed the highest concentrations for benzoylecgonine, followed by cocaine and EME.[90] The higher concentrations found for benzoylecgonine compared with those of cocaine were in accordance with the results of previous monitoring studies from the European Union (EU) countries and the USA (Table 13).[90] The occurrence of cocaine and benzoylecgonine was studied in influent and effluent samples from five treatment plants in the Netherlands that serve four cities (Utrecht, Eindhoven, Apeldoorn and Amsterdam) and the Schiphol international airport of Amsterdam.[87] Cocaine and benzoylecgonine were found in 94 and 100 % of influents, and 47 and 75 % of effluents respectively.[87] Moreover, influents and effluents that were collected from seven treatment plants, which served half of the population inhabiting the Ebro River basin in the north-eastern Iberian Peninsula (largest catchment in Spain), contained cocaine and benzoylecgonine in all influent samples and in 93–100 % of effluent samples.[3] Low sorption of cocaine and benzoylecgonine onto particulate matter has been reported at 0.9–1.8 and 0.0–0.2 % respectively of the total concentrations.[85]

### *Amphetamine-type stimulants*

Occurrence of amphetamine-type stimulants in wastewater treatment plants has been reported extensively in Switzerland, Italy, Spain, Germany, the Netherlands, Croatia, the UK, the USA and Canada (Table 14). Among amphetamine-type stimulants, amphetamine, methamphetamine, MDMA and MDA were the most commonly measured compounds. A study from Spain showed the occurrence of amphetamine, methamphetamine and MDMA in 93, 14 and 100 % of influents and 36, 43 and 100 % of effluents respectively.[3] These detection rates were similar to those reported from the Netherlands and Croatia.[24,82] The overall mean concentrations of amphetamine, methamphetamine, MDMA and MDA in influents (for all countries studied) were 200, 30, 30 and 4 ng $L^{-1}$ respectively, whereas those in effluents were 5, 14, 30 and 6 ng $L^{-1}$ respectively. The rank order of concentrations of amphetamine-type stimulants derivatives in wastewater was: amphetamine > methamphetamine > MDMA > MDA (Table 14). Occasionally higher concentrations of MDA compared with MDMA were observed, which was due to *N*-demethylation of MDMA in the wastewater treatment process.[119] Methamphetamine was reportedly used by airline travellers, because this compound was found only in wastewater treatment plant influents in airports but not in municipal plants in the Netherlands.[87] In general, amphetamine is removed efficiently in treatment plants (Table 14), but the remaining amphetamine-type stimulants were not removed efficiently in all plants. Sorption of up to 10 % of the total load was reported for amphetamine in wastewater influent in the UK.[85] The total mass of methamphetamine and MDMA in particulate matter respectively ranged from 1.6 to 2.3 % and from 1.0 to 1.6 % of the total mass in the influent.[114]

### *Cannabinoids*

Occurrence of cannabinoids in wastewater treatment plants has been reported extensively in Switzerland, Italy, Spain, Croatia, France and the Netherlands (Table 15). Among cannabinoids, $\Delta^9$-THCA and $\Delta^9$-THC were the most commonly measured compounds. The meta-analysis of reported mean concentrations for $\Delta^9$-THCA and $\Delta^9$-THC in influents were 102 and 84 ng $L^{-1}$ respectively (for all countries), whereas those in effluents were 31 and 13 ng $L^{-1}$ respectively. Of the two cannabinoids, $\Delta^9$-THCA is the most abundant compound in treatment plants (Table 15).

### *Lysergic compounds*

LSD and its metabolite OH-LSD have rarely been detected in wastewater, possibly owing to low consumption, low doses and the high degradability of these compounds.[3,12,84] The high potency of LSD leads to a very small average dose, and therefore its detection in the environment can be analytically challenging.[84]

### *Benzodiazepines*

Because benzodiazepines are halogenated compounds, they are presumed to be less susceptible to biodegradation.[95] Occurrence of benzodiazepines in wastewater treatment plants has been extensively reported in the UK, Netherlands, Germany, USA, South Korea and Taiwan (Table 16). Among benzodiazepines, oxazepam, nordiazepam, temazepam and diazepam were the most commonly measured compounds, of which oxazepam and temazepam were the most abundant in influents and effluents from all countries studied. 7-Aminoflunitrazepam, nitrazepam and chlordiazepoxide were not detected in influents or effluents.[92] The rank order of the detection rate of benzodiazepines in wastewater was: oxazepam > temazepam > nordiazepam > diazepam (Table 16).

Benzodiazepines are not removed efficiently in treatment plants. Wastewater samples from seven plants in France that employed one full-scale membrane bioreactor and five full-scale conventional tertiary treatments were studied for removal efficiencies for benzodiazepines.[97] Tertiary treatment processes (e.g. fast tertiary settling and sand filtration) achieved significant (30–70 %) removal for absorbable micropollutants (benzodiazepines included).[97] Nordiazepam was measured in tertiary effluents after polishing pond treatment at a concentration of 10 ng $L^{-1}$, whereas alprazolam, bromazepam and diazepam were not found.[97] Alprazolam, bromazepam, diazepam, and nordiazepam were measured in extremely low concentrations in tertiary effluents after reverse osmosis at a concentration of ~1 ng $L^{-1}$, denoting high removal.[97] Alprazolam, bromazepam, diazepam and nordiazepam were measured in tertiary effluents after ozonation at a concentration of 1, 4, 1 and 10 ng $L^{-1}$ respectively.[97] Alprazolam, bromazepam, and nordiazepam were measured in tertiary effluents after activated carbon filtration at a concentration of 1 ng $L^{-1}$, whereas diazepam was not found[97] (Table 16). Thus, tertiary treatment with activated carbon filtration was the most efficient technique for the removal of benzodiazepines, whereas treatments with fast settling or sand filtration were the least efficient techniques.[97]

Sorption of some benzodiazepines to particulate matter has been reported. Sludge samples collected from domestic wastewater treatment plants in South Korea contained alprazolam, lorazepam and diazepam at a detection rate of <40 %.[57] The median concentration of alprazolam was 11 ng $g^{-1}$ dry weight, which was ~7 times higher than that reported for biosolids from the USA.[57] Furthermore, diazepam was found at a median concentration of 3 ng $g^{-1}$ dry weight, which was ~7 times lower than that reported for sludge from France.[57]

### *Barbiturates: phenobarbital and pentobarbital*

A few studies have reported on the fate and occurrence of phenobarbital and pentobarbital in wastewater treatment plants[11,98,99] (Table 17). Low concentrations of pentobarbital were found, but because pentobarbital is not widely used, its

**Table 14. Concentrations of amphetamine-type stimulants reported in wastewater treatment plants (WWTPs) from several countries**
MDA, 3,4-methylenedioxy amphetamine; MDMA, 3,4-methylenedioxy-*N*-methylamphetamine; MDEA, 3,4-Methylenedioxy-N-ethyl-amphetamine

| Samples | Country | Range (or single value) (ng $L^{-1}$, unless stated otherwise) | Mean, geometrical mean or median (ng $L^{-1}$, unless stated otherwise) | References |
|---|---|---|---|---|
| Influents (7 treatment plants) | UK | Amphetamine: – | Mean: 830 | [92] |
| | | Methamphetamine: – | Mean: 2 | |
| | | MDA: – | Mean: 10 | |
| | | MDMA: – | Mean: 39 | |
| | | MDEA: not detected | Mean: – | |
| Effluents (7 treatment plants) | | Amphetamine: – | Mean: 8 | |
| | | Methamphetamine: – | Mean: 1 | |
| | | MDA: – | Mean: 15 | |
| | | MDMA: – | Mean: 38 | |
| | | MDEA: not detected | Mean: – | |
| Influents | Italy, Switzerland | Amphetamine: – | Mean: 15 (Italy); not quantified (Switzerland) | [29] |
| | | Methamphetamine: – | Mean: 16 (Italy); not quantified (Switzerland) | |
| | | MDA: – | Mean: 5 (Italy); not quantified (Switzerland) | |
| | | MDMA: – | Mean: 14 (Italy); 14 (Switzerland) | |
| | | MDEA: – | Mean: 1.5 (Italy); not quantified (Switzerland) | |
| Effluents | | Amphetamine: not quantified | – | |
| | | Methamphetamine: not quantified | – | |
| | | MDA: – | Mean: 1 (Italy); 1 (Switzerland) | |
| | | MDMA: – | Mean: 4 (Italy); 4 (Switzerland) | |
| | | MDEA: not detected | – | |
| Influents (7 treatment plants) | USA | Amphetamine: 80–550 | – | [25] |
| | | Methamphetamine: not detected–2000 | – | |
| | | MDA: not detected – 7 | – | |
| | | MDMA: not detected – 70 | – | |
| | | MDEA: not detected | – | |
| Influents (2 treatment plants) | Germany | Amphetamine: 783–2198 | – | [93] |
| | | Methamphetamine: not detected | – | |
| | | MDMA: <93 | – | |
| Effluents (2 treatment plants) | | Amphetamine: not quantified | – | |
| | | Methamphetamine: not detected | – | |
| | | MDMA: not quantified | – | |
| Influents (3 treatment plants) | Canada | Amphetamine: – | Median (range): 14–18 | [70] |
| | | Methamphetamine: – | Median (range): 3–44 | |
| | | MDMA: – | Median (range): 15–27 | |
| Effluents (3 treatment plants) | | Amphetamine: – | Median (range): not detected–7 | |
| | | Methamphetamine: – | Median (range): 2–56 | |
| | | MDMA: – | Median (range): 7–25 | |
| Influents (7 treatment plants) | Spain | Amphetamine: 3–664 | Median: 148 | [3] |
| | | Methamphetamine: 1–8 | Median: 5 | |
| | | MDMA: 4–180 | Median: 20 | |
| Effluents (7 treatment plants) | | Amphetamine: 1–58 | Median: 26 | |
| | | Methamphetamine: <1–8 | Median: 1 | |
| | | MDMA: 3–120 | Median: 13 | |
| Influents | Croatia | Amphetamine: <3–31 | Median: 7 | [24] |
| | | MDMA: 2–33 | Median: 3 | |
| Effluents | | Amphetamine: 1–9 | Median: 3 | |
| | | MDMA: <<1–8 | Median: 2 | |
| Influents (4 treatment plants) | Netherlands | Amphetamine: 107–581 | Median: 310 | [94] |
| | | Methamphetamine: 24–278 | Median: 151 | |
| | | MDA: not detected | – | |
| | | MDMA: 42–207 | Median: 102 | |
| Effluents (4 treatment plants) | | Amphetamine: 15 (found in one sample) | – | |
| | | Methamphetamine: 13–62 | Median: 33 | |
| | | MDA: 22 (found in one sample) | – | |
| | | MDMA: 17–537 | Median: 56 | |

presence was attributed to the metabolism of thiopental, an anaesthetic that belongs also to the class of barbiturates. Overall, phenobarbital and pentobarbital are not removed efficiently in the treatment plants.

### *Antipsychotics and antischizophrenia pharmaceuticals*

Very few studies have investigated the occurrence of antipsychotics and antischizophrenia pharmaceuticals in wastewater

**Table 15. Concentrations of cannabinoids reported in from several countries**
$\Delta^9$-THC, Δ9-tetrahydrocannabinol; $\Delta^9$-THCA, $\Delta^9$-tetrahydrocannabinolic acid

| Samples | Country | Range (or single value) (ng $L^{-1}$, unless stated otherwise) | Mean, geometrical mean or median (ng $L^{-1}$, unless stated otherwise) | References |
|---|---|---|---|---|
| Influents (5 treatment plants) | Spain (Catalonia) | $\Delta^9$-THCA: <13–96 | – | [8] |
| | | $\Delta^9$-THC: 8–32 | – | |
| Effluents (5 treatment plants) | | $\Delta^9$-THCA: 15–72 | – | |
| | | $\Delta^9$-THC: <8 | – | |
| Influents (14 treatment plants) | Spain | $\Delta^9$-THCA: 24–402 | Median: 24 | [10] |
| | | $\Delta^9$-THC: 11–127 | Median: 4 | |
| Effluents (14 treatment plants) | | $\Delta^9$-THCA: 15–72 | Median: 28 | |
| | | $\Delta^9$-THC: 21 (one sample) | – | |
| Influents (7 treatment plants) | Spain | $\Delta^9$-THCA: 11–22 | Median: 18 | [3] |
| | | $\Delta^9$-THC: 48 (one sample) | – | |
| Effluents (7 treatment plants) | | $\Delta^9$-THCA: 5–73 | Median: 8 | |
| | | $\Delta^9$-THC: 11–22 | Median: 18 | |
| Influents (Castellón treatment plants) | Spain | $\Delta^9$-THCA: – | Mean (weekly) for 2011 and 2012: 300 and 600 respectively | [89] |
| Influents | Croatia | $\Delta^9$-THCA: 21–128 | Median: 57 | [24] |
| Effluents | | $\Delta^9$-THCA: – | – | |
| Influents | Italy, Switzerland | $\Delta^9$-THCA: – | Mean: 63 (Italy); 91 (Switzerland) | [29] |
| Effluents | Italy, Switzerland | $\Delta^9$-THCA: not quantified (Italy); – | Mean: – (Italy); 7 (Switzerland) | |
| Influents (25 WWTPs) | France | $\Delta^9$-THCA: max. 1196 | – | [30] |
| Effluents (25 treatment plants) | | $\Delta^9$-THCA: max. 161 | – | |
| Influents (5 treatment plants) | Netherlands | $\Delta^9$-THCA: <33–375 | – | [87] |
| Effluents (5 treatment plants) | | $\Delta^9$-THCA: <7–22 | – | |

treatment plants.[100,101] Occurrence of chlorpromazine, clozapine and risperidone was reported in influents and effluents of five treatment plants in Beijing, China[100] (Table 18). The mean concentrations of chlorpromazine, clozapine and risperidone were <367, 17–12 800 and <69 ng $L^{-1}$ respectively in influents, and <99, 15–8180 and <12 ng $L^{-1}$ respectively in effluents.[100] Primary treatment did not remove these drugs in wastewater treatment plants (WWTPs)[100] (Table 18).

### *Anaesthetics*

Occurrence of anaesthetics in wastewater treatment plants has been reported in the UK, the Netherlands, Germany, the USA and Taiwan (Table 19). Among anaesthetics, lidocaine, ketamine, fentanyl and norketamine were the most commonly measured compounds. Overall, norketamine and norfentanyl (metabolites of ketamine and fentanyl respectively) were found at lower concentrations than their precursors. Norketamine was not detected in the particulate matter but was found in dissolved phase at concentrations below 20 ng $L^{-1}$.[85] The proportion of ketamine in the particulate matter to total mass ranged from 0.5 to 2.8 %.[85]

### *Anti-epileptics and mood stabilisers: carbamazepine and primidone*

Carbamazepine was found in influents, effluents and sewage sludge that were collected from three wastewater treatment plants in Catalonia, Spain.[96] The concentrations of carbamazepine ranged from a few hundred to thousands of nanograms per litre in wastewater.[96] In sludge, the concentration of carbamazepine was of the order of a few tens of nanograms per gram (Table 20).[96] Sewage sludge samples collected from three treatment plants in Scotland contained carbamazepine concentrations of 62–86 ng $g^{-1}$ (Table 20).[103] The median concentration of primidone in influents and effluents from 12 German treatment plants demonstrated that this chemical is not effectively removed (Table 20).[83]

### *Sympathomimetic amines: ephedrine and pseudoephedrine*

Few studies have investigated the occurrence of these sympathomimetic amines in wastewater treatment plants. Ephedrine was reported to occur in influents collected from seven plants in Spain, at a median concentration of 349 ng $L^{-1}$; in effluents, the median concentration was 92 ng $L^{-1}$ (Table 21).[3] In treatment plants from Aachen, Germany, ephedrine was found at concentrations ranging from <2 to 6 ng $L^{-1}$ in influents (Table 21).[93] A concentration as high as 6900 ng $L^{-1}$ was reported for ephedrine in influent samples collected from seven treatment plants in the USA (Table 21).[25] The high levels of ephedrine likely reflect prescription use.[25] Ephedrine and pseudoephedrine were not found in the particulate matter of wastewater from a UK treatment plant.[80]

## Chirality of drugs

There are only limited data concerning stereospecific analysis of drugs in the environment.[105] Stereoisomeric profiling is important because the stereoisomers differ in their potency and toxicity.[106,107] MDMA exists in two enantiomeric forms (Fig. 2a).[108] Even though the technical mixture of MDMA is racemic,[108] *S*(+)-MDMA is preferentially metabolised over *R*(−)-MDMA, which leads to an enrichment of *R*(−)-MDMA and preferential formation of *S*(+)-MDA at excretion.[108] Each MDMA enantiomer maintains a unique pharmacological activity; *S*(+) maintains a more amphetamine-like stimulant action, whereas *R*(−) maintains more of a hallucinogenic action.[108] *S*(+)-MDMA is a more potent neurotoxin than *R*(−)MDMA.[108] Effluent from a treatment plant in the UK was found enriched with the *R*(−) enantiomer owing to the involvement of enantioselective microbial degradation processes.[84,109] MDMA was found in wastewater predominantly in the *R*(−) form, which suggested sources arising from human excretion rather than direct disposal.[108]

**Table 16. Concentrations of benzodiazepines reported in wastewater treatment plants (WWTPs) from several countries**

| Samples | Country | Range (or single value) (ng $L^{-1}$, unless stated otherwise) | Mean, geometrical mean or median (ng $L^{-1}$, unless stated otherwise) | References |
|---|---|---|---|---|
| Influents (7 treatment plants) | UK | Temazepam: 17–255 | Median: 85 | [84] |
| | | Diazepam: 7–8 | Median: 8 | |
| | | Nordiazepam: 5–64 | Median: 16 | |
| | | Oxazepam: 6–155 | Median: 22 | |
| | | Chlordiazepoxide: not detected | – | |
| | | Nitrazepam: not detected | – | |
| Effluents (7 treatment plants) | | Temazepam: 17–250 | Median: 79 | |
| | | Diazepam: <1–7 | Median: 2 | |
| | | Nordiazepam: <1–16 | Median: 6 | |
| | | Oxazepam: 5–85 | Median: 33 | |
| | | Chlordiazepoxide: 1 | Median: 1 | |
| | | Nitrazepam: not detected | – | |
| Influents (4 treatment plants) | Netherlands | Temazepam: 255–813 | Median: 411 | [94] |
| | | Diazepam: not detected | – | |
| | | Nordiazepam: not detected | – | |
| | | Oxazepam: 602–2020 | Median: 1105 | |
| Effluents (4 treatment plants) | | Temazepam: 389–1016 | Median: 554 | |
| | | Diazepam: 2–5 | Median: 3 | |
| | | Nordiazepam: 13–31 | Median: 18 | |
| | | Oxazepam: 713–1746 | Median: 959 | |
| Influents (7 treatment plants) | UK | Temazepam: not detected | Mean: 167 | [92] |
| | | Diazepam: not detected | Mean: 5 | |
| | | Nordiazepam: not detected | Mean: 25 | |
| | | Oxazepam: not detected | Mean: 50 | |
| | | Chlordiazepoxide: not detected | – | |
| | | Nitrazepam: not detected | – | |
| | | 7-Aminoflunitrazepam: not detected | – | |
| Effluents (7 treatment plants) | | Temazepam: not detected | Mean: 135 | |
| | | Diazepam: not detected | – | |
| | | Nordiazepam: not detected | Mean: 10 | |
| | | Oxazepam: not detected | Mean: 58 | |
| | | Chlordiazepoxide: not detected | – | |
| | | Nitrazepam: not detected | – | |
| | | 7-Aminoflunitrazepam: not detected | – | |
| Influents (5 treatment plants) | Netherlands | Temazepam: 92–414 | – | [87] |
| | | Oxazepam: 109–915 | – | |
| | | Nordiazepam: 4–21 | – | |
| Effluents (5 treatment plants) | | Temazepam: 133–508 | – | |
| | | Oxazepam: 237–994 | – | |
| | | Nordiazepam: 5–10 | – | |
| Influents (12 treatment plants) | Germany | Temazepam: not detected | Median: 55 | [83] |
| | | Diazepam: not quantified | – | |
| | | Oxazepam: max. 860 | Median: 480 | |
| | | Nordiazepam: not detected | – | |
| | | Bromazepam: not detected | – | |
| Effluents (12 treatment plants) | | Temazepam: max. 180 | Median: 50 | |
| | | Diazepam: not detected | – | |
| | | Oxazepam: max. 630 | Median: 320 | |
| | | Nordiazepam: not detected | – | |
| | | Bromazepam: not detected | – | |
| Secondary treatment effluents | | Diazepam: – | Mean: 10 | [97] |
| | | Nordiazepam: – | Mean: 30 | |
| | | Bromazepam: – | Mean: 10 | |
| | | Alprazolam: – | Mean: 10 | |
| Advanced secondary treatment (Membrane Biological Reactor effluents | | Diazepam: – | Mean: 4 | |
| | | Nordiazepam: – | Mean: 20 | |
| | | Bromazepam: – | Mean: 20 | |
| | | Alprazolam: not quantified | – | |

(*Continued*)

**Table 16. (Continued)**

| Samples | Country | Range (or single value) (ng $L^{-1}$, unless stated otherwise) | Mean, geometrical mean or median (ng $L^{-1}$, unless stated otherwise) | References |
|---|---|---|---|---|
| Tertiary effluents after fast settling | | Diazepam: – | Mean: 10 | |
| | | Nordiazepam: – | Mean: 30 | |
| | | Bromazepam: – | Mean: 30 | |
| | | Alprazolam: – | Mean: 10 | |
| Tertiary effluents after sand filter | | Diazepam: – | Mean: 10 | |
| | | Nordiazepam: – | Mean: 30 | |
| | | Bromazepam: – | Mean: 10 | |
| | | Alprazolam: – | Mean: 10 | |
| Tertiary effluents after polishing pond | | Diazepam: not quantified | – | |
| | | Nordiazepam: – | Mean: 10 | |
| | | Bromazepam: not quantified | – | |
| | | Alprazolam: not quantified | – | |
| Tertiary effluents after reverse osmosis | | Diazepam: – | Mean: 1 | |
| | | Nordiazepam: – | Mean: 2 | |
| | | Bromazepam: – | Mean: 2 | |
| | | Alprazolam: – | Mean: 1 | |
| Tertiary effluents after ozone | | Diazepam: – | Mean: 1 | |
| | | Nordiazepam: – | Mean: 10 | |
| | | Bromazepam: – | Mean: 4 | |
| | | Alprazolam: – | Mean: 1 | |
| Tertiary effluents after activated carbon filter | | Diazepam: not quantified | – | |
| | | Nordiazepam: – | Mean: 1 | |
| | | Bromazepam: – | Mean: 1 | |
| | | Alprazolam: – | Mean: 1 | |
| Sludge | South Korea | Alprazolam: <5–14 ng $g^{-1}$ | Median: 11 ng $g^{-1}$ | [57] |
| | | Diazepam: 2–5 ng $g^{-1}$ | Median: 3 ng $g^{-1}$ | |
| | | Nordiazepam: 1–9 ng $g^{-1}$ | Median: 3 ng $g^{-1}$ | |
| | | Lorazepam: 12 ng $g^{-1}$ (one sample) | – | |
| Influents (7 treatment plants) | USA | Flunitrazepam: not detected | – | [25] |
| Influents (2 treatment plants) | Taiwan | Flunitrazepam: not detected | – | [86] |
| Effluents (2 treatment plants) | | Flunitrazepam: not detected | – | |

**Table 17. Concentrations of barbiturates reported in wastewater treatment plants (WWTPs) from several countries**

| Samples | Country | Range (or single value) (ng $L^{-1}$, unless stated otherwise) | Mean, geometrical mean or median (ng $L^{-1}$, unless stated otherwise) | References |
|---|---|---|---|---|
| Effluents (8 treatment plants) | Germany, Croatia | Pentobarbital: max. 5400 | – | [11] |
| Effluents (6 treatment plants) | Germany | Phenobarbital: – | Median: 90–210 | [65] |
| Influent (1 treatment plant) | USA | Pentobarbital: 92 | – | [99] |
| | | Phenobarbital: 101 | – | |
| Effluent (1 treatment plant) | | Pentobarbital: 67 | – | |
| | | Phenobarbital: 118 | – | |
| Horizontal subsurface flow bed influent (1 treatment plant) | Italy | Pentobarbital: 18 | – | [76] |
| | | Phenobarbital: 138 | – | |
| Effluent (1 treatment plant) | | Pentobarbital: 12 | – | |
| | | Phenobarbital: 114 | – | |

MDMA was also present in the racemic form, suggesting direct disposal of this drug into the sewage system.[108] Amphetamine is also found in two enantiomeric forms, *S*(+) and *R*(−) (Fig. 2b).[108] Similarly to MDMA, S(+)-MDA is preferentially metabolised, resulting in an enrichment of excreted *R*(−)-MDA.[106,108] Both *S*(+)- and *S*(+)/*R*(−)-amphetamine are prescription medications.[106] Nonetheless, amphetamine is also a metabolite of methamphetamine and certain other prescription drugs[106]; for instance, *R*(−)-amphetamine can be excreted following administration of selegiline, whereas *S*(+)-amphetamine is formed as a result of administration of benzphetamine, and *S*(+)/*R*(−)-amphetamine is formed as a result of administration of famprofazone.[41,108] In the Netherlands, the presence of amphetamine in racemic form in wastewater was due to its direct disposal.[108] In contrast, the *R*(−)-amphetamine form

**Table 18. Concentrations of antipsychotics and antischizophrenia pharmaceuticals reported in wastewater treatment plants (WWTPs) from several countries**

| Samples | Country | Range (or single value) (ng $L^{-1}$, unless stated otherwise) | Mean, geometrical mean or median (ng $L^{-1}$, unless stated otherwise) | References |
|---|---|---|---|---|
| Influents (5 treatment plants) | China | Chlorpromazine: – | Mean: <367 | [100] |
| | | Clozapine: 17–12 783 | – | |
| | | Risperidone: – | Mean: <69 | |
| Effluents (5 treatment plants) | | Chlorpromazine: – | Mean: <99 | |
| | | Clozapine: 15–8183 | – | |
| | | Risperidone: – | Mean: <12 | |
| Primary effluents (5 treatment plants) | | Chlorpromazine: – | Mean: <217 | |
| | | Clozapine:18–13 200 | – | |
| | | Risperidone: – | Mean: <45 | |
| Influents | USA | Risperidone: – | Mean: <3 | [101] |
| Effluents | | Risperidone: – | Mean: <1 | |

**Table 19. Concentrations of anaesthetics reported in wastewater treatment plants (WWTPs) from several countries**

| Samples | Country | Range (or single value) (ng $L^{-1}$, unless stated otherwise) | Mean, geometrical mean or median (ng $L^{-1}$, unless stated otherwise) | References |
|---|---|---|---|---|
| Influents (3 treatment plants) | Germany | Lidocaine: 91–217 | – | [62] |
| Influents (3 treatment plants) | Germany | Lidocaine: 70–257 | – | [102] |
| Effluents (3 treatment plants) | | Lidocaine: 55–183 | – | |
| Influents (5 treatment plants) | Netherlands | Ketamine: <10–17 | – | [87] |
| Effluents (5 treatment plants) | | Ketamine: <2–44 | – | |
| Influents (7 treatment plants) | UK | Fentanyl: – | Mean: 2 | [92] |
| | | Norfentanyl: – | Mean: 7 | |
| | | Ketamine: – | Mean: 79 | |
| | | Norketamine: – | Mean: 27 | |
| Effluents (7 treatment plants) | | Fentanyl: not quantified | – | |
| | | Norfentanyl: – | Mean: 1 | |
| | | Ketamine: – | Mean: 130 | |
| | | Norketamine: – | Mean: 28 | |
| Influents (1 treatment plant) | USA | Ketamine: – | Mean: 16 | [25] |
| Influents (4 treatment plants) | Netherlands | Ketamine: 2–28 | – | [94] |
| Influents (7 treatment plants) | UK | Fentanyl: 1–5 | – | [84] |
| | | Norfentanyl: not detected | – | |
| | | Ketamine: 5–447 | – | |
| | | Norketamine: 5–96 | – | |
| Effluents (7 treatment plants) | | Fentanyl: <1 | – | |
| | | Norfentanyl: not detected | – | |
| | | Ketamine: 7–278 | – | |
| | | Norketamine: 1–60 | – | |
| Influents (3 treatment plants) | Germany | Lidocaine: – | Mean: 135 | [62] |
| Effluents (3 treatment plants) | | Lidocaine: – | Mean: <100 | |
| Dissolved phase of influents | UK | Fentanyl: – | Mean: 1 | [85] |
| | | Norfentanyl: not detected | – | |
| | | Ketamine: 46–249 | – | |
| | | Norketamine: – | Mean: <20 | |
| Particulate matter of influents | | Fentanyl: – | Mean: 0.6 ng $g^{-1}$ | |
| | | Norfentanyl: not detected | – | |
| | | Ketamine: 1–7 ng $g^{-1}$ | – | |
| | | Norketamine: not detected | – | |
| Influents, effluents (2 treatment plants) | Taiwan | Fentanyl: 1 ng $L^{-1}$ in influents not detected in effluents | – | [86] |
| | | Ketamine: range: 147–343 | – | |
| Influents, effluents (5 treatment plants) | Spain | Fentanyl: not quantified | – | [8] |

was enriched in wastewater from the UK, which indicated sources arising from abuse of this drug.[108]

Methamphetamine also exists in two enantiomeric forms, *S*(+) and *R*(−),[106] with the *S*(+) form being the more pharmacologically potent enantiomer.[106] Between the two, *S*(+)-methamphetamine is the more commonly used drug, whereas *R*(−)-methamphetamine is mainly used as a decongestant.[106] The *R*(−) form is also formed as a result of metabolism of certain prescription medications.[106] On the basis of the data obtained from four treatment plants in the

**Table 20. Occurrence of anti-epileptics and mood stabilisers in wastewater treatment plants (WWTPs)**

| Samples | Country | Range (or single value) (ng $L^{-1}$, unless stated otherwise) | Mean, geometrical mean or median (ng $L^{-1}$, unless stated otherwise) | References |
|---|---|---|---|---|
| Influents (5 treatment plants) | Korea | Carbamazepine: 43–127 | Mean: 72 | [104] |
| Effluents (5 treatment plants) | | Carbamazepine: 40–74 | Mean: 55 | |
| Sewage sludge (3 treatment plants) | Scotland | Carbamazepine 62–86 ng $g^{-1}$ | – | [103] |
| Influents (12 treatment plants) | Germany | Primidone: – | Median: 440 | [83] |
| Effluents (12 treatment plants) | | Primidone: – | Median: 420 | |

**Table 21. Concentrations of sympathomimetic amines reported in wastewater treatment plants (WWTPs) from several countries**

| Samples | Country | Range (or single value) (ng $L^{-1}$, unless stated otherwise) | Mean, geometrical mean or median (ng $L^{-1}$, unless stated otherwise) | References |
|---|---|---|---|---|
| Influents (7 treatment plants) | Spain | Ephedrine: – | Median: 349 | [3] |
| Effluents (7 treatment plants) | | Ephedrine: – | Median: 92 | |
| Influents | Germany | Ephedrine: 2–6 | – | [93] |
| Influents (7 treatment plants) | USA | Ephedrine: max. 6900 ng $L^{-1}$ | – | [25] |
| Dissolved phase | UK | Ephedrine: 501–1080 | – | [85] |
| | | Pseudoephedrine: not detected | – | |
| Particulate matter of wastewater influents | | Ephedrine: not detected | – | |
| | | Pseudoephedrine: not detected | – | |

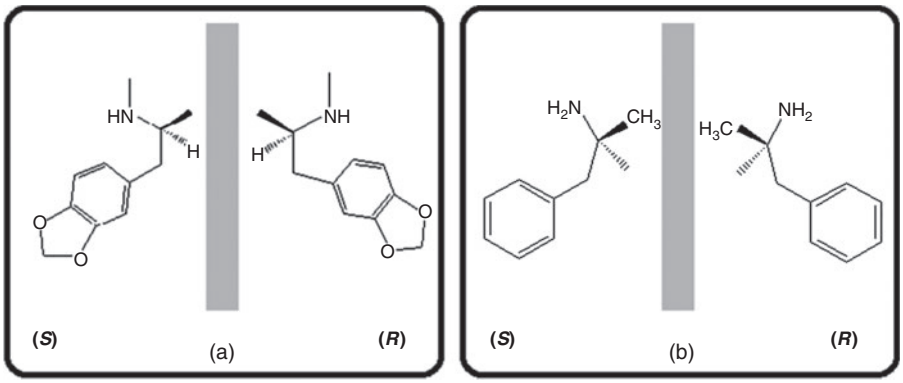



**Fig. 2.** MDMA (3,4-methylenedioxy-*N*-methylamphetamine) (a), and amphetamine (b) enantiomers.

UK, methamphetamine was found in raw wastewater either in racemic form or enriched with the *S*(+) enantiomer.[106] Nevertheless, all effluents of the plants were enriched with the *R*(−) enantiomer,[106] which suggested enantiomer-specific degradation of this drug in wastewater treatment processes.

Ephedrine and pseudoephedrine have stereoisomers, namely 1*R*,2*S*(−)-ephedrine, 1*S*,2*R*(+)-ephedrine, 1*S*,2*S*(+)-pseudoephedrine and 1*R*,2*R*-(−)-pseudoephedrine. 1*R*,2*S*(−)-ephedrine and 1*S*,2*S*(+)-pseudoephedrine can occur naturally in the environment.[106] In the UK, 1*R*,2*S*(−)-ephedrine was frequently found in wastewater influents and effluents, whereas 1*S*,2*R*(+)-ephedrine was detected at low levels only in influents from certain treatment plants.[106] Raw wastewater was found to be enriched with 1*S*,2*S*(+)-pseudoephedrine in winter, but with 1*R*,2*S*(−)-ephedrine in spring and summer time. This difference in stereoisomer profile between seasons was attributed to higher use of cold medications that contain 1*S*,2*S*(+)-pseudoephedrine for the treatment of cold symptoms during winter, or differences in microbial removal processes between seasons.[106]

Chirality studies should be encouraged in the future; these studies will greatly help our understanding the sources, environmental fate and toxicity of drugs in the environment.

## Sewage epidemiology in wastewater analysis

Until recently, drug consumption rates and patterns in a community were calculated based on population surveys along with medical records, drug production, seizure rates and crime statistics.[109–148] Data gathered from such approaches, however, can be inaccurate owing to the subjective nature of the data collection; for example, population surveys using questionnaires have been shown to be unreliable.[110] In the last decade, an innovative methodology for calculation of drug consumption rates in a community, known as 'sewage epidemiology approach', has been introduced based on measured concentrations of drugs and their metabolites in wastewater from centralised treatment plants.[111,112] This approach can also be used to complement the aforementioned methods of estimating drug usage in a community. Thus far, the methodology has been mainly applied for illicit drugs such as cocaine, amphetamine, methamphetamine, MDMA, methadone, heroin and $\Delta^9$-THCA.[110,111,113–126] The critical parameters needed for the calculation of usage of a specific drug are drug concentration in wastewater influents, an adequate knowledge of the pharmacokinetics of the drug, information on the population

served by the treatment plant, and the daily flows of sewage into the plant.[40]

Consumption estimates for cocaine, amphetamine, methamphetamine, MDMA and $\Delta^9$-THCA using the sewage epidemiology approach from five recent environmental studies (Subedi and Kannan,[119] Östman et al.,[121] Khan et al.,[122] Yargeau et al.[123] and Thomas et al.[134]) that involved various countries are summarised in Figs 3–7 (63 locations from Europe, USA and China).

Consumption of methamphetamine in the Czech Republic was estimated to be in the range 293–627 mg day$^{-1}$ per 1000

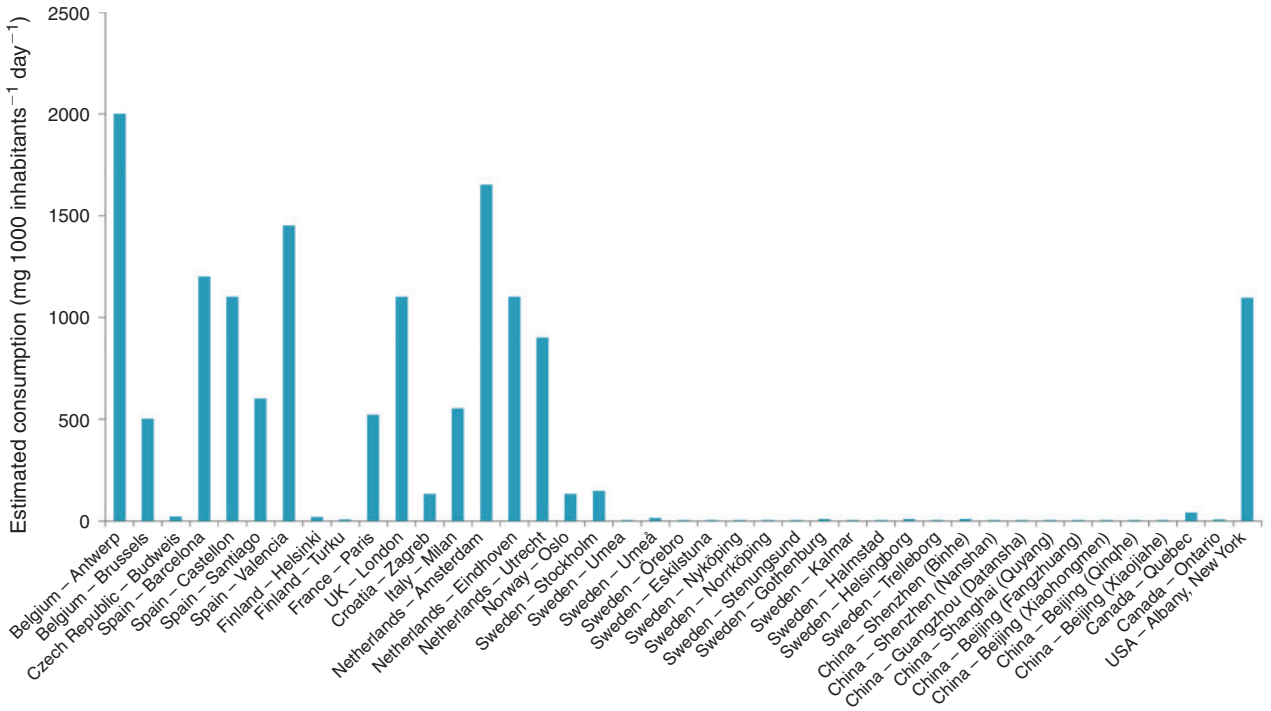



**Fig. 3.** Estimated consumption per 1000 inhabitants per day (mg 1000 inhabitants$^{-1}$ day$^{-1}$) of cocaine from different locations worldwide.[119,121–123,134]

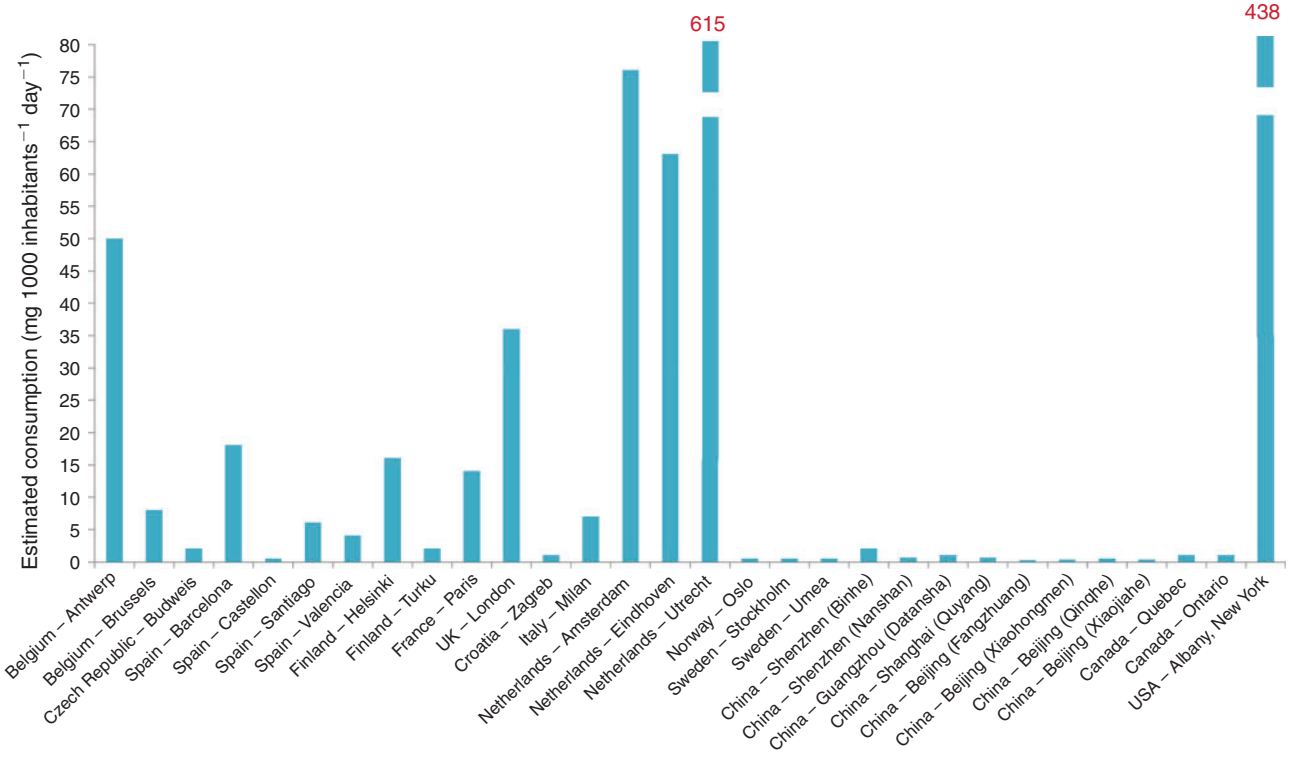



**Fig. 4.** Estimated consumption per 1000 inhabitants per day (mg 1000 inhabitants$^{-1}$ day$^{-1}$) of MDMA (3,4-methylenedioxy-*N*-methylamphetamine) from different locations worldwide.[119,121–123,134]

people, with a weekly average of 412 mg day$^{-1}$ per 1000 people, and this estimate was much higher than those reported in other studies from Europe (average of ~2 mg day$^{-1}$ per 1000 people reported in Belgium and Spain).[114] The high values reported in the Czech Republic were attributed to the large number of people entering methamphetamine medical treatment.[114] Consumption of MDMA was estimated to be in the range 21–173 mg day$^{-1}$ per 1000 people, with a weekly average of

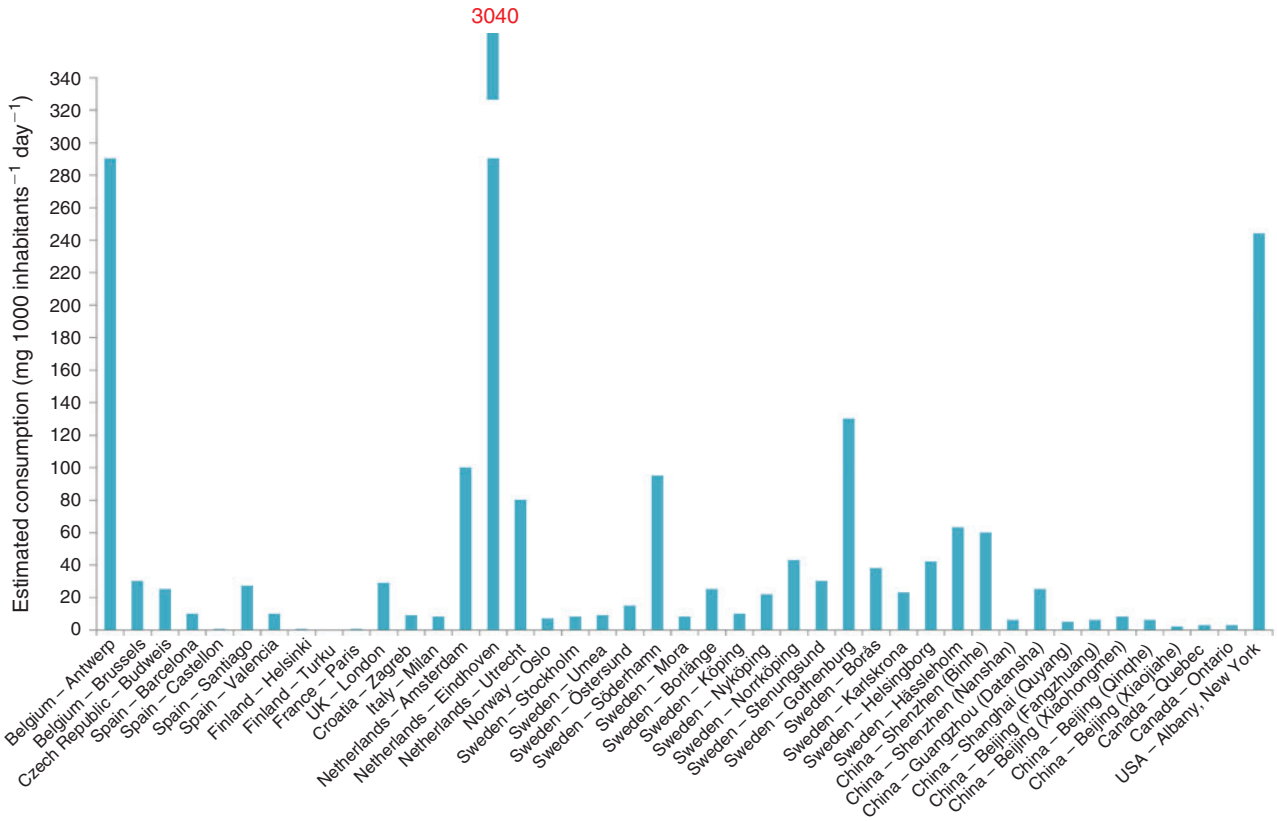



**Fig. 5.** Estimated consumption per 1000 inhabitants per day (mg 1000 inhabitants$^{-1}$ day$^{-1}$) of amphetamine from different locations worldwide.[119,121–123,134]

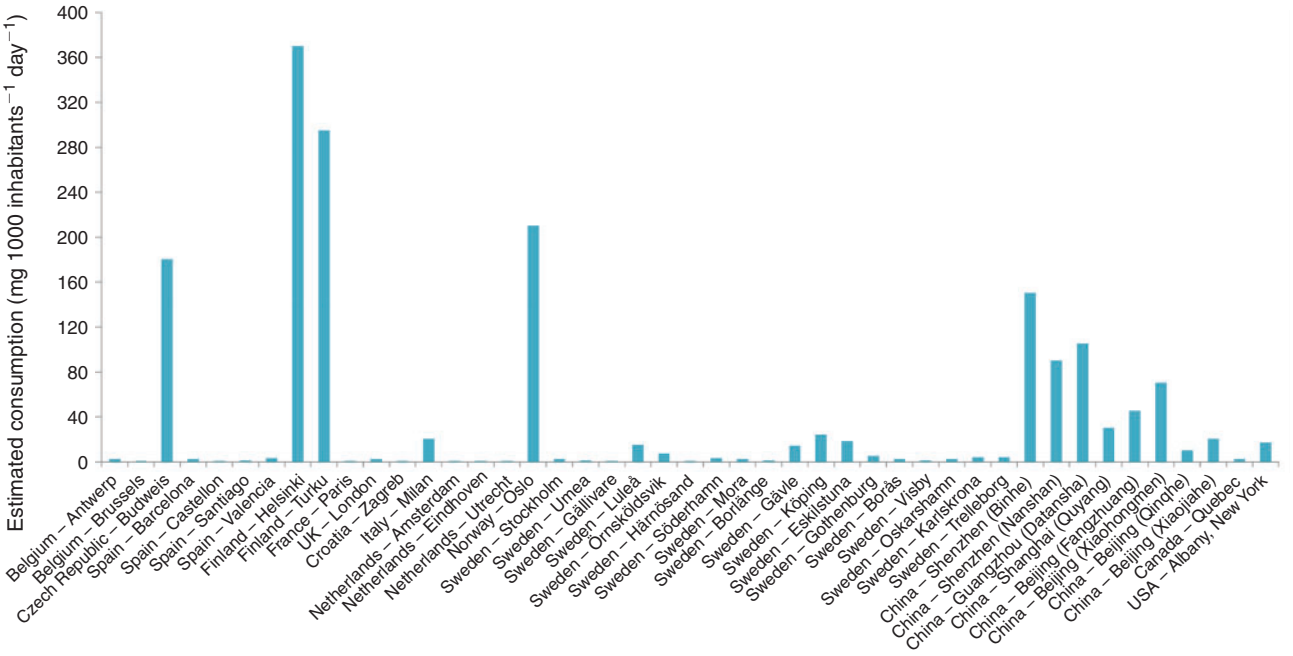



**Fig. 6.** Estimated consumption per 1000 inhabitants per day (mg 1000 inhabitants$^{-1}$ day$^{-1}$) of methamphetamine from different locations worldwide.[119,121–123,134]

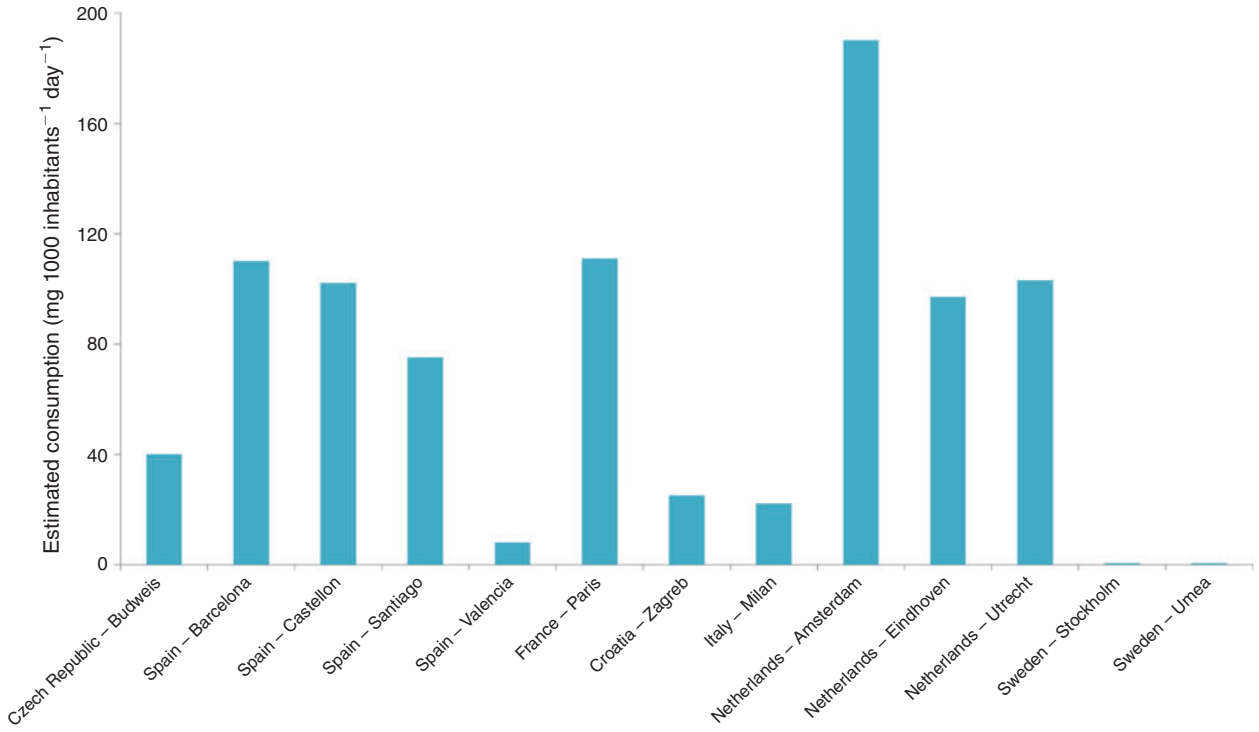



**Fig. 7.** Estimated consumption per 1000 inhabitants per day (mg 1000 inhabitants$^{-1}$ day$^{-1}$) of $\Delta^9$-THCA ($\Delta^9$-tetrahydrocannabinolic acid) from different locations worldwide[119,121–123,134]

162 mg day$^{-1}$ per 1000 people.[114] The average consumption of MDMA in the Czech Republic was one of the highest values reported in Europe.[114]

Although the sewage epidemiology approach is increasingly being used, there is a potential for underestimation because a certain fraction of drugs or metabolites can be lost (e.g. by degradation or absorption) before reaching the sampling points.[110] However, information on the stability, degradation, partitioning and sorption of the drug in the environment will enable accurate assessment of its usage in a community.[110] Lower uncertainties in such assessment can be obtained by implementing continuous monitoring of a drug in both influents and effluents.[110] Moreover, the use of an average drug-to-metabolite fractional conversion factor would reduce the uncertainties associated with assumptions on drug pharmacokinetics and metabolism.[127] The major distinguishing advantage of the sewage epidemiology approach is the near-real-time monitoring of drug usage in a community.[110] By applying the sewage epidemiology approach, a study in Dublin calculated the use of cocaine in a community by measuring the concentrations of cocaine in the wastewater, and using a factor of 10 % for the dosage of the parent compound excreted into urine.[113] That study, however, did not include the primary metabolite of cocaine, benzoylecgonine, based on the assumption that cocaine was fairly stable.[113,128] Another study, from the Czech Republic, used the concentrations of drugs in raw wastewater and particulate matter in the calculation of drug usage in a community.[114] Measured total concentrations (particulate matter plus dissolved phase) of analytes were used in the estimation of drug usage with a specific emphasis on the inclusion of particulate matter in such calculations.[114] Furthermore, the stability of target analytes (from sampling to analysis) was taken into account in such calculations.[114] By use of this additional information, the drug consumption of a community can be calculated with a higher degree of certainty. It is noteworthy that without the analysis of particulate matter, calculations of methadone usage would be significantly underestimated by up to 50 %.[114]

Castiglioni et al. suggested a 'Best Practice Requirement Guide' for various steps involved in the estimation of community drug use through the measurement of sewage drug biomarkers and the assessment of uncertainty values under various environmental conditions.[129] The excretion profile for cocaine is fairly well known for all possible administration routes (intravenous, intranasal, oral and smoked). Castiglioni et al. incorporated this knowledge to estimate cocaine usage in a community.[129,130] The frequency of cocaine use through different routes of administration can be also used to weigh benzoylecgonine excretion data.[129] Moreover, a flow- or volume-proportional sampling method (instead of time-proportional sampling) was suggested for the avoidance of systematic errors in sampling.[129] In a sewerage system, amphetamine-type stimulants are, in general, considered stable, $\Delta^9$-THCA and benzoylecgonine are moderately stable, and cocaine and EME are unstable.[129] Castiglioni et al. did not incorporate cocaine and EME concentrations in the estimation owing to their instability in sewage, and stated that calculations were not affected by more than 10 % (relative standard deviation).[129] The authors also pointed out that potential cocaine biotransformation in sewage should be accounted for because it could lead to an increase in benzoylecgonine concentration.[129] Cocaine and EME are not stable even under refrigerated conditions (4 °C), and the concentration of benzoylecgonine in samples may increase by up to 20 % over 24 h at 4 °C.[129] Nevertheless, the cocaine/benzoylecgonine ratio can be used to check for excessive biotransformation of cocaine to benzoylecgonine during the storage of samples.[129,131]

Uncertainties in the estimation of drug usage based on the sewage epidemiology approach can arise from several factors such as the composition of sewage (i.e. industrial, domestic or mixed), the reliability of census data and the methodology used to calculate population equivalents.[115,129] The composition of sludge can severely influence the hydrochemical parameters of the target analytes.[129] The expert knowledge from treatment plant staff would aid in the planning horizon, the actual loading (recent hydrochemical parameters) and the running design capacity conditions of the plant.[129] Suitable biomarkers such as prescription drugs, creatinine, caffeine, acesulfame, nitrogen, phosphorus, and chemical and biological oxygen demands can be incorporated to better estimate the population served by a wastewater treatment plant.[39,115,129,132,133]

Use of both the census data and the estimation of population served by the treatment plant based on atenolol load have been suggested.[116] The estimated drug usage rates based on the two population estimates were 623–1370 and 364–1410 mg for $\Delta^9$-THC; 176–531 and 129–614 mg for cocaine estimated based on cocaine, 109–450 and 98.8–521 mg for cocaine estimated based on benzoylecgonine; 146–298 and 110–345 mg for methamphetamine estimated based on methamphetamine, 161–312 and 123–360 mg for methamphetamine estimated based on amphetamine; and 77–297 and 45–343 mg for ecstasy (MDMA).[116] The estimated drug usage rates based on the two population estimates were in good agreement for all drugs and provided additional confirmation for the estimation.

A year-round sewage epidemiology study was conducted in a plant in Belgium for amphetamine, MDMA, methamphetamine, heroin and methadone.[132] Calculations for drug usage were based on the stability of the target compounds in aquatic systems and on their excretion profiles.[132] Concentrations of nitrogen, phosphorus and oxygen in the wastewater samples were used to estimate the number of inhabitants in the catchment area.[132] It was demonstrated that the use of the design capacity of the treatment plant does not reflect the real amount of served inhabitants and should be replaced by real-time calculations of this parameter.[132] Calculations for cocaine usage were accomplished in three ways, based on benzoylecgonine concentrations, EME concentrations, and both benzoylecgonine and EME concentrations,[132] and returned average values for cocaine consumption that were remarkably similar: 519 mg day$^{-1}$ per 1000 people for calculations based on benzoylecgonine, 523 mg day$^{-1}$ per 1000 people for calculations based on EME, and 519 mg day$^{-1}$ per 1000 people for calculations based on both cocaine metabolites.[132] The average value of methamphetamine consumption was 2 mg day$^{-1}$ per 1000 people, and it was in agreement with the observations made by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (methamphetamine is not widely used in Europe).[132] The average values for methadone, heroin (which used 6-monoacetylomorphine concentrations for calculations), cocaine, amphetamine and MDMA consumption were 138, 415, 519, 76 and 13 mg day$^{-1}$ per 1000 people respectively.[132] The value calculated for amphetamine in Belgium was similar to those reported in other sewage epidemiology studies in Canada, Croatia and Spain.[132] Overall, cocaine and heroin were found to be the most widely used illicit drugs, followed by amphetamine and MDMA.[132]

In 2012, a Europe-wide study on sewage epidemiology was conducted whereby usage rates of cocaine, amphetamine, MDMA, methamphetamine and $\Delta^9$-THCA were compared among 19 European cities. For the first time, a uniform protocol was applied across several countries in Europe (Figs 3–7).[134] The results from the sewage epidemiology approach were found to be in good agreement with officially reported drug use data in various countries.[134] Higher concentrations of illicit drugs, including amphetamine-type stimulants and cocaine, were observed during weekends in comparison with weekdays, and after Christmas and New Year holidays.[135] These diurnal variations and holiday-specific increases in drug usage were supported in several studies.[135] In addition, inhabitants of a catchment are a dynamic parameter that is also affected by holiday periods, festivals and community events and celebrations.[132,136]

## Conclusions and recommendations

In the present review, information concerning the occurrence of 50 bioactive chemicals in wastewater treatment processes has been compiled. The current analysis is based on predetermined target drugs (parent compounds and their known metabolites) and does not cover the possibility of other forms of the same drug existing in wastewaters (e.g. glucuronidated derivatives of morphine and codeine). Current analytical methods do not account for total mass of the compound (in various forms) present in the sewage system, and efforts to identify other forms of drugs are needed for an accurate assessment of loadings into the environment. It is deemed necessary to further intensify our efforts towards the design of wastewater treatment plants that are capable of removing a broad range of pollutants effectively. If complete removal of pollutants from wastewater is possible, then the 'breakthrough' in technology would contribute to increasing available water resources, alleviate water scarcity and minimise global pollution.

As demonstrated in the current review, most studies on wastewater contaminants are from western and central Europe, and therefore studies from other parts of the world are needed to enhance knowledge, raise awareness and protect our water supply. Those studies from western and central Europe mostly deal with opioids, cocaine compounds, amphetamine-type stimulants, cannabinoids and benzodiazepines, and these compounds are distributed in quite high concentrations in wastewater treatment plants. Our meta-analysis (based on the literature values) indicated that cocaine compounds and opioids were the most abundant drugs in wastewater. On a global scale, cocaine, benzoylecgonine (main metabolite of cocaine), EDDP (main metabolite of methadone), codeine and morphine are present at the highest concentrations and detection frequencies. Cocaine and benzoylecgonine exhibited high removal rates in wastewater treatment plants, whereas in most cases, EDDP, codeine and morphine concentrations did not differ significantly between influents and effluents, indicating low removal rates. Cocaine and opioids, which are mainly characterised as abuse drugs, were found in even higher abundances than the neuropsychiatric pharmaceuticals that are legally prescribed. The widespread occurrence of abuse drugs in wastewater stresses the severity of the situation, because it indicates that illegal cocaine and opioids trafficking is increasing globally. Studies from the other parts of the world are also needed to extend our knowledge of drugs in wastewaters with the goal of protecting our precious water supply.

There is a lack of information on the stereoselectivity of drugs in the aquatic environment, and hence an urgent requirement for research on the stereoselective fate and toxicity of neuropsychiatric pharmaceuticals and illicit drugs in wastewater

treatment processes.[137–148] Novel stereoselective analytical methods need to be developed for the determination of enantiomers in wastewater.[140] Furthermore, enantiomeric profiling in sewage epidemiology can give additional valuable information on consumption of illicit drugs, metabolism, or even direct disposal and dumping.

Many drugs in sewage influents are not removed by current treatment processes. It is of high priority to assess the effects of these chemicals on ecosystems because wastewater effluents are major contributors to river flows (that are also used as potable water in many countries), and consequently affect water quality. Future studies on the fate of drugs in wastewater treatment plants should consider analysing both the aqueous and particulate fractions.

The application of the sewage epidemiology approach to estimate consumption of illicit drugs in a community provides consistent results that can be corroborated with usage statistics from forensic departments. More research is needed in this area (perhaps under some ethical research guidelines[141]), especially in Asia, Africa and Latin America. Untargeted analytical methods for 'designer' drugs in wastewater samples can provide valuable information regarding various types of yet unidentified illicit drugs for which analytical standards are not available. Furthermore, ecotoxicological studies and environmental monitoring surveys of drugs are needed.[69]

The sewage epidemiology approach can also be applied for other legal pharmaceuticals. There is a need for stringent and uniform quality assurance and specific quality guidelines from sampling to analysis and data interpretation to be developed and improved. Knowledge on stability and metabolism of drug residues and their metabolites must be enhanced. Furthermore, extensive research is required with regard to the pharmacokinetics of drugs, routes of drug intake, sampling strategies, flow rate and population size in a catchment.[142] Thus, future studies on sewage epidemiology must broaden its application and address the aforementioned limitations.

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