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Review

Psychiatric pharmaceuticals in the environment

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ABSTRACT

Psychiatric pharmaceuticals, such as anxiolytics, sedatives, hypnotics, and antidepressants, are among the most prescribed active substances throughout the world. The occurrence of these widely used compounds in environmental matrices (wastewaters, surface, ground and drinking waters, soils, sediments, bio-solids and tissue), as well as the first studies indicating their high persistence and toxicity to non-target organisms, justify the growing concern about these emerging environmental pollutants. Despite this increasing interest, there is a considerable lack of knowledge about the environmental fate of a large number of psychiatric pharmaceuticals and further research about this topic is needed. This paper aims to review the literature data related to the occurrence, persistence, environmental fate and toxicity for non-target organisms of this group of pharmaceuticals. The analytical methods developed for the determination of psychiatric medicines in environmental matrices are also highlighted.

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1. Introduction

Pharmaceuticals are a large and diverse group of organic compounds used in very high quantities throughout the world (Daughton and Ternes, 1999; Jones et al., 2001, 2004; Bound and Voulvoulis, 2004; Petrović and Barceló, 2007). Nowadays, and in the European Union, there are more than 3000 active substances in the market (Redshaw et al., 2008). The first known reports specifically referring to the incomplete removal of some pharmaceuticals by wastewater treatments and their discharge into the environment by wastewaters treatment plants (WWTP) were published in the 1960s and 1970s (Stumm-Zollinger and Fair, 1965; Hignite and Azarnoff, 1977). Despite these first findings indicating pharmaceuticals as a potential group of environmental

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contaminants, this issue did not attract significant attention until the 1990s (Purdom et al., 1994; Desbrow et al., 1998; Routledge et al., 1998) when it was discovered that some compounds have the ability to interfere with ecosystems in concentrations as low as a few nanograms per liter (Halling-SØrensen et al., 1998). It was also during that decade that the first optimized analytical methods for the quantification of pharmaceuticals in environmental samples were developed, allowing the determination of very small quantities in aquatic environments (Eckel et al., 1993; Holm et al., 1995; Ternes, 1998; Ternes et al., 1998; Snyder et al., 1999). Since then, as a consequence of several published studies reporting the occurrence of these compounds in the environment (Ternes, 1998; Ternes et al., 2001; Kolpin et al., 2002; Al-Rifai et al., 2007; Conley et al., 2008), as well as the large amounts of pharmaceuticals produced and their increasing use and diversity (Bound and Voulvoulis, 2004), the existence of pharmaceutical drugs and pharmaceutically active metabolites in the environment has been considered one of the emerging concerns in environmental sciences (Halling-SØrensen et al., 1998; Daughton and Ternes, 1999; Heberer, 2002a; Carlsson et al., 2006). Despite the growing number of studies published about this subject in the last years, there is still much to be understood about environmental transformations, fate (Löffler et al., 2005; Kwon and Armbrust, 2006; Redshaw et al., 2008) and effects of these compounds (Calleja et al., 1994; Brooks et al., 2003a,b; Brain et al., 2004; Johnson et al., 2007; Gaworecki and Klaine, 2008; Gust et al., 2009). In addition, and taking into consideration that pharmaceuticals do not occur in environment individually but as complex mixtures, several investigations showed that toxicity of pharmaceuticals to non-target organisms may be occurring at environmentally relevant concentrations due to combined and synergistic effects (Henry and Black, 2007; Pomati et al., 2007, 2008; DeLorenzo and Fleming, 2008; Painter et al., in press; Quinn et al., 2009; Schnell et al., 2009).

Until now, a large diversity of pharmaceuticals has been found in the environment: analgesics, antibiotics, antiepileptics, β-blockers, blood-lipid regulators, antidepressants, anxiolytics, sedatives, contraceptives, etc. (Jones et al., 2006). This paper will be specifically focused on psychiatric drugs (comprising anxiolytics, sedatives, hypnotics, antidepressants – selective serotonin re-uptake inhibitors, tricyclic antidepressants and others). Psychiatric drugs are a group of pharmaceuticals commonly prescribed (Schultz and Furlong, 2008). For instance, in North America in 2007, 12 of the 100 most prescribed active substances were psychoactive pharmaceuticals (NDC Health, 2009).

Pharmaceuticals are used with the intent of having some type of biological or physiological effect in humans or animals. Among their specific characteristics, these compounds have the ability to pass through cellular membranes and are relatively persistent in order not to be inactivated before having the desired therapeutic effect (Sanderson et al., 2003; Petrović & Barceló, 2007). In the particular case of nervous system related pharmaceuticals, and in addition to the referred intrinsic properties, these have great relevance on the regulation of behavior, having the aptitude to directly affect the central nervous system and disrupt neuro-endocrine signaling. The alteration of the reproduction patterns in non-target aquatic organisms (Brooks et al., 2003b; van der Ven et al., 2004, 2006) is one good example that illustrates the possible adverse effects in test organisms, thus reflecting the action mode of this particular group of pharmaceuticals. Several studies have demonstrated that these compounds can affect physiological systems at very low concentrations (van der Ven et al., 2006; Schultz and Furlong, 2008). van der Ven et al. (2006) demonstrated that mianserin, a tetracyclic antidepressant, has estrogenic activity and produces endocrine disruption in zebrafish. A number of other studies on fluoxetine, diazepam, sertraline, paroxetine, and others, clearly showed significant adverse effects of antidepressants and anxiolytics in living organisms of aquatic matrices (Fong, 1998; Brooks et al., 2003a,b; Pascoe et al., 2003; Henry et al., 2004; Richards and Cole, 2006; Johnson et al., 2007; Fong and Molnar, 2008; Gaworecki and Klaine, 2008; Gust et al., 2009).

Similarly to other groups of pharmaceuticals, psychiatric drugs are not completely metabolized by the human body and are excreted as the unchanged parent compound or as metabolites or conjugates (generally, glucuronides) (Heberer, 2002a). Even if pharmaceuticals are extensively metabolized, their metabolites may continue to be biologically active or, in some cases, be easily transformed to the parent compound under environmental conditions, due to bacterial action (Halling-SØrensen et al., 1998; Richards and Cole, 2006). Preferentially, pharmaceuticals enter the environment through the WWTPs effluents and land application of sludge (Sanderson et al., 2003; Kinney et al., 2006a,b; Gómez et al., 2007; Conkle et al., 2008; Zhang et al., 2008; Loganathan et al., 2009), as result of the inadequacy of removal treatment methods. Also, these compounds can reach aquatic and terrestrial environments not only due to their use as human therapeutics, but also because of their use in veterinary treatments, release from production industries, use of treated wastewater in irrigation (Pedersen et al., 2005; Kinney et al., 2006a,b; Ruhoy and Daughton, 2008) and incorrect household disposal (Bound et al., 2006; Ruhoy and Daughton, 2008). In 2005, Bound and co-workers performed a survey, inquiring approximately 400 householders from the South-East of England, about the disposal and perception of risk of pharmaceuticals to the environment (Bound and Voulvoulis, 2005; Bound et al., 2006). Their survey revealed that antidepressants, among the eight pharmacological groups targeted, are perceived to be one of the most hazardous groups to the environment by 64.9% of interviewees. Despite none of the interviewed people admitted having disposed the unused antidepressants into the sink, 66.7% disposed the unused packages into the bin together with the common organic domestic residues. Even though, the excretion by patients is thought to be a more relevant source of pharmaceutical contamination when compared to the incorrect disposal of unused packages (Cunningham et al., 2006).

The assessment of contamination levels and potential novel contaminants must address different aspects of this environmental problem. It is important to identify and determine the environmental concentrations of pharmaceuticals and their metabolites; understand their metabolism and excretion patterns; evaluate the efficiency of the wastewater treatments in the removal of these pollutants, comprehend their dispersion, mobility and persistence under environmental conditions (biotic and abiotic degradability) and the uptake and effects on non-target organisms (Halling-SØrensen et al., 1998; JØrgensen and Halling-SØrensen, 2000; Heberer, 2002a; Jjemba, 2006). In this context, this paper aims to present a review of the literature data concerning the environmental impact of psychiatric drugs (anxiolytics, sedatives, hypnotics and antidepressants) in six sections: in Section 2, the occurrence of psychiatric pharmaceuticals in different environmental matrices, as well as their environmental concentrations, are summarized; Section 3 is related to the metabolization of psychiatric pharmaceuticals and the respective excretion rates as the principal pathway to environmental contamination; Section 4 addresses the removal efficiency of these compounds by WWTP methods; Section 5 presents literature data about the environmental persistence and resistance to biotic and abiotic degradation of several anxiolytics and antidepressants; Section 6 is aimed to detail chronic and acute toxicity data of these pharmaceuticals to aquatic organisms and finally, Section 7 provides information on the optimization of analytical methods for the determination of psychiatric drugs in environmental complex matrices.

2. Occurrence of psychiatric drugs in the environment

The structures of several environmental relevant psychiatric pharmaceuticals are illustrated in Fig. 1.

2.1. Anxiolytics, sedatives and hypnotics

Pharmaceuticals with anxiolytic, sedative and hypnotic effects comprise, essentially, benzodiazepines, buspirone (an azapirone), zoplicone (a cyclopyrrolone), zolpidem (an imidazopyridine) and barbiturates (Chouinard et al., 1999; Kar, 2007). Among these, the group of benzodiazepines (with special relevance to diazepam) is the most extensively studied as potential environmental contaminants. Table 1 gives an overview of anxiolytics, sedatives and hypnotics found in aquatic environments.

Benzodiazepines are one of the most prescribed pharmaceuticals (van der Ven et al., 2004). In 2007, Europe registered as the Continent with the highest consumption of benzodiazepines;

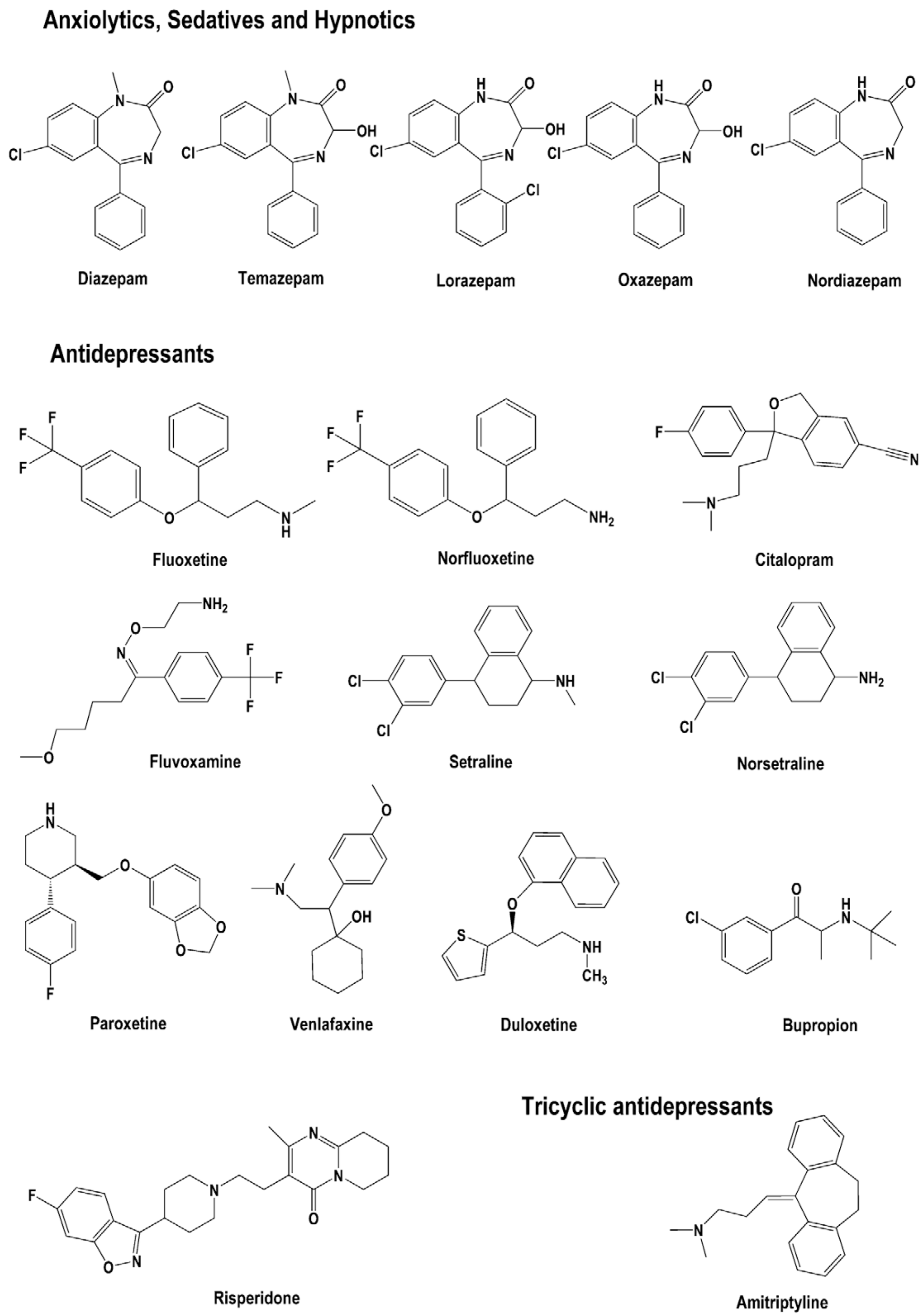

Fig. 1. Structure of several relevant psychiatric drugs in an environmental context.

Table 1
Occurrence of psychiatric pharmaceuticals in the environment.

Pharmaceutical	Concentration found in the environment	Sample	Method of analysis	Reference	Additional information
Diazepam	0.04 μg L^{-1}	Municipal sewage treatment plant (STP) effluents; Germany	GC–MS	(Ternes, 1998, 2001)	Analysis performed between 1996 and 1998
	<LOD[a] (0.030 μg L^{-1})	Rivers and streams; Germany	GC–MS	(Ternes, 1998, 2001)	Analysis performed between 1996 and 1998
	<LOQ[b] (0.20 μg L^{-1})	Influent of a municipal Hessian STP; Germany	LC–ES-MS/MS	(Ternes et al., 2001)	Analysis performed between 26/06/00 and 30/06/00
	<LOQ (0.050 μg L^{-1})	Effluent of a municipal Hessian STP; Germany	LC–ES-MS/MS	(Ternes et al., 2001)	Analysis performed between 26/06/00 and 30/06/00
	0.053 μg L^{-1}	Municipal STP effluent; Germany	LC–ES-MS/MS	(Ternes et al., 2001)	–
	0.033 μg L^{-1}	Rivers and streams; Germany	LC–ES-MS/MS	(Ternes et al., 2001)	–
	0.88 μg L^{-1}	Surface waters; Germany	HPLC–MS/MS	(Ternes, 2001)	Analysis performed in 2000
	3–62 ng L^{-1}	Lake Mead; USA	GC–MS	(Snyder et al., 2001)	Analysis performed between 1997 and 1999
	<1 μg L^{-1}	Sewage effluent; UK	Not provided	(Halling-SØrensen et al., 1998)	Analysis performed in 1981
	∼10 ng L^{-1}	River water; UK	Not provided	(Halling-SØrensen et al., 1998; Jones et al., 2005a)	Analysis performed in 1981
	∼10 ng L^{-1}	Potable water; UK	Not provided	(Halling-SØrensen et al., 1998; Jones et al., 2005a)	Analysis performed in 1981
	>0.01 μg L^{-1}; 0.59 μg L^{-1}; 1.18 μg L^{-1}	STP influent; Belgium	LC-ES–MS/MS	(van der Ven et al., 2004)	–
	>0.01 μg L^{-1}; 0.66 μg L^{-1}	STP influent; Belgium	LC-ES–MS/MS	(van der Ven et al., 2004)	–
	23.5 ng L^{-1}	Drinking water; Italy	HPLC–MS/MS	(Zuccato et al., 2000)	–
	0.13–2.13 ng L^{-1}	Po and Lambro rivers; Italy	HPLC–MS	(Calamari et al., 2003)	Diazepam was found in all the eight samples collected in different locations. Sampling performed in October, 2001.
	120 ng L^{-1}	Waste water sewer; Germany	LC–MS/MS	(Wolf et al., 2004)	Sampling between 2001 and 2003
	310 ng L^{-1}	Waste waster inflow; WWTP in Germany	LC–MS/MS	(Wolf et al., 2004)	Sampling between 2001 and 2003
	33.6 ± 7.1; 30.8 ± 9.3 and 27.9 ± 5.1 ng L^{-1}	River water; Romania	GC–MS	(Moldovan, 2006)	–
Nordiazepam	8.3 ng L^{-1}	WWTP effluent; France	GC–MS	(Togola and Budzinski, 2008)	–
	2.4 ng L^{-1}	Surface waters; France	GC–MS	(Togola and Budzinski, 2008)	–
Oxazepam	0.25 μg L^{-1}	STP effluent; Germany	GC–MS	(Heberer, 2002b)	–
Pentobarbitol	Qualitative analysis	Groundwater near a landfill; USA	GC–MS/MS	(Eckel et al., 1993; Jones et al., 2001)	Analysis performed in 1991. The landfill received medical wastes in 1968 and 1969
	5.4 μg L^{-1}	River Mulde; Germany	GC–MS	(Peschka et al., 2006)	Analysis performed in April 2004
Butalbital	5.3 μg L^{-1}	River Mulde; Germany	GC–MS	(Peschka et al., 2006)	Analysis performed in April 2004
Phenobarbital	0.2–1.3 μg L^{-1}	Irrigation field; Germany	GC–MS	(Peschka et al., 2006)	Analysis performed in 2004/2005
	0.03 μg L^{-1}	STP effluent; Germany	GC–MS	(Heberer, 2002b)	–
5,5-diallylbarbituric acid	Qualitative analysis	Groundwater near a landfill; Denmark	HPLC–UV	(Holm et al., 1995)	The landfill received ∼85 000 tones of pharmaceutical industrial and domestic wastes between 1962 and 1975
Meprobamate	43 ng L^{-1}	Finished drinking waters; USA	Not provided	(Snyder, 2008)	–
	Qualitative analysis	Groundwater near a landfill; USA	GC–MS/MS	(Eckel, 1993; Jones et al., 2001)	Analysis performed in 1991. The landfill received medical wastes in 1968 and 1969

Fluoxetine	0.012 μg L^{-1}	Surface waters; USA	LC–(ESI(+))–MS	(Kolpin et al., 2002)	Analysis performed between 1999 and 2000
	0.099 μg L^{-1}	Effluents of the sewage treatment plants; Canada	GC–MS	(Metcalfe et al., 2003)	–
	Between 0.1 ng g^{-1} and 10 ng g^{-1}	Tissues (muscle, brain and liver) of fish residing in a municipal effluent-dominated stream; USA	GC–MS	(Brooks et al., 2005)	Fish species: *Lepomis macrochirus*, *Ictalurus punctatus*, *Cyprinus carpio* and *Pomoxis nigromaculatus*
	12 ± 3; 20 ± 10 and 12 ± 5 ng L^{-1}	5–1762 m of distance downstream from the Pecan Creek Water Reclamation Plant; USA	LC(ESI)–MS/MS	(Schultz and Furlong, 2008)	–
	<0.00050 μg L^{-1}	Finished drinking water; USA	Not provided	(Snyder, 2008)	–
	100–4700 μg kg^{-1} organic carbon	9 bio-solids produced by 8 WWTPs; USA	HPLC–(ESI)-MS	(Kinney et al., 2006b)	–
	Between 0.14 and 1.02 μg kg^{-1}	Fish tissues; Canada	LC–(APCI)-MS/MS	(Chu and Metcalfe, 2007)	Fish species: *Ameiurus nebulosus*, *Dorosoma cepedianum* and *Morone americana*
Norfluoxetine	0.83 ± 0.01; 1.0 ± 0.5 and 0.9 ± 0.2 ng L^{-1}	5–1762 m of distance downstream from the Pecan Creek Water Reclamation Plant; USA	LC–(ESI)-MS/MS	(Schultz and Furlong, 2008)	–
	Between 0.1 ng g^{-1} and 10 ng g^{-1}	Tissues (muscle, brain and liver) of fish residing in a municipal effluent-dominated stream; USA	GC–MS	(Brooks et al., 2005)	Fish species: *L. macrochirus*, *I. punctatus*, *C. carpio* and *P. nigromaculatus*
	Between 0.15 and 1.08 μg kg^{-1}	Fish tissues; Canada	LC–(APCI)-MS/MS	(Chu and Metcalfe, 2007)	Fish species: *A. nebulosus*, *D. cepedianum* and *M. americana*
Paroxetine	2.1 ± 0.4; 3 ± 1 and 2.2 ± 0.2 ng L^{-1}	5–1762 m of distance downstream from the Pecan Creek Water Reclamation Plant; USA	LC–(ESI)-MS/MS	(Schultz and Furlong, 2008)	–
	Between 0.48 and 0.58 μg kg^{-1}	Fish tissues; Canada	LC–(APCI)-MS/MS	(Chu and Metcalfe, 2007)	Fish species: *A. nebulosus*, *D. cepedianum* and *M. americana*
Sertraline	Between 0.1 ng g^{-1} and 10 ng g^{-1}	Tissues (muscle, brain and liver) of fish residing in a municipal effluent-dominated stream; USA	GC–MS	(Brooks et al., 2005)	Fish species: *L. macrochirus*, *I. punctatus*, *C. carpio* and *P. nigromaculatus*
	36 ± 5; 49 ± 9 and 33 ± 8 ng L^{-1}	5–1762 m of distance downstream from the Pecan Creek Water Reclamation Plant; USA	LC–(ESI)-MS/MS	(Schultz and Furlong, 2008)	–
Norsertraline	Between 0.1 ng g^{-1} and 10 ng g^{-1}	Tissues (muscle, brain and liver) of fish residing in a municipal effluent-dominated stream; USA.	GC–MS	(Brooks et al., 2005)	Fish species: *L. macrochirus*, *I. punctatus*, *C. carpio* and *P. nigromaculatus*
	5 ± 3; 7 ± 3 and 3 ± 1 ng L^{-1}	5–1762 m of distance downstream from the Pecan Creek Water Reclamation Plant; USA	LC–(ESI)-MS/MS	(Schultz and Furlong, 2008)	–
Citalopram	90 ± 20; 40 ± 30 and 80 ± 30 ng L^{-1}	5–1762 m of distance downstream from the Pecan Creek Water Reclamation Plant; USA	LC–(ESI)-MS/MS	(Schultz and Furlong, 2008)	–
Duloxetine	1.5 ± 0.2; 2 ± 2 and 1.2 ± 0.9 ng L^{-1}	5–1762 m of distance downstream from the Pecan Creek Water Reclamation Plant; USA	LC–(ESI)-MS/MS	(Schultz and Furlong, 2008)	–
Bupropion	50 ± 20; 60 ± 40 and 50 ± 10 ng L^{-1}	5–1762 m of distance downstream from the Pecan Creek Water Reclamation Plant; USA	LC–(ESI)-MS/MS	(Schultz and Furlong, 2008)	–
Venlafaxine	600 ± 200; 1000 ± 400 and 900 ± 300 ng L^{-1}	5–1762 m of distance downstream from the Pecan Creek Water Reclamation Plant; USA	LC–(ESI)-MS/MS	(Schultz and Furlong, 2008)	–
Risperidone	0.00034 μg L^{-1}	Finished drinking water; USA.	Not provided	(Snyder, 2008)	–
Amitriptyline	0.5–21 ng L^{-1}; 0.5–3 ng L^{-1};0.5–17 ng L^{-1}; 0.5–13 ng L^{-1}	Rivers in South Wales, UK	HPLC–MS/MS	(Kasprzyk-Hordern et al., 2008)	–
	6.0 ng L^{-1}	WWTP effluent; France	GC–MS	(Togola and Budzinski, 2008)	–
	1.4 ng L^{-1}	Drinking water; France	GC–MS	(Togola and Budzinski, 2008)	–
Lofepramine	<4 ng L^{-1}	Estuaries; UK	LC–(ESI)-MS/MS	(Thomas and Hilton, 2004)	–

[a] LOD: limit of detection.
[b] LOQ: limit of quantification.

globally, the International Narcotics Control Board (2009) accounts for the consumption of 27 billion S-DDD (defined daily doses for statistical purposes per thousand inhabitants per day) of the 22 benzodiazepines generally classified as anxiolytics. The benzodiazepine diazepam is the most traded substance of the group being consumed across all the regions of the world (International Narcotics Control Board, 2009). These compounds act on the central nervous system and are mainly indicated to treat anxiety, amnesia and to produce sedation (van der Ven et al., 2004; Kar, 2007; Brunton et al., 2008); they are also effective anticonvulsants (Brunton et al., 2008). Nowadays, there are 35 benzodiazepines under international control for therapeutic use (International Narcotics Control Board, 2009). However, these compounds are not exclusively used for human therapeutics: benzodiazepines prescription is also common in veterinary treatments (Courtheyn et al., 2002; Gaskins et al., 2008). Generally, benzodiazepines have anxiolytic and appetite stimulant effects in domestic and wild animals (Gaskins et al., 2008). Benzodiazepam injections are frequently used to induce anesthesia and diazepam can be used as an anxiolytic and sedative in the transportation of sheep, and other domestic animals, to prevent injuries caused by stressful transport conditions. Brotizolam is also recommended to stimulate the appetite of weak animals (Courtheyn et al., 2002).

Diazepam, a 1,4-benzodiazepine, is the most extensively studied active substance with anxiolytic effects (Halling-SØrensen et al., 1998; Ternes, 1998, 2001; Ternes et al., 2001; Dębska et al., 2004). No data is available on the occurrence of the large majority of other benzodiazepines as well as on buspirone, zolpicone and zolpidem. Diazepam was first determined in the environment by Waggot (1981) who reported concentrations of <1 $\mu g\ L^{-1}$ in a sewage effluent and $\sim$10 $ng\ L^{-1}$ in river and potable drinking waters (Halling-SØrensen et al., 1998). Subsequently, several studies indicated the presence of this broadly used anxiolytic in WWTPs effluents and influents, rivers and lakes located in distinct parts of the world. The concentrations found range from 0.04 $\mu g\ L^{-1}$, in a municipal WWTP in Germany, to 1.18 $\mu g\ L^{-1}$, in a WWTP in Belgium (Ternes, 1998, 2001; van der Ven et al., 2004). In surface waters, a maximum concentration of 0.88 $\mu g\ L^{-1}$ was determined in Germany (Ternes, 2001). Recently, a study on pharmaceutical contaminants and associated potential concerns to pregnant women and children reported that a cumulative ingestion of 5% of a minimum clinical dose of diazepam may occur during pregnancy (taking as reference the ingestion of 2 L of water per day, during 36 weeks, and a determined diazepam concentration in drinking water of 0.235 $\mu g\ L^{-1}$) (Collier, 2007). In the author's opinion, this fact may not be ignored as there is strong evidence that diazepam cause the occurrence of several dysfunctions when used in the later stages of pregnancy (such as the withdrawal and the Floppy infant syndrome) (Collier, 2007).

The other referred pharmaceutical group with anxiolytic, sedative and hypnotic action is the barbiturates' group which is constituted by derivatives of barbituric acid (Peschka et al., 2006). Until the 1970s, barbiturates derivatives were the most common active substances in sleeping pills (Holm et al., 1995) and were also commonly used to treat anxiety symptoms (Kar, 2007). This group has also an important therapeutic application as narcotics (Peschka et al., 2006). Nevertheless, with the exception of some specific usages, barbiturates have been replaced by benzodiazepines, effectively due to the severe adverse effects to the human body (Kar, 2007; Brunton et al., 2008). Nowadays, barbiturates are used mainly as veterinary drugs (Peschka et al., 2006). Despite the small number of barbiturates prescriptions to human, it is relevant to refer that a few studies reported the occurrence of these compounds in the environment (Eckel et al., 1993; Holm et al., 1995; Jones et al., 2001). An investigation performed by Eckel et al. (1993), determined pentobarbital in groundwaters near a landfill in Florida that used to receive medical wastes in 1968 and 1969, thus demonstrating that this pharmaceutical had persisted in the environment during 21 years (Eckel et al., 1993). A distinct research done by Holm et al. (1995) revealed a similar situation with 5,5-diallybarbituric acid. Holm analyzed groundwater close to a landfill, in Denmark, which received, approximately, 85 000 tones of industrial and domestic wastes between 1962 and 1975. Once more, the barbiturate was identified in the analyzed samples, indicating an environmental persistence of more than 20 years (Holm et al., 1995).

2.2. Antidepressants

Antidepressants are also largely prescribed pharmaceuticals (Jjemba, 2002; Kwon and Armbrust, 2008; Paterson and Metcalfe, 2008; Schultz and Furlong, 2008). One of the most common classes of antidepressants is known as selective serotonin re-uptake inhibitors (SSRIs) and act by modulating the levels of the neurotransmitter serotonin (Brooks et al., 2005). They are largely prescribed to treat clinical depression, compulsive–obsessive disorder, panic disorder, as well as to other cases in which selective inhibition of serotonin re-uptake is desirable (Brooks et al., 2003a; Schultz and Furlong, 2008; Unceta et al., 2008). Presently, there are five SSRIs available in the market: fluoxetine, fluvoxamine, paroxetine, sertraline and citalopram (Johnson et al., 2007). There are other antidepressants usually prescribed when SSRIs are not effective. These include venlafaxine and duloxetine (selective serotonin and norepinephrine re-uptake inhibitors (SSNRIs)), bupropion (that acts by inhibiting the uptake of dopamine and norepinephrine) (Schultz and Furlong, 2008) and also tricyclic and tetracyclic antidepressants such as amitriptyline and mianserin, respectively. Some of these, and particularly amitriptyline, are also administered to animals (Halling-SØrensen et al., 1998). The usage of antidepressants in animals is recommended to treat pathologies such as separation anxiety, obsessive–compulsive and fearful behavior among other behavioral problems (Mills, 2003).

A large number of antidepressants have already been identified in water, sludge and biological tissues of aquatic organisms and, as for the case of anxiolytics, sedatives and hypnotics, the encountered concentrations range from ng to $\mu g\ L^{-1}$ or ng to $\mu g\ kg^{-1}$ (Kolpin et al., 2002; Metcalfe et al., 2003; Brooks et al., 2005; Kinney et al., 2006b; Schultz and Furlong, 2008). Fluoxetine and its metabolite norfluoxetine are the most commonly investigated antidepressants throughout the world. However, the antidepressants found in the highest concentrations were venlafaxine, citalopram and bupropion ($1000 \pm 400\ ng\ L^{-1}$, $90 \pm 20\ ng\ L^{-1}$, $60 \pm 40\ ng\ L^{-1}$, respectively, in samples collected downstream from a Water Reclamation Plant) (Schultz and Furlong, 2008). Until now, the maximum determined concentration of fluoxetine was 0.099 $\mu g\ L^{-1}$ in WWTP effluents in Canada (Metcalfe et al., 2003). Moreover, very high quantities of fluoxetine were found in bio-solids produced by a WWTP, varying from 100 to 4700 $\mu g\ kg^{-1}_{\text{organic carbon}}$ (Kinney et al., 2006b). These fluoxetine concentrations may be a helpful tool to understand the probable environmental fate of fluoxetine in water/sediment systems and also to identify the usage of sludge in agricultural fields, and other usual similar applications, as significant pathways to the entrance of this compound into the environment (Xia et al., 2005). Besides the occurrence in surface waters (Metcalfe et al., 2003; Thomas and Hilton, 2004; Johnson et al., 2005; Richards and Cole, 2006; Kasprzyk-Hordern et al., 2008), amitriptyline, fluoxetine and risperidone were also recently found in treated drinking waters at low concentrations (Snyder, 2008; Togola and Budzinski, 2008; Benotti et al., 2009), revealing the inefficiency of drinking water treatments to remove these compounds. Additionally, several antidepressants were determined in biological fish tissues, emphasizing the possibility of bioaccumulation by aquatic organisms. Brooks et al. (2005) found concentrations in the range of 0.1–10 ng g^{-1} of fluoxetine, sertraline and their metabolites (norfluoxetine and desmethylsertraline, respectively) in muscle, liver and brain tissues of four fish species in a municipal effluent-dominated stream, in Texas, USA. A similar experiment by Chu and Metcalfe (2007) reported concentrations between 0.14 and 1.02 μg kg^{-1} of fluoxetine, 0.15 and 1.08 μg kg^{-1} of norfluoxetine and 0.48 and 0.58 μg kg^{-1} of paroxetine in other four fish species.

Detailed information about the environmental occurrence of antidepressants is presented in Table 1.

3. Metabolization of psychiatric pharmaceuticals

As it was mentioned above, pharmaceuticals ingested by humans are almost always not completely metabolized, resulting in the excretion of variable percentages of active compound along with several metabolites and conjugates in urine and feces (Carlsson et al., 2006). As the excretion by patients is considered to be the main pathway for the entrance of pharmaceuticals into environmental matrices (Sanderson et al., 2003; Cunningham et al., 2006), the understanding of human metabolism and excretion rates of psychiatric drugs is of crucial importance to the assessment of environmental concentrations of this pharmacological subgroup.

Psychiatric pharmaceuticals, and in particular benzodiazepines, are usually excreted in urine, being first extensively metabolized in the liver to form pharmacologically inactive glucuronides conjugates (Chouinard et al., 1999). Despite the pharmacological inactivity of glucuronides conjugates, it is thought that these metabolites are easily decomposed by bacterial action and reconverted in the parent active compound (Halling-SØrensen et al., 1998; Ternes, 2001; Ashton et al., 2004; Carballa et al., 2004). It seems to be highly probable that glucuronides conjugates are readily deconjugated in domestic wastewaters and WWTPs due to the generalized presence of the fecal bacteria *Escherichia coli*, responsible for the production of very large amounts of the enzyme β-glucuridase (Ternes, 1998; Jones et al., 2005b; Petrović and Barceló, 2007). This deconjugation process results in the increase of the parent compound's quantity in sewage conditions.

For a more detailed analysis of this subject, Table 2 presents a compilation of literature data about the excretion rates and principal metabolites of some psychiatric drugs that occur in the environment. Large discrepancies of the excretion rates are found in the literature; even though, the amounts of pharmaceuticals excreted in the unchanged or conjugate forms can vary considerably from 1% to 75% of a single dose, thus justifying the importance of the excretion by humans and/or animals as a preferential route for environmental contamination.

4. Resistance to WWTPs removal methods and occurrence in sludge

WWTP effluents are continuously introducing pharmaceuticals into the environment and are considered to be the major source of aquatic environmental contamination (Buchberger, 2007). Generally, literature data on pharmaceuticals in the environment suggests that the large majority (if not all) of urban wastewaters are contaminated with these compounds (Jones et al., 2005b). The type and abundance of active substances found in different countries is strictly related to the local rates of consumption. Their widespread consumption emphasizes the importance of understanding the fate and behavior of psychiatric drugs in WWTPs. Their behavior may be a noteworthy tool to assess the probable concentrations of these compounds in effluents and sludges, in order to evaluate their potential effects in the environment (Jones et al., 2005b). Besides the presence of pharmaceuticals in WWTPs influents, it was proved by several studies that pharmaceuticals are not completely removed by wastewater treatments, being also present in WWTPs effluents and treated sludge (Ternes, 1998; Dębska et al., 2004; Xia et al., 2005; Gómez et al., 2007; Conkle et al., 2008; Zhang et al., 2008; Loganathan et al., 2009) (see Table 1 for data about pharmaceuticals in WWTPs effluents and sludge). Actually, WWTPs were not specifically intended to remove bioactive xenobiotics and their removal efficiencies can range from zero to almost complete removal, depending on the specific treatment methods used in more or less sophisticated WWTP facilities (Petrović & Barceló, 2007). Moreover, following the disappearance of a pharmaceutical in the liquid phase is not sufficient to conclude that it was completely removed by a specific treatment method as it may pass into the solid phase, or exist in a different form of the parent compound due to chemical transformations (Petrović & Barceló, 2007). Liquid effluents are commonly discharged in surface waters; this can lead to indirect water reuse in areas where these surface waters are the source used to produce potable water (Drewes et al., 2002; Jones et al., 2005a; Glassmeyer et al., 2008). Also, WWTPs effluents are increasingly being used for the irrigation of crops and arid areas and ground water recharge in several countries throughout the world (Drewes et al., 2002; Pedersen et al., 2005; Glassmeyer et al., 2008). Moreover, nowadays, the use of Slow Rate Systems (SRS) to purify wastewaters is becoming more and more common, consisting on its application on land, taking advance of physical, chemical, and biological mechanisms (such as filtration, degradation, soil adsorption, chemical precipitation, denitrification, volatilization, and plant uptake) that occur concurrently in the soil–water–atmosphere environment (Paranychianakis et al., 2006). These practices have the obvious advantage of reducing the demand for water supplies, but provide, due to the reasons explained above, the main pathways for the introduction of pharmaceuticals in soils and surface and ground waters through runoff and infiltration (Pedersen et al., 2005).

Several psychiatric drugs partially or totally resist to wastewater treatments. In Table 3 are gathered the available data concerning the removal efficiency of the anxiolytic diazepam. In this particular case, several methods have removal efficiencies bellow 10%, being evident the large amount of diazepam which passes unaffected through WWTPs. Moreover, just three of the presented methods are able to remove this benzodiazepine almost entirely (more than 90% of efficiency) and several of them show a large variability in the removal percentage. These facts justify the frequent occurrence of this pharmaceutical in environmental samples. In Table 4 is shown a set of data focused on fluoxetine, meprobamate and diazepam. Meprobamate, a barbiturate that was identified in finished drinking waters in the United States (Snyder, 2008), has particularly low efficiencies of removal remaining, in some cases, completely unaltered.

Another important aspect is due to a deconjugation phenomenon which is very likely to occur in WWTPs, as was stated before (Jones et al., 2005b). The most relevant consequence of this deconjugation process is the increase of biologically active compounds in influents and, consequently, in effluents and sludge (Ternes, 1998; Petrović & Barceló, 2007). The hypothesis on the deconjugation of pharmaceutical conjugates is supported by investigations which concluded that the concentration of parent compound found in WWTPs effluents is considerable higher than the concentration of the conjugated form, contradicting the excretion patterns and underlining the possibility of, at least, partial cleavage of the conjugates (Ternes, 1998).

It is essential to consider the presence of psychiatric pharmaceuticals in sludge that result, inevitably, from wastewater treatments (Chenxi et al., 2008; Lapen et al., 2008; Gielen et al.,

Table 2
Metabolites and excretion rates of psychiatric drugs which occur in the environment.

Pharmaceutical	Excretion rates	Additional information
Diazepam	10% unchanged (Carballa et al., 2008)	Metabolized in the liver to produce nordiazepam that is further converted in oxazepam e temazepam (Ariffin et al., 2007)
	1% unchanged (Smith-Kielland et al., 2001)	
	Conjugated metabolites can be 22–43% of a single intake dose (Smith-Kielland et al., 2001)	After a single dose of diazepam, urinary concentrations of desmethyldiazepam, temazepam e oxazepam were 29.6 ± 22.3, 57.4 ± 47.0 and 18.4 ± 16.7 ng/mL (Chiba et al., 1995)
	<5% of the parent compound excreted (Jjemba, 2006)	0.5–0.2%, 3.6–4.4%, 9.0–6.4%, and 8.7–6.3% of a single ingested dose were excreted into the urine as diazepam, desmethyldiazepam, temazepam and oxazepam, respectively (Chiba et al., 1995)
	Mean amounts of diazepam and its metabolites excreted: 20%. Temazepam (6.6%), desmethyldiazepam (3.9%) and oxazepam (2.8%) (Chiba et al., 1995)	
Nordiazepam	–	Metabolized to oxazepam and oxazepam glucuronides (Moffat et al., 2005)
Tetrazepam	13–49% as diazepam (Pavlic et al., 2007)	Principal metabolites are 3-hydroxy-tetrazepam, hydroxy-tetrazepam, norhydroxytetrazepam, diazepam and nordazepam (Pavlic et al., 2007)
Lorazepam	Negligible amounts unchanged (Ghasemi et al., 2006)	Extensively metabolized to its glucuronide conjugate (Ghasemi et al., 2006)
Oxazepam	75% unchanged (Carballa et al., 2008)	
	70–80% is excreted in the urine almost entirely as oxazepam glucuronide with traces of unchanged oxazepam and other minor metabolites. 10% is eliminated in the feces unchanged (Moffat et al., 2005)	–
Citalopram	12–20% unchanged (Rao, 2007)	Metabolites: desmethylcitalopram, didesmethylcitalopram, citalopram-N-oxide and a propionic acid derivative. The metabolites have some pharmacological activity. (Moffat et al., 2005)
Fluoxetine	<5% of the parent compound excreted (Jjemba, 2006)	Principal metabolites include fluvoxamine and norfluoxetine. These metabolites inhibit the metabolization of benzodiazepines (Chouinard et al., 1999)
	<10% unchanged parent compound in urine (Brooks et al., 2003a; Moffat et al., 2005)	Principal metabolite: norfluoxetine (Brooks et al., 2003a; Moffat et al., 2005)
	20–30% remains unchanged in urine (Fong and Molnar, 2008)	The metabolite norfluoxetine is biologically active and considered to be a more potent SSRIs when compared to its precursor (Fong and Molnar, 2008)
Sertraline	Less than 0.2% are excreted unchanged in urine (Moffat et al., 2005)	It suffers extensive metabolization in the body through: N-demethylation, oxidative deamination and subsequent reduction, hydroxylation and glucuronide conjugation (Moffat et al., 2005)
Norsertraline	–	Norsertraline is a N-demethylated metabolite of sertraline. It is eliminated more slowly than sertraline and has pharmacological activity (Brunton et al., 2008)
Paroxetine	2% as parent compound (Moffat et al., 2005) in urine and 1% feces (Cunningham et al., 2004).	–
	62% and 36% excreted in urine and feces, respectively, in the form of inactive metabolites(Cunningham et al., 2004)	
Venlafaxine	Excreted in urine: 1–10% as the unchanged drug, 30% O-desmethylvenlafaxine, 6–19% N,O-didesmethylvenlafaxine and 1% N-desmethylvenlafaxine. 2% is excreted in feces (Moffat et al., 2005).	–
Amitriptyline	Negligible amounts unchanged (Kasprzyk-Hordern et al., 2008)	Excreted as nortriptyline, 10-hydroxyamitriptyline (active), 10-hydroxynortriptyline (active) (Kasprzyk-Hordern et al., 2008)
	50% is excreted as 10–hydroxynortriptyline and its glucuronide conjugate and 27% as10–hydroxyamitriptyline (mainly conjugated); unchanged drug constitutes less than 5% of the excreted material. 8% may be eliminated in the feces as parent compound (Moffat et al., 2005)	
Phenobarbitone	6–39% of the parent compound excreted (Jjemba, 2006)	Enzymatic hydroxylation and carboxylation of aliphatic side chains following conjugation to glucuronides (Peschka et al., 2006)
	35% excreted unchanged (Kar, 2007)	
	25% is excreted in urine as unchanged drug and up to about 17% as 4-hydroxyphenobarbital (half of which in the form of glucuronide conjugate) (Moffat et al., 2005)	Major metabolites: N-glucopyranosylphenobarbital and 4–hydroxyphenobarbital and its glucuronide conjugate (Moffat et al., 2005)
Meprobamate	90% is excreted in urine. About 10–20% of the dose is excreted as unchanged drug and the remainder as metabolites (Moffat et al., 2005)	Major metabolites: 2–hydroxypropylmeprobamate and meprobamate N-glucuronide (Moffat et al., 2005)
Pentobarbitone	1% remained unchanged in urine (Moffat et al., 2005)	–
Butalbital	About 5% is excreted in urine as the parent compound (Moffat et al., 2005)	Major metabolite excreted in urine: 5-(2,3-dihydroxypropyl)-5-isobutylbarbituric acid (20–60%) (Moffat et al., 2005)

2009). In the United States, a WWTP produces an average of 240 kg (dry weight) of bio-solids per million of liters of treated wastewater (Kinney et al., 2006b); in the European Union, it is estimated to be produced between 9 and 38 kg (dry weight) of bio-solids per capita per year (Lapen et al., 2008). Considering the moderate lipofilicity of 1,4-benzodiazepines (Chouinard et al., 1999), medium octanol–water partitioning coefficients (e.g. 2.19 for temazepam and 2.7 for diazepam (Stein et al., 2008)) and low water solubility, benzodiazepines might partition preferentially into the organic rich bio-solids phase (Löffler et al., 2005). Relatively to antidepressants, Kinney et al. (2006b) found fluoxetine in nine samples of bio-solids collected in eight different WWTPs with considerably high concentrations in the range of 100–4700 μg kg^{-1}. These relatively high sorptions to soils/sediments enable the removal of the pharmaceuticals from wastewaters. However, the bio-solids produced in WWTPs may be a significant source of pharmaceuticals into the environment seeing that these contaminated bio-solids are used in agricultural soils, large-scale landscaping, domestic

Table 3
Removal of diazepam in wastewater treatment plants; adapted from the EU-Project POSEIDON final report, 2005 (Ternes et al., 2005b).

Removal treatment method	Removal (%)	Removal treatment method	Removal (%)
Primary treatment	<10	Effluent ozonation	10–50
COD removal (SRT $\leqslant$ 2 d)	<10	Ozonation	10–50
Nitrification (SRT 10–15 d)	<10	AOPs (Advanced oxidation processes)	50–90
Sludge stabilization (SRT $\geqslant$ 25 d)	<10	GAC	>90
Membrane bioreactor (SRT $\geqslant$ 25 d)	No data available	Ultrafiltration/PAC	>90
Biofilter	No data available	Nanofiltration	>90
Soil, unsaturated zone	No data available	UV	No data available
Groundwater, saturated zone	10–50	Chlorination	<10
Sludge anaerobic treatment	10–50	Chlordioxide	<10
Fenton process	<10		

Table 4
Removal of diazepam, fluoxetine and meprobamate in wastewater treatment plants.

Removal treatment method	<30% Removal	30–70% Removal	>70% Removal	References
Free chlorine (3.5 mg L^{-1})	Diazepam; Fluoxetine; Meprobamate			(Snyder, 2008)
UV at 40 mJ cm^{-2}	Diazepam; Fluoxetine; Meprobamate			(Snyder, 2008)
Ozone (2.5 mg L^{-1} dose)		Meprobamate	Diazepam; Fluoxetine	(Snyder, 2008)
PAC (dose 5 mg L^{-1})			Fluoxetine (96%)	(Westerhoff et al., 2005)
Flocculation with ferric chloride	Diazepam (0%); Fluoxetine (0%); Meprobamate (0%)			(Shon et al., 2006)
Flocculation with Aluminum	Diazepam (5%); Fluoxetine (20%); Meprobamate (0%)			(Shon et al., 2006)
Chlorination pH 5.5	Fluoxetine (20%); Meprobamate (16%)		Diazepam (71%)	(Shon et al., 2006)
Ozone/H_2O_2		Meprobamate (61%)	Diazepam (85%); Fluoxetine (98%)	(Shon et al., 2006)
Adsorption	Meprobamate (0%)	Diazepam (53%)	Fluoxetine (92%)	(Shon et al., 2006)

landscaping and soil-surface revegetation (Jones et al., 2005b; Kinney et al., 2006b; Lapen et al., 2008). More detailed data about the sorption and persistence of psychiatric drugs in soils/sediments will be given along the next section.

5. (A)biotic degradability and persistence in the environment

The degradability (through abiotic or biotic processes) and persistence of pharmaceuticals in water/sediment compartments are of great relevance to the assessment of chronic exposure of organisms living in these environments. However, and as far as psychiatric pharmaceuticals are concerned, few data is available on this issue (Löffler et al., 2005; Jones et al., 2006), despite the strong evidences of considerable high persistence and resistance to (bio)degradation of several compounds from these pharmaceutical group (Boreen et al., 2003; Ternes et al., 2005b; Kwon and Armbrust, 2006; Peschka et al., 2006).

5.1. Anxiolytics, sedatives and hypnotics

Generalized occurrence of diazepam in rivers, lakes and WWTP influents and effluents, suggests limited degradation of these compounds in environmental conditions (Redshaw et al., 2008). A study on the biodegradability of diazepam and related pharmaceuticals (oxazepam and temazepam), performed in liquid and solid matrices containing bacterial cultures typical of sewage sludge-amended soils, reported that diazepam is the most persistent of the considered pharmaceuticals. No losses caused by biotic or abiotic factors were observed during a 60 d experiment. Oxazepam underwent a loss of 40% due to biodegradation but the study also revealed the hypothesis of being transformed in another biologically active and persistent metabolite (Redshaw et al., 2008). Temazepam and oxazepam may undergo more abiotic losses because of a phenomenon of sorption to humic substances (Redshaw et al., 2008). Löffler et al. (2005) also considered diazepam as a highly persistent pharmaceutical, with a dissipation time (DT_{90}) $\gg$ 365 d and oxazepam as moderately persistent in water/sediment systems. Diazepam suffers rapid and extensive sorption onto sediments; it is highly stable in soils and during the wastewaters treatments (Löffler et al., 2005) and remains stable in ground waters (Ternes et al., 2005b). Diazepam is also considered to undergo photochemical degradation in environmental conditions; this photoreactivity may constitute a feasible mechanism for the decrease of its concentration in surface waters (Boreen et al., 2003). Differences in behavior between several 1,4-benzodiazepines, which are detailed in some of the referred investigations, are associated with differences in functional substituent groups. This fact underlines the importance of analyzing a wide range of extensively prescribed benzodiazepines to minimize the lack of information on the fate and persistence of this type of pharmaceuticals in environmentally relevant conditions. Overall, the literature data suggests that diazepam is being potentially accumulated in the environment.

Another relevant study related with the persistence of anxiolytics, sedatives and hypnotics is presented by Peschka et al. (2006). The biotic and abiotic degradability of several barbiturates (butalbital, secobarbital, hexobarbital, aprobarbital, phenobarbital, and pentobarbital) were assessed and the barbiturates were subjected to biodegradability under aerobic conditions and to hydrolysis. None of the barbiturates showed any evidence of degradation, stressing their high stability in the environment (Peschka et al., 2006). This behavior was also suggested by two distinct investigations that reported the identification of barbituratures in landfills which did not receive industrial or domestic wastes for more than 20 years (Eckel et al., 1993; Holm et al., 1995; Jones et al., 2001).

5.2. Antidepressants

Published information about biodegradability of fluoxetine and related compounds (such as its active metabolite norfluoxetine) stated that the selective serotonin re-uptake inhibitor fluoxetine is, apparently, one of the most resistant pharmaceuticals in the environment, raising several concerns about accumulation in environmental matrices (Redshaw et al., 2008). This SSRI persist in aquatic environments for relatively long periods of time when compared to other pharmaceuticals (Paterson and Metcalfe, 2008). Several experiments have already demonstrated that fluoxetine and norfluoxetine are resistant to biodegradation processes occurring in liquid and soil cultures of bacteria of sewage sludge-amended soils (Kwon and Armbrust, 2006; Redshaw et al., 2008). No fluoxetine (HCl) losses were observed during a 270 d essay (Redshaw et al., 2008). Fluoxetine also revealed to be hydrolytically and photolytically stable in aquatic environments (with half-lives greater than 100 d) (Kwon and Armbrust, 2006). Nevertheless, the major concern about fluoxetine environmental fate should not be focused on its persistence in water but in sediments/soils. Fluoxetine rapidly dissipates from water compartments as a result of high adsorption to sediments of water/sediments systems, where it appears to be greatly persistent (Kwon and Armbrust, 2006; Redshaw et al., 2008). In general, SSRIs have sorption capacities greater than 91% (Kwon and Armbrust, 2008) and yet, these values could not be explained by high octanol–water partition coefficient. The octanol–water partition coefficient (K_{ow}) is related with the compounds hydrophobicity (Sabljić et al., 1995). For neutral and hydrophobic pharmaceuticals it is known that the organic carbon content of biomass, soils or sediments may be related with sorption mechanisms and therefore plausibly well correlated with K_{ow} (Kwon and Armbrust, 2008). In the particular case of SSRIs, K_{ow} values vary from 1.12, for fluvoxamine, and 1.39, for citalopram; additionally these pharmaceuticals also have relatively high water solubilities (3.022–15.460 mg L^{-1}). Hence, hydrophobic interactions could not justify the sorption mechanism of these pharmaceuticals and, consequently, K_{ow} is not an adequate parameter to properly predict their fates in environmental conditions (Kwon and Armbrust, 2008). A study performed by Wells (2006) presented D_{ow}, the pH dependent octanol–water distribution ratio (a combination of K_{ow} and pK_a) as a more appropriate physicochemical parameter to understand the distribution of pharmaceuticals in water/sediment systems. This parameter takes into account the hydrophilic character of a pharmaceutical at a specific pH, allowing to understand the mobility of a compound at environmentally relevant pH conditions (Wells, 2006). Also, multiple mechanisms may be useful to describe high SSRIs sorption onto soils/sediments based, for instance, on cation exchange, cation bridging at clay surfaces, surface complexation or hydrogen bonding (Kwon and Armbrust, 2008).

As far as other antidepressants are concerned, very limited data is available, resulting in a substantial lack of knowledge about these emerging environmental pollutants. However, the information gathered indicates that persistence and accumulation are very likely to occur. One example is the case of the tricyclic antidepressant amitriptyline which was shown to be non biodegradable under sewage treatment conditions (Halling-SØrensen et al., 1998), highlighting the importance of performing more studies on the (bio)degradation of these pharmaceuticals in environmentally relevant conditions.

6. Toxicity of psychiatric drugs for non-target organisms

Psychiatric pharmaceuticals, similarly to other pharmacological groups, occur in the environment in the range of ng L^{-1}–μg L^{-1} (Bound et al., 2006). Although these concentrations are below the levels predicted to cause harm to humans, as well as to cause acute or even chronic toxicity to non-target organisms, it is pertinent to take into account that these compounds do not occur isolated but as complex mixtures (Bound et al., 2006). In this context, and due to having an intrinsic biological activity that would affect nervous and endocrine systems, psychiatric pharmaceuticals are one of the most significant groups in what concerns the evaluation of ecotoxicological effects in terrestrial and aquatic non-target organisms (van der Ven et al., 2006). Furthermore, the increasing number of studies about chronic toxicity on non-target aquatic organisms pointed out that no extrapolations between acute and chronic toxicity should be done, underlining the need of developing a distinct approach to better clarify this issue (Cunningham et al., 2006). In fact, seeing that aquatic organisms are extensively exposed to pharmaceuticals, it would be more important to understand life cycle toxicity rather than perform acute toxicity tests (Halling-SØrensen et al., 1998; Petrović & Barceló, 2007).

6.1. Anxiolytics, sedatives and hypnotics

The toxicity data for anxiolytics, sedatives and hypnotics is gathered in Table 5. In fact, to the best of our knowledge, diazepam is the only pharmaceutical with anxiolytic, sedative or hypnotic properties that was studied and evaluated in this context. Acute toxicity tests on several aquatic organisms revealed that the concentrations needed to the observation of acute adverse effects (in the mg L^{-1} scale) are well above the environmental concentrations of diazepam (the maximum concentration detected in surface waters was 0.88 μg L^{-1} (Ternes, 2001)). Nonetheless, a study performed by Pascoe et al. (2003), comparing acute and chronic toxicity of diazepam to an aquatic invertebrate sedentary organism (*Hydra vulgaris*), described visible adverse effects (deficient regeneration of polyps) at concentrations of 10.0 μg L^{-1}. With these first findings, and as the continuous discharge of these compounds in the environment results in exposures during the entire life cycle of the organisms (Halling-SØrensen et al., 1998; Pascoe et al., 2003), it is of great relevance to refer the lack of chronic toxicity studies for other organisms or for other pharmaceuticals with the same mode of action.

6.2. Antidepressants

Schwab et al. (2005) investigated the effects of the environmental occurrence of 14 different drug classes on human health. This study analyzed the antidepressant fluoxetine and one metabolite of the antidepressant paroxetine and concluded that there is no appreciable risk to human health caused by the exposure to pharmaceuticals occurring in surface and drinking waters. Despite the scientific consensus about the lack of an appreciable risk to human health because of environmental exposure to pharmaceuticals, the possible effects of antidepressants on aquatic organisms are not yet completely understood (Cunningham et al., 2006).

A large number of studies are focused on the potential environmental adverse effects of steroids and other estrogens, since their interference with the endocrine responses of aquatic organisms was discovered (Brooks et al., 2003a). On the contrary, little attention has been paid to non-steroidal pharmaceuticals that have the same ability, which is directly related to the mode of action of antidepressants; not only can they affect the neuronal system but also disrupt neuro-endocrine signaling causing perturbations on the reproductive behavior (Foran et al., 2004; van der Ven et al., 2006; Henry and Black, 2008; Péry et al., 2008; Gust et al., 2009; Sánchez-Argüello et al., 2009). Fluoxetine is one possible example of an antidepressant that is suspected to be hormonally active (Kolpin et al., 2002). In primary producers (invertebrates and fish), the mechanistic responses to SSRIs are not completely clarified. However, several fish species were identified for the possession of serotonin receptors, making it possible to predict that SSRIs can modulate serotonin levels in these animals (Brooks et al.,

Table 5
Toxicity data of psychiatric pharmaceuticals for non-target organisms.

Pharmaceutical	Test species (taxonomic group)	Acute toxicity test	Acute toxicity data	Chronic toxicity data	Reference	Additional information
Diazepam	*D. magna* (Invertebrates)	EC_{50}, 24 h	14.1 mg L^{-1}	–	(Calleja et al., 1994)	–
	D. magna (Invertebrates)	EC_{50}	13.9 mg L^{-1}; 4.3 mg L^{-1}	–	(Halling-Sørensen et al., 1998)	–
	PLHC-1 and RTG-2 cell lines (Fish)	EC_{50}	0.363 mM; 0.440 mM; 0.604 mM	–	(Caminada et al., 2006)	–
	D. magna (Invertebrates)	LC_{50}	13.9 mg L^{-1}	–	(Lilius et al., 1995)	–
	D. magna (Invertebrates)	LC_{50}	4.3 mg L^{-1}	–	(Halling-Sørensen et al., 1998)	–
	Tetraselmis chuii (unicellular marine algae)	IC_{50}	16.5 mg L^{-1} (16.45–16.47)	–	(Nunes et al., 2005)	The most toxic compound between clofibric acid, SDS and clofibrate
	Artemia parthenogenetica (crustacean)	LC_{50}	12.2 mg L^{-1} (11.99–12.32)	–	(Nunes et al., 2005)	The most toxic compound between clofibric acid, SDS and clofibrate
	Gambusia holbrooki (euryhaline fish)	LC_{50}	12.7 mg L^{-1} (12.57–12.85)	–	(Nunes et al., 2005)	The second most toxic compound between clofibric acid, SDS and clofibrate
	H. vulgaris (Invertebrate – cnidarian)	Evaluation of the capacity for regenerate polyps	<1 mg L^{-1}	10.0 μg/L^{-1}	(Pascoe et al., 2003)	–
Fluoxetine	*Xenopus laevis*	EC_{50}	6.4 mg L^{-1}; 6.6 mg L^{-1}	–	(Richards and Cole, 2006)	–
	PLHC-1 and RTG-2 cell lines (Fish)	EC_{50}	0.0205 mM; 0.0242 mM; 0.0110 mM	–	(Caminada et al., 2006)	–
	Pseudokirchneriella subcapitata (Algae – green)	EC_{50}	24 μg L^{-1}	–	(Brooks et al., 2003a)	–
	C. dubia (Invertebrates – waterflea)	EC_{50}	234 μg L^{-1}	–	(Brooks et al., 2003a)	–
	D. magna (Invertebrates – waterflea)	EC_{50}	820 μg L^{-1}	–	(Brooks et al., 2003a)	–
	P. promelas (fish)	EC_{50}	705 μg L^{-1}	–	(Brooks et al., 2003a)	–
	Hyalella azteca	EC_{50}	>43 μg kg^{-1}	–	(Brooks et al., 2003a)	–
	Chironomus tentans	EC_{50}	15.2 μg kg^{-1}	–	(Brooks et al., 2003a)	–
	P. subcapitata (Algae – green)	EC_{50}	24–39 μg L^{-1}	–	(Brooks et al., 2003b)	–
	C. dubia (Invertebrates – waterflea)	LC_{50}	234 μg L^{-1}	–	(Brooks et al., 2003b)	–
	D. magna (Invertebrates – waterflea)	LC_{50}	820 μg L^{-1}	–	(Brooks et al., 2003b)	–
	P. promelas (fish)	LC_{50}	705 μg L^{-1}	–	(Brooks et al., 2003b)	–
	C. tentans	LC_{50}	15.2 mg kg^{-1}	–	(Brooks et al., 2003b)	–
	P. subcapitata (Algae – green)	IC_{10};IC_{50}, 96 h	31.34 ± 1.93; 44.99 ± 1.76 μg L^{-1}	–	(Johnson et al., 2007)	–
	Scendesmus acutus (Algae)	IC_{10};IC_{50}, 96 h	55.60 ± 4.73; 91.23 ± 2.74 μg L^{-1}	–	(Johnson et al., 2007)	–
	S. quadricauda (Algae)	IC_{10};IC_{50}, 96 h	97.76 ± 13.54; 212.98 ± 16.13 μg L^{-1}	–	(Johnson et al., 2007)	–
	Chlorella vulgaris (Algae)	IC_{10};IC_{50}, 96 h	2901.57 ± 1218.97; 4339.25 ± 446.09 μg L^{-1}	–	(Johnson et al., 2007)	–
	Unspecified (Algae – green)	–	–	0.001 mg L^{-1}	(Crane et al., 2006)	–
	C. dubia (Invertebrates – waterflea)	–	–	0.056 mg L^{-1}	(Brooks et al., 2003a)	–
	C. dubia (Invertebrates – waterflea)	LC_{50}, 48 h	0.51 ± 0.07 mg L^{-1} (n = 3)	0.089 mg L^{-1} (NOEC affecting the mean number of neonates produced)	(Henry et al., 2004)	Range of acute test concentration: 0.19–2.92 mg L^{-1}
	Japanese medaka (Oryzias latipes)	LC_{50}, 96 h	5.5, 1.3 and 0.20 mg L^{-1} at pH 7, 8 and 9, respectively	–	(Nakamura et al., 2008)	–
	D. magna (Invertebrates – waterflea)	–	–	8.9 and 31 μg L^{-1} (NOEC and LOEC affecting the length of newborns, respectively)	(Péry et al., 2008)	

(*continued on next page*)

Table 5 (*continued*)

Pharmaceutical	Test species (taxonomic group)	Acute toxicity test	Acute toxicity data	Chronic toxicity data	Reference	Additional information
	Potamopyrgus antipodarum (Mollusc gastropod)	–	–	13 and 69 μg L^{-1} (NOEC and LOEC affecting reproduction, respectively)	(Péry et al., 2008)	
	P. antipodarum (Mollusc gastropod)	–	–	33.3 and 100 μg L^{-1} (NOEC and LOEC affecting the cumulate number of neonates, respectively)	(Gust et al., 2009)	42 d chronic exposure
	P. promelas (fish)	LC_{50}, 48 h	212; 198 and 216 μg L^{-1} for R-fluoxetine, rac-fluoxetine and S-fluoxetine, respectively	170; 174 and 101 μg L^{-1} (LOEC survival test with R-fluoxetine, rac-fluoxetine and S-fluoxetine, respectively)	(Stanley et al., 2007)	7 d chronic exposure
	D. magna (Invertebrates – waterflea)	–	–	429; 430 and 444 μg L^{-1} (LOEC survival test with R-fluoxetine, rac-fluoxetine and S-fluoxetine, respectively)	(Stanley et al., 2007)	21 d chronic exposure
Paroxetine	*X. laevis*	EC_{50}	4.6 mg L^{-1}		(Richards and Cole, 2006)	–
	C. dubia (Invertebrates – waterflea)	LC_{50}, 48 h	0.58 ± 0.13 mg L^{-1} (n = 3)	–	(Henry et al., 2004)	Range of acute test concentration: 0.22–6.96 mg L^{-1}
Citalopram	*C. dubia* (Invertebrates – waterflea)	–	–	0.8 mg L^{-1}	(Crane et al., 2006)	–
	C. dubia (Invertebrates – waterflea)	LC_{50}, 48 h	3.90 ± 0.27 mg L^{-1} (n = 3)	4 mg L^{-1} (LOEC affecting the mean number of neonates produced)	(Henry et al., 2004)	Range of acute test concentration: 0.59–7.84 mg L^{-1}
Fluvoxamine	Unspecified (Algae – green)	–	–	31 mg L^{-1}	(Crane et al., 2006)	–
	C. dubia (Invertebrates – waterflea)	LC_{50}, 48 h	0.84 ± 0.41 mg L^{-1} (n = 3)	0.366 mg L^{-1} (NOEC affecting the mean number of neonates produced)	(Henry et al., 2004)	Range of acute test concentration: 0.10–2.21 mg L^{-1}
	P. subcapitata (Algae – green)	IC_{10};IC_{50}, 96 h	3987.38 ± 322.88; 4002.88 ± 142.52 μg L^{-1}	–	(Johnson et al., 2007)	–
	S. acutus (Algae)	IC_{10};IC_{50}, 96 h	2503.65 ± 328.78; 3620.24 ± 134.96 μg L^{-1}	–	(Johnson et al., 2007)	–
	S. quadricauda (Algae)	IC_{10};IC_{50}, 96 h	1662.91 ± 157.16; 3563.34 ± 118.94 μg L^{-1}	–	(Johnson et al., 2007)	–
	C. vulgaris (Algae)	IC_{10};IC_{50}, 96 h	6162.86 ± 814.30; 10208.47 ± 379.24 μg L^{-1}	–	(Johnson et al., 2007)	–
Sertraline	*P. subcapitata* (Algae – green)	IC_{10};IC_{50}, 96 h	4.57 ± 0.66; 12.10 ± 1.00 μg L^{-1}	–	(Johnson et al., 2007)	–
	S. acutus (Algae)	IC_{10};IC_{50}, 96 h	54.59 ± 6.52; 98.92 ± 6.74 μg L^{-1}	–	(Johnson et al., 2007)	–
	S. quadricauda (Algae)	IC_{10};IC_{50}, 96 h	48.19 ± 3.27; 317.02 ± 21.46 μg L^{-1}	–	(Johnson et al., 2007)	–
	C. vulgaris (Algae)	IC_{10};IC_{50}, 96 h	152.73 ± 5.09; 763.66 ± 25.42 μg L^{-1}	–	(Johnson et al., 2007)	–
	X. laevis	EC_{50}	4.6 mg L^{-1}	–	(Richards and Cole, 2006)	–
	C. dubia (Invertebrates – waterflea)	LC_{50}, 48 h	0.12 ± 0.05 mg L^{-1} (n = 3)	0.045 mg L^{-1} (LOEC affecting the mean number of neonates produced)	(Henry et al., 2004)	Range of acute test concentration: 0.04–1.84 mg L^{-1}
Risperidone	Unspecified (Algae-cyanobacteria)	–	–	<100 mg L^{-1}	(Crane et al., 2006)	–
	Unspecified (Algae – green)	–	–	<10.0 mg L^{-1}	(Crane et al., 2006)	–

2005). An investigation of chronic and acute toxicity of SSRIs to *Ceriodaphnia dubia* by Henry et al. (2004) confirmed that the reproduction patterns of these invertebrates are affected by the exposure to these antidepressants. SSRIs have the ability to reduce the number of neonates and the number of broods per female with a lowest-observable-effects concentration (LOEC) of 0.045 mg L^{-1}. Several SSRIs have also been found to be directly related to gonadal maturation, induction of parturition, metamorphosis and spawning in aquatic organisms (Henry et al., 2004; Fong and Molnar, 2008). Concentrations as low as 32 ng L^{-1} were shown to induce spawning in male zebra mussels (*Dreissena polymorpha*) (Fong, 1998). There are also experimental evidences that norfluoxetine induces spawning in zebra mussels and dark false mussels at concentrations of 1 μM (Fong, 1998; Fong and Molnar, 2008). A similar study with fluoxetine showed that it also induces spawning in zebra mussels and dark false mussels but at concentrations between 10 and 20 times lower than norfluoxetine (Fong, 1998; Fong and Molnar, 2008). Moreover, fluoxetine causes parturition in fingernail clams (*Sphaerium striatinum*) at concentrations of 10 μM (Fong, 1998; Fong et al., 1998; Fong and Molnar, 2008). Consequently, this class of pharmaceuticals may constitute a real concern as, in this particular case, the induction of spawning and parturition in the wrong time of the year may increase the percentage of early stage mortality due to the scarcity of food for juvenile development, resulting in serious negative consequences for these species (Fong and Molnar, 2008). Another research about the acute and chronic toxicity of citalopram, fluvoxamine, fluoxetine, sertraline and paroxetine to *C. dubia* established that the mortality of *C. dubia* increase with increasing SSRIs concentration exposure (Henry et al., 2004). LC_{50} values range from 0.12 mg L^{-1} for sertraline to 3.90 mg L^{-1} for citalopram. The locomotion capabilities of *C. dubia* were also negatively affected at SSRIs concentrations below the determined LC_{50} values (Henry et al., 2004). The experiment also assessed the effects of chronic exposure during 7–8 d. The authors concluded that chronic SSRIs exposure resulted in the decrease of the number of neonates produced by *C. dubia* and the number of broods also declines after exposure to fluvoxamine, fluoxetine and paroxetine. Once again, despite the determined environmental concentrations being below the concentrations required to produce the reported effects, these organisms are exposed to a extremely complex mixture of compounds (several with similar mode of action) that can have additive effects (Henry et al., 2004; Henry and Black, 2007). Stanley et al. (2007) investigated potencial enantiospecific effects in *Pimephales promelas* and *Daphnia magna.* The tested organisms where exposed for 7 and 21 d, respectively, to S-fluoxetine, R-fluoxetine and a racemic mixture. The performed survival test revealed that S-fluoxetine presents a higher toxicity to *P. promelas* than the R enantiomer (LOEC of 101 and 170 μ L^{-1} for S-fluoxetine and R-fluoxetine, respectively), potentially due to differences in the potency of the primary active metabolites of the two enantiomers. This study highlights the importance of considering enantiospecific toxicity in future risk assessment investigation of chiral pharmaceuticals (Stanley et al., 2007).

A distinct approach by Hansen et al. (2008) alerts to the fact that the results of the toxicity tests undertaken in this research area are affected by a strong interactive effect between food quality and toxicity response of *D. magna* to fluoxetine. Nitrogen and phosphorus rich algae food increases the toxicity due to fluoxetine, demonstrating the need to consider the effects of food in ecotoxicological testing protocols.

Relatively to the possibility of bioaccumulation, the uptake and depuration of fluoxetine was investigated in freshwater fish species. Paterson and Metcalfe (2008) exposed the Japanese Medaka (*Oryzias latipes*) to a fluoxetine concentration of 0.64 μg L^{-1} during seven days followed by a 21 d period of depuration. The concentrations of fluoxetine and its active metabolite norfluoxetine increased during the uptake period and decreased during the depuration phase. Uptake of fluoxetine and norfluoxetine was observed in the first 5 h of exposure and a maximum concentration was determined on the third day. The depuration phase permitted to determine the fluoxetine half-life in the fish tissues (9.4 ± 1.1 d), clearly indicating that fluoxetine and norfluoxetine can persist and present a large potential for bioaccumulation in fish tissues.

Detailed information about the toxicity of other antidepressants to aquatic organisms can be found in Table 5.

7. Analytical methods for the determination of psychiatric pharmaceuticals in environmental matrices

One of the main problems in monitoring the occurrence of psychiatric pharmaceuticals in waste, surface and ground waters (as for all pharmaceuticals, in general), is the lack of simple, sensitive and cost effective analytical methods to quantify pharmacologically active substances (and their metabolites) in the concentration range of ng L^{-1}–μg L^{-1} (Ternes, 2001; Dębska et al., 2004; Buchberger, 2007). However, nowadays, major advances have been done with the development of new analytical methods that allow the quantification of trace amounts of pharmaceuticals (Dębska et al., 2004; Kostopoulou & Nikolaou, 2008). Moreover, one of the most important difficulties in analyzing pharmaceuticals in environmental matrices (such as wastewaters and sludge) relies on the complexity of the samples, being this another reason for the requirement of analytical techniques with very high resolution and extremely low quantification limits (Jones et al., 2005b). Hence, the fundamental step of this type of analysis is considered to be sample preparation (Sliwka-Kaszyńska et al., 2003; Ramirez et al., 2007). Another relevant recent advance is the possibility of analyzing at once a large number of pharmaceuticals in aqueous matrices (Ternes, 2001); in the past, the majority of the literature reported the determination of only a single pharmaceutical in environmental samples.

In the particular case of psychiatric pharmaceuticals, a summary of the analytical methods optimized for their determination is presented in Table 6. The most frequently used techniques include GC–MS, (HP)LC–MS and (HP)LC–MS/MS (Gros et al., 2006; Kot-Wasik et al., 2007; Terzić et al., 2008).

LC–MS/MS is the most used technique due to its versatility, specificity and selectivity. However, one of the major disadvantages of LC–MS/MS based methods is their susceptibility to matrix interferences, in particular when they are associated with the electrospray ionization mode (ESI), leading to the suppression of the analyte signals (most commonly) and erroneous results (Kot-Wasik et al., 2007). Therefore, the use of this technique requires an extensive preliminary study of the matrix effects (Gros et al., 2006). To overcome this difficulty, Vasskog et al. (2006) developed a HPLC–(ESI)-MS method with a two-step sample cleaning procedure including SPE (Solid Phase Extraction) and LLE (Liquid–liquid Extraction), resulting in a very sensitive and selective method with limits of quantification in the order of pg L^{-1}. Another way of minimizing these effects was investigated by Chu and Metcalfe (2007) that optimized the HPLC–MS technique for the determination of antidepressants, using the atmospheric pressure chemical ionization technique that is less affected by the mentioned matrix effects. Specifically, HPLC–(ESI)-MS was already developed for the quantification of diazepam in environmental water samples (Ternes, 2001; Dębska et al., 2004; Ramirez et al., 2007), consisting of a sample pretreatment (filtration with glass filters, 1 μm pore diameter, at pH 7.0) and a SPE enrichment (column RP 18 using MeOH for the elution, evaporation to dryness in gentle stream nitrogen and redissolution in phosphate buffer) prior to HPLC–(ESI)-MS

Table 6
Performance of several analytical methods optimized for the determination of psychiatric pharmaceuticals in environmental samples.

Pharmaceutical	Method	Sample	Sample preparation	[a]REC ± 1σ	[a]LOQ	References
Diazepam	GC–MS	Surface water and drinking water ($n = 5$)	SPE[a]; residues from the extraction procedure dissolved in hexane (clean-up step)	102 ± 14%	20 ng L^{-1}	(Ternes et al., 1998)
	GC–MS	STP effluent ($n = 5$)	SPE; residues from the extraction procedure dissolved in hexane (clean-up step)	102 ± 14%	100 ng L^{-1}	(Ternes et al., 1998)
	LC–MS/MS	Sludge	USE[a] followed by SPE	37 ± 6% (activated sludge, absolute recovery); 59 ± 11% (activated sludge, relative recovery); 25 ± 3% (digested sludge, absolute recovery); 48 ± 10% (digested sludge, relative recovery)	20 ng g^{-1}	(Ternes et al., 2005a)
	GC–MS	Tap water	SPE	73%	22 ng L^{-1}	(Sacher et al., 2001)
	GC–MS	Surface water	SPE	99%	22 ng L^{-1}	(Sacher et al., 2001)
Butalbital	GC–MS	Rhine river water	Filtration through glass fiber filters followed by SPE	105 ± 1%	5 ng L^{-1}	(Peschka et al., 2006)
Secobarbital	GC–MS	Rhine river water	Filtration through glass fiber filters followed by SPE	86 ± 1%	5 ng L^{-1}	(Peschka et al., 2006)
Pentobarbital	GC–MS	Rhine river water	Filtration through glass fiber filters followed by SPE	103 ± 4%	1 ng L^{-1}	(Peschka et al., 2006)
Hexobarbital	GC–MS	Rhine river water	Filtration through glass fiber filters followed by SPE	91 ± 1%	5 ng L^{-1}	(Peschka et al., 2006)
Aprobarbital	GC–MS	Rhine river water	Filtration through glass fiber filters followed by SPE	64 ± 1%	1 ng L^{-1}	(Peschka et al., 2006)
Phenobarbital	GC–MS	Rhine river water	Filtration through glass fiber filters followed by SPE	74 ± 2%	1 ng L^{-1}	(Peschka et al., 2006)
Paroxetine	LC–APCI-MS/MS	Fish tissues ($n = 8$)	PLE[a] followed by SPE	99.2 ± 3.5%	0.24 ng g^{-1}	(Chu and Metcalfe, 2007)
	LC–(ESI)-MS/MS	Surface waters	SPE	95 ± 5% (high spiking level); 110 ± 12% (low spiking level)	20 ng L^{-1}	(Gros et al., 2006)
	LC–(ESI)-MS/MS	WWTP effluent	SPE	65 ± 3% (high spiking level); 76 ± 12% (low spiking level)	26 ng L^{-1}	(Gros et al., 2006)
	LC–(ESI)-MS/MS	WWTP influent	SPE	96 ± 1% (high spiking level); 84 ± 4% (low spiking level)	22 ng L^{-1}	(Gros et al., 2006)
Fluoxetine	LC–APCI-MS/MS	Fish tissues ($n = 8$)	PLE followed by SPE	96.2 ± 2.9%	0.07 ng g^{-1}	(Chu and Metcalfe, 2007)
	LC–(ESI)-MS/MS	Surface waters	SPE	105 ± 6% (high spiking level); 74 ± 12% (low spiking level)	76 ng L^{-1}	(Gros et al., 2006)
	LC–(ESI)-MS/MS	WWTP effluent	SPE	60 ± 2% (high spiking level); 74 ± 2% (low spiking level)	70 ng L^{-1}	(Gros et al., 2006)
	LC–(ESI)-MS/MS	WWTP influent	SPE	108 ± 4% (high spiking level); 67 ± 12% (low spiking level)	100 ng L^{-1}	(Gros et al., 2006)
	HPLC–(ESI)-MS	STP influents and effluents	SPE and LLE[a]	64–92% (different samples)	120 pg L^{-1}	(Vasskog et al., 2006)
Citalopram	HPLC–(ESI)-MS	STP influents and effluents	SPE and LLE	36–72% (different samples)	160 pg L^{-1}	(Vasskog et al., 2006)
Fluvoxamine	HPLC–(ESI)-MS	STP influents and effluents	SPE and LLE	56–82% (different samples)	150 pg L^{-1}	(Vasskog et al., 2006)
Setraline	HPLC–(ESI)-MS	STP influents and effluents	SPE and LLE	52–85% (different samples)	290 pg L^{-1}	(Vasskog et al., 2006)
Norfluoxetine	LC–APCI-MS/MS	Fish tissues ($n = 8$)	PLE followed by SPE	85.6 ± 4.2%	0.14 ng g^{-1}	(Chu and Metcalfe, 2007)
Paroxetine	HPLC–(ESI)-MS	STP influents and effluents	SPE and LLE	71–92% (different samples)	120 pg L^{-1}	(Vasskog et al., 2006)

[a] LOQ – limit of quantification; SPE – solid phase extraction; PLE – pressurized liquid extraction; LLE – liquid–liquid extraction; USE – ultra sonic solvent extraction; REC – extraction recovery.

analysis. Recently, Schultz and Furlong (2008) developed a quantitative method for the determination of eight antidepressants and two derivatives in environmental aqueous samples, comprising a pretreatment using SPE followed by LC–(ESI)-MS/MS. The analyzed samples were collected from several municipal wastewater effluents and from a waste-dominated stream.

GC–MS, commonly used in the determination of pharmaceuticals in biological samples (Wille et al., 2005), was also optimized for the determination of antidepressants in environmental samples (Wille et al., 2005; Chu and Metcalfe, 2007). A large number of active substances included in this pharmacological group are considered as "neutral pharmaceuticals" (designation used for compounds which do not have acidic functional groups) (Ternes, 2001). As a consequence, these pharmaceuticals can be enriched at neutral pH using SPE (Solid Phase Extraction) and sorbents can subsequently be analyzed by GC–MS without derivatization (Ternes, 2001). Togola and Budzinski (2008) developed a GC–MS based method for the simultaneous determination of the anxiolytics and antidepressants amitryptiline, imipramine, doxepine, nordiazepam and diazepam without derivatization. This technique has also been optimized for the determination of diazepam, consisting on an initial sample pretreatment (filtration with glass filters, 1 μm, at pH 7.5) followed by an enrichment step using SPE (column RP 18 using MeOH for the elution). The sample was then analyzed by GC–MS using MSTFA for the derivatization (Ternes, 2001; Dębska et al., 2004). Despite the decline in the use of barbiturates as human therapeutics, recently, a method based in GC–MS techniques was developed for the determination of 6 barbiturates in aquatic environment, with a detection limit of 1 ng L^{-1} (Peschka et al., 2006).

Few examples of immunoanalysis applications and their comparison with reference analytical techniques were reported (Valentini et al., 2002; Dębska et al., 2004; Huo et al., 2007; Shelver et al., 2008). This method and its full potential (such as, the reduced number of sample preparation steps and high sensitivity) have not been properly explored in the determination of pharmaceuticals and, in particular, in the determination of psychiatric drugs. This technique may be an excellent tool to a quick and inexpensive environmental screening (Buchberger, 2007). Although immunoassay techniques are not suitable for the determination of several structurally different analytes, diazepam and fluoxetine were pointed out to be considered as reference relatively to other pharmaceuticals with similar mode of action (Cunningham et al., 2006) and they might constitute good indicators of the presence of psychiatric drugs in environmental samples (Buchberger, 2007).

8. Concluding remarks and future research needs

The data presented in this paper confirm the widespread occurrence of psychiatric pharmaceuticals in the environmental. The excretion of the unchanged or conjugated forms by the human body, along with the inadequacy of WWTPs removal methods constitute the major pathways of entrance of psychiatric pharmaceuticals into the environment. The reviewed literature show large discrepancies in the amount of psychiatric pharmaceuticals removed by WWTPs. In addition, some of the methods used in wastewater treatment have removal efficiencies bellow 10%. Consequently, large amounts of active substance pass through the WWTPs completely unaffected. These facts justify the high occurrence of these pharmaceuticals in environmental matrices and underline the need to find viable alternatives to improve the removal efficiency. It is of great relevance to develop strategies of remediation with a view to decrease the impact of this problem in the future.

The investigations performed until now emphasize the possibility of psychiatric pharmaceuticals, such as diazepam and fluoxetine, being accumulated in water/sediment environments due to their high persistence and resistance to biotic and abiotic degradation processes. Therefore, living organisms of aqueous environments are continuously being exposed to concentrations of these pharmaceuticals in the range of ng–μg L^{-1}, and there are several evidences of bioaccumulation. Although these concentrations are below the acute toxicity levels, very few data is available about chronic toxicity to better assess the exposure risks for aquatic organisms. In our opinion, the study of life cycle toxicity as well as the investigation of the adverse effects caused by the exposure to complex mixtures of psychiatric pharmaceuticals with the same mode of action should be addressed in the near future.

Despite the increasing number of investigations performed in this area, which is possible because of the development of analytical methods optimized for the determination of psychiatric pharmaceuticals in environment, it is essential to perform more research to clarify the real impact of these relatively recent environmental pollutants and to develop strategies that allow an effective global screening of the contamination levels.

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