Chapter 2
Pharmaceuticals in the Environment: Case Study of Psychiatric Drugs

Abstract The ecotoxicological assessment of pharmaceuticals is discussed in this chapter, under the light of a growing local and international legal framework that is meant to control the environmental impact of an intensive consumption of such molecules, mainly those used in psychiatric conditions. The specific pathways for pharmaceuticals metabolism are evaluated and the resulting accumulation of those medicines in different matrices is presented. Non-target organisms may suffer different effects when exposed to those pharmaceuticals or to their metabolites and the first attempts to quantify this contamination are reviewed.

Keywords Ecotoxicological assessment · Metabolic pathways · Non-target organisms

2.1 Introduction

Pharmaceuticals are a vast and diverse group of chemicals with different functionalities, physicochemical and biological properties (Kümmerer 2009), that have been used worldwide by the human and veterinary medicine (Calisto and Esteves 2009; Christen et al. 2010; Fent et al. 2006; Furuhagen et al. 2014). In order to achieve optimal therapeutic function, pharmaceuticals are chemically designed to pass through the cellular membrane, to fit a specific molecular target, which is often evolutionary conserved and have orthologs in a variety of organisms (Furuhagen et al. 2014), and to resist inactivation before having the desire therapeutic effect (Calisto and Esteves 2009; Christen et al. 2010). These properties raise concerns for the following reasons:

(i) As pharmaceuticals do not occur individually in the environment, but as complex mixtures, the interaction of these compounds with wildlife that might have high similarity with the molecular targets, the so-called non-target organisms (Furuhagen et al. 2014; Rand-Weaver et al. 2013), may occur at

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relevant environmental concentrations, due to combined and synergistic effects (Calisto and Esteves 2009);

(ii) For some pharmaceuticals, the specific mode of action is not well characterized and often different modes of action are possible;

(iii) Some pharmaceuticals are responsible for antibiotic resistance, while others have the aptitude to directly affect the central nervous system and disrupt neuro-endocrine signaling (Calisto and Esteves 2009; Chen et al. 2006; Jones et al. 2001; Saussereau et al. 2013).

Considering that regulations over the development and production of pharmaceuticals are usually extremely supervised by human health agencies, which generally have limited experience and knowledge on issues of environmental scope and that, until recently: (a) pharmaceuticals were not considered as potential pollutants, thus not being subjected to detailed research regarding their impact on the environment (Jones et al. 2001); (b) the ecotoxicological assessments of pharmaceuticals have been based on acute toxicity experiments performed by standard tests according to the existing guidelines using laboratory organisms belonging to different trophic levels such as algae, zooplankton, other invertebrates and fish, it is possible to infer that the information about the chronic toxicity or bioaccumulation potential of pharmaceuticals in biota and food chains is extremely scarce (Christen et al. 2010).

Pharmaceuticals, either in their original form or as metabolites with residual activities, are being introduced into the environment at variable degrees and on a continuously basis, mainly through wastewater and sewage treatment plants (WWTP and STP, respectively), as a consequence of the inadequacy of the treatment processes applied in these facilities (Chen et al. 2006; Furuhagen et al. 2014; Ginebreda et al. 2010; Saussereau et al. 2013; Zuccato et al. 2006). According to Calisto and Esteves (2009) the first reports referring explicitly to the incomplete removal of some pharmaceuticals by wastewater treatments and their discharge into the environment by WWTP were published in the 60s and 70s. However, only in the 90s was it established that some pharmaceuticals have the ability to interfere with the ecosystem, even in concentrations as low as few nanograms per litre (ng/L). Since then, and as a consequence of the growing number of published studies focused on pharmaceuticals and their persistence in the environment, as well as of the large amount of pharmaceuticals produced, their increasing use, diversity and potential toxicological effects on non-target organisms, pharmaceuticals and pharmaceutically active metabolites are now unanimously considered as an important group of emergent environmental pollutants (Calisto et al. 2011; Calisto and Esteves 2009).

Although knowledge concerning the removal pathways, fate, environmental transformation and the effects of these compounds once they are release into on the environment, is reduced, it is possible to reach a general consensus on the main features of this emerging problem (Ginebreda et al. 2010): (a) pharmaceuticals are intrinsically bioactive compounds, being therefore able to cause potential damage on living systems, target and non-target organisms; (b) there is a continuous and

worldwide increase on their use and thus on their subsequent introduction into the environment; (c) there are plenty of different pharmaceuticals that are currently and regularly used simultaneously, being therefore susceptible to interaction and synergistic effects that are basically unknown and (d) information regarding effects on the aquatic and terrestrial ecosystems resulting from long-term low-dose exposure to pharmaceuticals is scarce.

This chapter will be specifically focused on the psychiatric pharmaceuticals as emergent pollutants, their occurrence in environmental matrices and the effect on non-target organisms.

2.2 Pharmaceuticals as Emerging Pollutants: Occurrence of Psychiatric Drugs in Environmental Matrices

The term *pharmaceutical* comprise a large and diverse group of synthetic or natural chemicals with substantial variability in structure, function, behaviour and activity (Jones et al. 2001, 2005; Monteiro and Boxall 2010). The intensive use and increasing consumption of pharmaceuticals worldwide, which is intrinsically associated with the continuous ageing of the population, better access to health care and life quality improvement (Verlicchi et al. 2012a), have made pharmaceuticals a crucial and indispensable element of modern society. This situation is particularly relevant in high-income countries due to the increased number of obese and elderly people with chronic health problems (Arnold et al. 2014).

Most of pharmaceutical substances are polar compounds with a molecular weight that ranges typically from 200 to 500/1000 Da (Kümmerer 2009) and present low volatility, thus increasing the probability of pharmaceuticals to be transported to surface waters (Brausch et al. 2012). Both administration and production of pharmaceuticals may vary between countries and over time, fluctuating not only on an annual basis, but also through the years (Verlicchi et al. 2012b). Table 2.1 and Fig. 2.1 summarize, respectively, the main psychiatric pharmaceuticals consumed in the last years in several countries and the volume of antidepressants consumed between 2000 and 2012 in daily dose (DDD) units.

The consumption of antidepressants has practically doubled on average in EU countries between 2000 and 2012 (Fig. 2.1). This exponential increase is strictly related with the epidemiological context as it is the insecurity created by the economic crisis.

There are many scattered ways by which pharmaceuticals can enter the environment (Chen et al. 2006; Zuccato et al. 2006). The main pathway from human and animals contribution includes ingestion, following excretion and disposal in wastewater (Fent et al. 2006). Once administered, pharmaceuticals are metabolized to varying degrees and excreted in urine and feces as metabolite and/or unaltered parent compounds.

Table 2.1 Volume of pharmaceutically active compounds sold in different countries (kg/year)

Therapeutical class	Pharmaceutical	Countries				
		France (2004)[a]	UK (2004)[b]	Spain (2004)[c]	Austria (1997)[d]	Switzerland (2004)[d]
Antidepressants SSRIS	Fluoxetine	3740	4826	4200	–	
	Paroxetine	5515	2663	–	–	
	Citalopram	3487	4799	1600	368	
	Sertraline	6224				
Anxiolytic	Bromazepam	2604				
	Diazepam	526			207	51
	Prazepam	2166				
	Oxazepam	6195				

[a]Besse et al. (2008)
[b]Monteiro and Boxall (2010)
[c]Carballa et al. (2008)
[d]Fent et al. (2006)

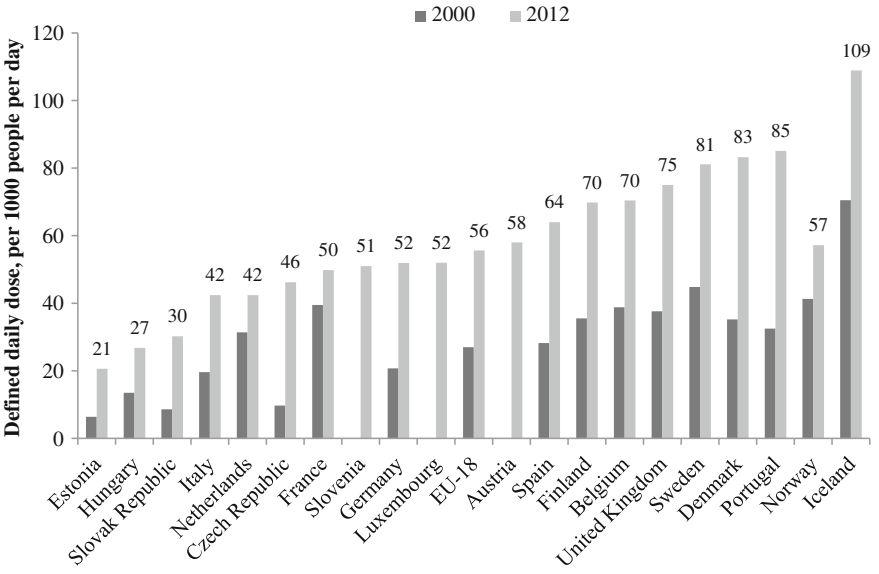


Fig. 2.1 Consumption of antidepressants in the EU countries between 2000 and 2012 (adapted from OECD 2014)

A significant amount of the original substance may also be excreted in their native form and undergo further modification due to biological, chemical and physical processes in sewage treatment facilities, receiving water bodies (Jones et al. 2005). It is estimated that 30–90 % of an administered dose of most antibiotics, human and veterinary, may be excreted as active substances. As a

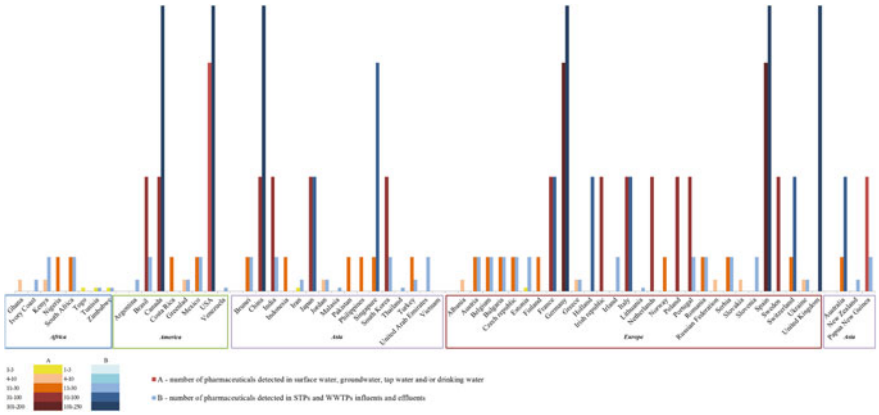


Fig. 2.2 Global occurrence of pharmaceuticals in different environmental matrices (adapted from IWW 2014)

consequence, several veterinary pharmaceuticals are present in manure, therefore able to affect and contaminate groundwater due to leaching or surface water due to runoff from agricultural fields (Chen et al. 2006). Unwanted or expired pharmaceuticals are also usually improperly disposed directly in wastewater, thus reaching the WWTP and STP in considerable amount. Other sources of pharmaceuticals contamination are, for example, the pharmaceutical manufacturing facilities and the veterinary pharmaceuticals that are applied in animal husbandry and are subsequently released into the soil, where manure is used as fertilizer (Boxall et al. 2003). Since the majority of biological treatments do not completely remove pharmaceuticals, in fact removal efficiencies range from less than 20 % to more than 80 % for individual pharmaceuticals (Larsson et al. 2007), residues are released into rivers, lakes groundwater aquifers (Chen et al. 2006; Zuccato et al. 2006) and soil (Arnold et al. 2014), Fig. 2.2. When in the environment, pharmaceuticals and their residues can undergo a series of transformations and degradation reactions that alter their mobility, persistence and fate. This has increased the concern regarding the potential ecological and hazardous effects on living beings (Fent et al. 2006), particularly on aquatic species, since they are exposed to wastewater residues along their whole lifecycle (Brausch et al. 2012).

Pharmaceuticals have been detected in different environmental matrices such as surface water, manure, soil, sewage effluents, groundwater and other environmental matrices (Fig. 2.2). Canada, China, USA, Japan, Germany, France, Italy and Spain stand out for their high number of detected pharmaceuticals (equal or higher than 31–100 pharmaceuticals detected, for all matrices).

It is important to highlight that a pharmaceutical of environmental concern does not necessarily correspond to a high production volume per se, but its environmental persistence and critical biological activity such as high toxicity and high impact on biological key functions may be relevant. A common example is the synthetic steroid hormone in contraceptive pills, such as 17α-ethinylestradiol (EE2).

The annual production of this hormone lies in a couple of hundreds kilograms per year in the EU, nevertheless it is extremely potent, very persistent in the environment and shows estrogenic activity in fish at 1–4 ng/L, or lower. Therefore, pharmaceuticals having environmental relevance share the following properties: often, but not always, high production volume combined with environmental persistence and biological activity, mainly after long-term exposure (Fent et al. 2006).

In this chapter, special attention will be given to the psychiatric pharmaceuticals, particularly their occurrence in environmental matrices. Psychiatric pharmaceuticals, such as sedatives, hypnotics, anxiolytics (including antiepileptics), antidepressants and antipsychotics are among the most prescribed substances. These are defined as a group of pharmaceuticals that directly act on the central nervous system and disrupt neuro-endocrine signaling (Calisto et al. 2011; Calisto and Esteves 2009). Emerging pollutants, also known as contaminants of emerging concern—CEC, are defined as substances that are not currently covered by existing water-quality regulations and are thought to be potential threats to environmental ecosystems, human health and safety (Deblonde et al. 2011). Emerging pollutants do not necessarily need to be new compounds. Some have been present in the environment for decades and were only recently discovered through the use of advanced analytical methods.

For example, the sedative-hypnotic diazepam (the most extensively studied psychiatric pharmaceutical) has been found in all environment matrices—wastewater, surface, ground and drinking water, soils, sediments, bio-solids and tissues (Calisto et al. 2011). Diazepam was found in concentrations lower than 1 µg/L in sewage effluent, in concentrations of 10 ng/L in rivers and potable water (Waggot 1981). Caffeine was detected in sewage water in concentrations of 1 µg/L, in potable water in concentrations higher than 1 µg/L (Richardson and Bowron 1985) and in wastewater effluents in concentrations between 16 and 292 µg/L (Rogers 1996). Recent analytical studies in Italy, confirm that several pharmaceuticals are poorly removed in STP and that several commonly used pharmaceuticals such as erythromycin, cyclophosphamide, naproxen, sulphamethoxazole or sulphasalazine, persist in the environment for periods of time longer than one year (Zuccato et al. 2006). López-Serna et al. (2012) reported the occurrence of pharmaceuticals, their metabolites and transformation products in the Ebro river basin, in the Northeast of Spain. Twenty-four samples of water were collected along the basin and subsequently analyzed. In total, 17 metabolites, 7 of which still had pharmacologic activity, 2 transformation products, along with 58 parent pharmaceuticals were detected. Metabolites and transformation products were found at concentrations of the same order of magnitude as their corresponding parent pharmaceuticals, with the exception of 10,11-epoxicarbamazepine which was found in a concentration approximately 10 times higher than its corresponding parent pharmaceutical carbamazepine. These authors also reported that, with the exception of 14 compounds, among them the aforementioned 10,11-epoxicarbamazepine with a maximum concentration of more than 1600 ng/L, the levels of all target compounds were below 100 ng/L. Other pharmaceuticals such as propyphenazone (analgesic), carbamazepine (psychiatric), clarithromycin and sulfadiazine (antibiotic), propranolol

(β-blocker), tamoxifen (antineoplastic) were found to be ubiquitous in all analyzed samples. Studies conducted in Europe and North America demonstrated that carbamazepine is one of the most frequently detected pharmaceuticals in WWTP effluents, river water (Mohapatra et al. 2014), final sewage effluents, surface water, drinking water and groundwater (Monteiro and Boxall 2010). Different studies conducted in Portuguese regions confirm the presence of several pharmaceuticals such as citalopram and paroxetine (Silva et al. 2014), carbamazepine, fenobric acid, propranolol, sulphamethoxazole and trimethoprim (Madureira et al. 2011a, b), acetaminophen, acetylsalicylic acid, carboxyibuprofen, diclofenac, hydroxyibrufen, ibufren, naproxen, nimesulide and ketoprofen in seawater (Lolić et al. 2015). Brooks et al. (2005) reported the occurrence of fluoxetine, norfluoxetine, sertraline and desmethylsertraline in tissue samples (muscle, liver and brain) of several fishes —*Lepomis macrochirus* (bluegill), *Ictalurus punctatus* (channel catfish) and *Pomoxis nigromaculatus* (black crappie)—from Pecan Creek Water Reclamation Plant, Denton County, Texas (U.S.A). For all fish samples, the highest concentrations was observed in brain (fluoxetine, 1.58 ± 0.74 ng/g; norfluoxetine, 8.86 ± 5.9 ng/g; sertraline, 4.27 ± 1.4 ng/g; desmethylsertraline, 15 ± 14.3 ng/g) and liver tissues (fluoxetine, 1.34 ± 0.65 ng/g; norfluoxetine, 10.27 ± 5.73 ng/g; sertraline, 3.59 ± 1.67 ng/g; desmethylsertraline, 12.94 ± 10.45 ng/g). The lowest concentrations were detected in the muscle tissue (fluoxetine, 0.11 ± 0.03 ng/g; norfluoxetine, 1.07 ± 0.41 ng/g; sertraline, 0.34 ± 0.09 ng/g; desmethylsertraline, 0.69 ± 0.59 ng/g). According to those authors, the fact that the average levels of norfluoxetine and desmethylsertraline were higher in the brain, liver and muscle tissue, compared to the average fluoxetine and sertraline levels, reveal a general similarity to the data obtained by Fuller et al. (1995), DeVane et al. (2002) and Weigel et al. (2004), documenting slow accumulation and dispositional differences among these compounds in rat models and humans. Ramirez et al. (2007) also reported the presence of psychiatric medicines (carbamazepine 1.16 ng/g of wet weight, and norfluoxetine 4.37 ng/g of wet weight) in muscle tissues of *Lepomis* sp., also collected in Pecan Creek Water Reclamation Plant. Studies conducted by Beretta et al. (2014) in sediments from the Todos os Santos Bay (Brazil), identified in all sediments samples concentrations of several pharmaceuticals such as carbamazepine, ibuprofen, diclofenac, atenolol, diazepam and erythromycin, at levels of parts per billion of dry sediment.

These observations reinforce the importance and the need to study the effect and impact of psychiatric drugs in non-target organisms, as well as to develop accurate and precise methods for their quantification in different and diversified matrices. A factor that influences the accuracy of the quantification process of pharmaceuticals is the sensibility of the equipment and the development of an internationally standardized analytical protocol. The existence of such protocol would help to ensure both quality and comparability of data.

The effects that psychiatric pharmaceuticals exert on non-target organisms which are summarized in Table 2.2, will be addressed in the next section whereas the analytical techniques used for the detection and quantification of psychiatric pharmaceuticals will be discussed in Chap. 4.

Table 2.2 Main psychiatric pharmaceuticals used extensively by the population and detected in the environment

Therapeutical class	Pharmaceutical	Commercial name	Concentration found in the environment	Matrix	Country
Antidepressants	Fluoxetine	Prozac	0.012 µg/L	Surface water	USA[a], Canada[a]
			17 ± 3 ng/L	Psychiatric hospitals WWTP influents	China[f]
			21 ± 2 ng/L	Psychiatric hospitals WWTP primary effluents	China[f]
			10 ± 1 ng/L	Psychiatric hospitals WWTP secondary effluents	China[f]
			na	WWTP, Wastewaters effluents and influents	Portugal[d]
			nd–0.099 µg/L	STP effluents	USA[c], Canada[c]
			0.1–10 ng/g	Tissues (muscle, brain, and liver) of fish residing in a municipal effluent-dominated stream	USA[a]
			0.14–1.02 µg/kg	Fish tissues	Canada[a]
			0.099 µg/L	STP effluents	Canada[a]
			0.055–0.19 µg/L; 0.010–0.063 µg/L	WWTP influents and effluents	Italy[b]
			0.024–0.033 µg/L; 0.035–0.069 µg/L	Hospital effluents	Italy[b]

(continued)

Table 2.2 (continued)

Therapeutical class	Pharmaceutical	Commercial name	Concentration found in the environment	Matrix	Country
Antidepressants	Paroxetine	Paxil	2.1 ± 0.4 ng/L; 3 ± 1 ng/L; 2.2 ± 0.2 ng/L	Pecan creek water reclamation plant	USA[a]
			na	WWTP, wastewaters effluents and influents	Portugal[d]
			0.020–0.080 μg/L; 0.010–0.018 μg/L	WWTP influents and effluents	Italy[b]
			0.056–0.076 μg/L	Hospital effluents	Italy[b]
			0.48–0.58 μg/kg	Fish tissues	Canada[a]
	Citalopram	Celexa	90 ± 20 μg/L; 40 ± 30 μg/L; 80 ± 30 μg/L	Pecan creek water reclamation plant	USA[a]
			67 ± 5 ng/L; 261 ± 14 ng/L	Psychiatric hospitals WWTP influents	China[f]
			322 ± 23 ng/L	Psychiatric hospitals WWTP primary effluents	China[f]
			19 ± 1 ng/L; 162 ± 9 ng/L	Psychiatric hospitals WWTP secondary effluents	China[f]
			0.4 ng/L; 3 ng/L; 4 ± 1 ng/L	Municipal WWTP influents	China[f]
			1 ng/L	Municipal WWTP primary effluents	China[f]
			2 ng/L; 4 ng/L; 5 ± 2 ng/L	Municipal WWTP secondary effluents	China[f]
			na	WWTP, Wastewater effluents and influents	Portugal[d]

(continued)

Table 2.2 (continued)

Therapeutical class	Pharmaceutical	Commercial name	Concentration found in the environment	Matrix	Country
Antidepressants	Sertraline	Zoloft	0.1–10 ng/g	Tissues (muscle, brain, and liver) of fish residing in a municipal effluent-dominated stream	USA[a]
			29 ± 8 ng/L; 106 ± 28 ng/L	Psychiatric hospitals WWTP influents	China[f]
			99 ± 7 ng/L	Psychiatric hospitals WWTP primary effluents	China[f]
			9 ± 5 ng/L; 59 ± 3 ng/L	Psychiatric hospitals WWTP secondary effluents	China[f]
			na	WWTP, Wastewater effluents and influents	Portugal[d]
			36 ± 5 ng/L; 49 ± 9 ng/L; 33 ± 8 ng/L	Pecan creek water reclamation plant	USA[a]
	Duloxetine	Cymbalta	1.5 ± 0.2 ng/L; 2 ± 2 ng/L; 1.2 ± 0.9 ng/L	Pecan creek water reclamation plant	USA[a]
	Venlafaxine	Effexor	600 ± 200 μg/L; 1000 ± 400 μg/L; 900 ± 300 μg/L	Pecan creek water reclamation plant	USA[a]
	Bupropion	Wellbutrin	50 ± 20 μg/L; 60 ± 40 μg/L; 50 ± 10 μg/L	Pecan creek water reclamation plant	USA[a]

(continued)

Table 2.2 (continued)

Therapeutical class	Pharmaceutical	Commercial name	Concentration found in the environment	Matrix	Country
Antipsychotics	Chlorpromazine	Thorazine	5 ± 4 ng/L; 364 ± 173 ng/L	Psychiatric hospitals WWTP influents	China[f]
			217 ± 21 ng/L	Psychiatric hospitals WWTP primary effluents	China[f]
			99 ± 6 ng/L	Psychiatric hospitals WWTP secondary effluents	China[f]
Anxiolytics/Hypnotics	Diazepam	Valium	0.053 µg/L	Municipal STP effluents	Germany[a], UK[a], Italy[a]
			0.002–0.010 µg/L	WWTP influents and effluents	Italy[b]
			0.021–0.038 µg/L	Hospital effluents	Italy[b]
			0.88 µg/L	Surface water	Germany[a]
			0.033 µg/L	Rivers and Streams	Germany[a]
			3–62 ng/L	Lake mead	USA[a]
			>0.01 µg/L; 0.59 µg/L; 1.18 µg/L	STP influents	Belgium[a]
			33.6 ± 7.1 ng/L	River water	Romania[a]
			23.5 ng/L	Drinking water	Italy[a]
			0.13–2.13 ng/L	Po and Lambro rivers	Italy[a]
			nd–0.053 (Germany)	STP effluents	Germany[c], UK[c], Italy[c],
			0.39 ± 0.24 ng/g dry weight	Sediments collect in the Todos os Santos Bay	Brasil[g]
			~10 ng/L	Potable water	UK[a]
	Nordiazepam	Nordaz	8.3 ng/L	WWTP effluent	France[a]
			2.4 ng/L	Surface waters	France[a]

(continued)

Table 2.2 (continued)

Therapeutical class	Pharmaceutical	Commercial name	Concentration found in the environment	Matrix	Country
Anxiolytics/Hypnotics	Oxazepam	Serax	0.25 μg/L	STP effluents	Germany[a], USA[a]
			942 ± 155 ng/L; 286 ± 42 ng/L	Psychiatric hospitals WWTP influents	China[f]
			297 ± 10 ng/L	Psychiatric hospitals WWTP primary effluents	China[f]
			751.7 ± 34 ng/L; 186 ± 14 ng/L	Psychiatric hospitals WWTP secondary effluents	China[f]
	Zaleplon	Sonata	23 ± 7 ng/L	Psychiatric hospitals WWTP influents	China[f]
			30 ± 2 ng/L	Psychiatric hospitals WWTP primary effluents	China[f]
			33 ± 1 ng/L	Psychiatric hospitals WWTP secondary effluents	China[f]
	Alprazolam	Xanax	na	WWTP, Wastewaters effluents and influents	Portugal[d]
			30 ± 1 ng/L	Psychiatric hospitals WWTP influents	China[f]
			32 ± 0.2 ng/L	Psychiatric hospitals WWTP primary effluents	China[f]
			29 ± 2 ng/L	Psychiatric hospitals WWTP secondary effluents	China[f]

(continued)

Table 2.2 (continued)

Therapeutical class	Pharmaceutical	Commercial name	Concentration found in the environment	Matrix	Country
Anxiolytics/Hypnotics	Lorazepam	Ativan	0.8–54.5 ng/L	Wastewater influents	Portugal[d]
			0.3–49.2 ng/L	Wastewater effluents	Portugal[d]
			294 ± 40 ng/L	Psychiatric hospitals WWTP influents	China[f]
			353 ± 22 ng/L	Psychiatric hospitals WWTP primary effluents	China[f]
			205 ± 22 ng/L	Psychiatric hospitals WWTP secondary effluents	China[f]
			0.62–0.79 μg/L; 0.17–0.20 μg/L; 0.46–0.70 μg/L	Hospital effluents	Italy[b]
			0.17–0.25 μg/L; 0.08–0.14 μg/L	WWTP influents and effluents	Italy[b]
Mood-stabilizers	Carbamazepine	Tegretol	0.64–0.87 μg/L; 0.76–1.2 μg/L; 0.75–1.1 μg/L	Hospital effluents	Italy[b]
			88 ± 16 ng/L; 161 ± 72 ng/L	Psychiatric hospitals WWTP influents	China[f]
			240 ± 10 ng/L	Psychiatric hospitals WWTP primary effluents	China[f]
			184 ± 10 ng/L	Psychiatric hospitals WWTP secondary effluents	China[f]

(continued)

Table 2.2 (continued)

Therapeutical class	Pharmaceutical	Commercial name	Concentration found in the environment	Matrix	Country
Mood-stabilizers	Carbamazepine	Tegretol	23 ± 2 ng/L; 22 ± 3 ng/L; 19 ± 5 ng/L	Municipal WWTP influents	China[f]
			24 ± 3 ng/L	Municipal WWTP primary effluents	China[f]
			22 ± 7 ng/L; 13 ± 2 ng/L; 17 ± 7 ng/L	Municipal WWTP secondary effluents	China[f]
			291.1 ng/L	STPS	Italy[e]
			175.3 ng/L	Lambro River	Italy[e]
			23.1–34.2 ng/L	Po River	Italy[e]
			0.0325*–6.3 (Germany)	STP effluents	Italy[c], Canada[c], Switzerland[c], France[c], Germany[c], Greece[c], Sweden[c], USA[c]
			0.30–1.17 µg/L; 0.28–0.44 µg/L	WWTP influents and effluents	Italy[b]
			0.41 ± ng/g dry weight	Sediments collect in the Todos os Santos Bay	Brasil[g]

The psychiatric pharmaceuticals are grouped according to their therapeutic class
na—not available; *nd*—not detected; * mean value
[a]Calisto and Esteves (2009)
[b]Verlicchi et al. (2012a)
[c]Monteiro and Boxall (2010)
[d]Pereira et al. (2015)
[e]Zuccato et al. (2006)
[f]Yuan et al. (2013)
[g]Beretta et al. (2014)

2.3 Effects of Psychotropic Drugs on Non-target Organisms

The presence of pharmaceuticals in the aquatic environment, due to their incomplete removal in wastewater treatments and their subsequent discharge into the environment was acknowledged in the 60s and 70s (Calisto and Esteves 2009; Jones et al. 2005). However, according to Brausch et al. (2012) the awareness of this subject emerged with the publication of two critical reviews performed by Halling-Sørensen et al. (1998) and Daughton and Ternes (1999), which coincided with a period of intensive concern and attention by the public and scientific community, on the presence and potential effects of endocrine active compounds, and with the advances in analytical detection. The fact that pharmaceutical formulations may also incorporate adjuvants, and in some cases pigments and dyes which are commonly considered of minor importance in terms of environmental significance and impact, intensifies the concern about the potential effects of these compounds when in the environment. This associated with the fact that pharmaceuticals development and synthesis are strictly regulated for efficiency, welfare and wellness of the patient, highlights the lack of knowledge regarding the environmental impact of these compounds, the lack of studies and research regarding their persistence in the environment, their biologic activity, forms of degradation and fate. It also highlights the lack of concise regulations for ecological risk assessment (Fent et al. 2006) and environmental legislation concerning the discharge of these compounds into surface water bodies (Verlicchi et al. 2012b).

The first ecotoxicity testing as pre-requisite for pharmaceuticals registration and the corresponding Note for Guidance (EMEA 1998) for veterinary pharmaceuticals was established in 1995, according to the European Union (EU) Directive 92/18 EEC. The European Commission released a draft guideline, the Directive 2001/83/EC, specifying that an authorization for a medicinal product for human use must be accompanied by an environmental risk assessment (EMEA 2005). In contrast to what happens with veterinary medicine, where environmental assessments of veterinary pharmaceuticals are required by the U.S.A Food and Drug Administration (FDA) since 1980 and by the EU since 1997 (Boxall et al. 2003), only in 1998 the FDA published a guidance for the assessment of human pharmaceuticals, requiring an environmental assessment report whenever the expected introduction concentration of the active compound of the pharmaceutical in the aquatic environment is ≥1 μg/L (FDA-CDER 1998).

As it was previously mentioned, pharmaceuticals are biologically active substances that specifically affect the control mechanisms in living organisms, influencing hormonal balance, regulating metabolism or relieving signal transmission between cells. Since most pharmaceuticals are administered by ingestion and almost none is completely metabolized, the excretion products contain relevant amounts of the active substance with different metabolites and conjugates, in urine and feces. As the excretion process by humans and animals is considered to be the main pathway for the appearance of pharmaceuticals into environment, the

understanding of human metabolism and excretion rates of psychiatric drugs is of vital importance to the assessment of environmental concentrations of this pharmacological subgroup (Calisto and Esteves 2009).

According to Kümmerer (2009), in order to avoid any misunderstanding in addressing different molecules and processes, the term metabolite should only be used for compounds which have been changed within or on the human body, the bodies of treated animals and plants, but not environmental bacteria or fungi, whereas the term transformation product should be used for molecules resulting from the change of the structure of a molecule after excretion (hydrolysis, photo-oxidation and oxidation) (Fig. 2.3).

The biochemical processes leading to the pharmaceutical metabolism, largely determine the duration of the action, of the elimination process and the toxicity of such a drug. How far may these processes be controlled to produce beneficial medical results on the patient, relies on numerous variables that have been the scope of considerable study (Jr et al. 2007). After administration of a medicine, its absorption and distribution must occur before the pharmaceutical reaches the interior of the body (Fig. 2.4). As with the vast majority of pharmaceuticals, psychiatric pharmaceuticals absorption occurs by simple diffusion and is usually affected by several physicochemical properties such as degree of ionization, molecular size and shape and relative lipid solubility (Wilkinson 2001). Cell

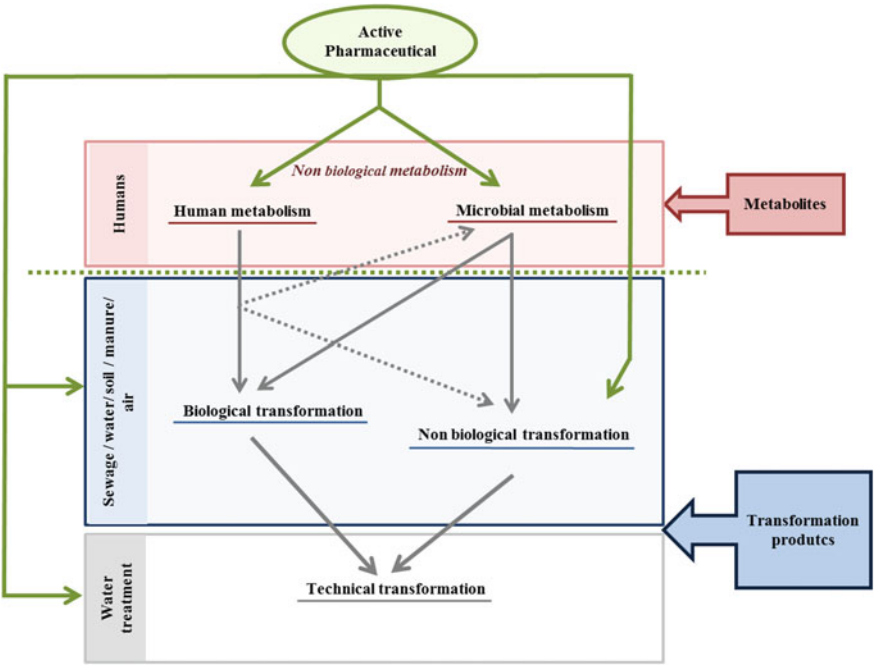


Fig. 2.3 Metabolites and transformation products of active pharmaceuticals (adapted from Kümmerer 2009)

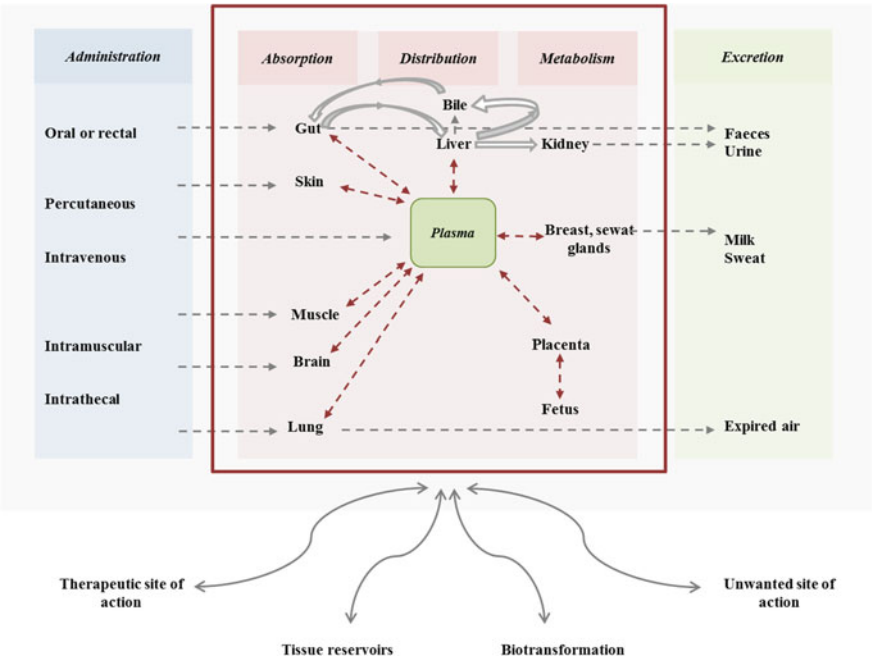


Fig. 2.4 Interrelationship between adsorption, distribution, metabolism and excretion of a pharmaceutical (adapted from Wilkinson 2001)

membranes retain lipid constituents that allow lipophilic substances to cross membranes rapidly and easily. After absorption, the pharmaceutical goes into circulation and after performing its action, it may be metabolized, usually through specialized enzymatic systems, to a more hydrophilic substance for excretion.

Pharmaceutical metabolism can result in toxification (activation) or detoxification (deactivation) of the active compound. Although both processes may occur, the majority of pharmaceutical metabolites are detoxification products.

According to Halling-Sørensen et al. (1998) the metabolism of pharmaceuticals involves two consecutive metabolic pathways: Phase I and Phase II (Fig. 2.5; Table 2.3).

The majority of pharmaceuticals are metabolized to either Phase I or Phase II metabolites. Both phases alter the physical-chemical behaviour of pharmaceuticals (metabolites are more soluble that the parent compounds and products of Phase I are often more toxic than the parent compound). Phase I biotransformations involve primary covalent chemical oxidative modification (hydroxylation, N-oxidation, deamination,), reduction or hydrolysis reactions (Jr et al. 2007). If Phase I metabolites are sufficiently polar, they may be immediately excreted. However, many metabolites of this phase are not quite eliminated and undergo a subsequent reaction in which an endogenous substrate combines with the recently incorporated functional group to form a highly polar conjugate.

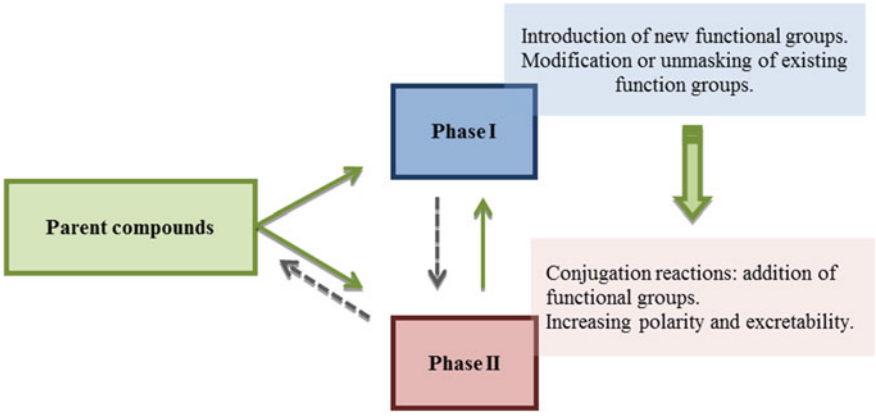
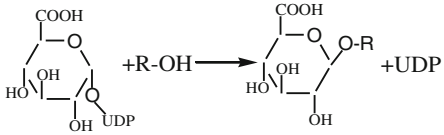


Fig. 2.5 An overview of the metabolization of parent compound into Phase I and Phase II metabolites. *Solid line*—transformation into more water-soluble compounds; *dotted line*—reactivation of the Phase II metabolites (adapted from Halling-Sørensen et al. 1998)

Phase II reactions comprise the synthesis or conjugation of an endogenous polar species to either the parent compound of the Phase I product (Jr et al. 2007), as for example the addition of a glucuronic acid, sulfate, acetate or amino acids, and are usually detoxifying in nature, involving the interaction of polar functional groups of Phase I metabolites (Monteiro and Boxall 2010). If the pharmaceutical remains lipophilic, it will be once again reabsorbed and will last in the body for a longer period (Monteiro and Boxall 2010; Galbraith et al. 2004). Usually, pharmaceuticals metabolism originates more polar metabolites with lower activity and easily excreted.

Only in the last years, regulatory agencies have issued detailed guidelines regarding on how pharmaceuticals should be assessed for possible unwanted effects on the environment (Fent et al. 2006). In 2006, the European Medicines Agency (EMEA) delivered a guideline regarding the environment risk assessment of medicinal products for human purpose. This guideline aimed to estimate the potential environmental risks of human pharmaceuticals by a stepwise procedure describe below. In a first stage (Phase I) the predicted environmental concentrations (PEC) of a particular medicine in surface water is assessed. This assessment is made taking into consideration several parameters such as maximum daily dose consumed per inhabitant, the volume of wastewater produced per inhabitant per day, the percentage of market penetration and the dilution effect that pharmaceuticals suffer when entering the environment. If the value obtained for PEC is lower than 0.01 µg/L and there are no other apparent environmental concerns, it can be assumed that the pharmaceutical is unlikely to represent a risk for the environment. However, if the value obtained for PEC is equal or higher than 0.1 µg/L, it is necessary to proceed to as second stage (Phase II), which is divided in two sub-phases (Tier A and Tier B) and this aims to evaluate the environmental fate and effect of the pharmaceutical in question. In Tier A, the environmental fate of pharmaceutical is assessed in ready biodegradability tests, through the examination

Table 2.3 Reactions involved in pharmaceuticals metabolism (Adapted from Wilkinson 2001)

Phase I	Reaction	Examples
1. Oxidation reactions		
Aliphatic hydroxylation	$RCH_2CH_3 \rightarrow RCHCH_3$ (OH)	Ibuprofen
Deamination	$RCHCH_3$ (NH_2) $\rightarrow$ $R\text{-}C\text{-}CH_3$ (OH, NH_2) $\rightarrow$ $R\text{-}C\text{-}CH_3$ (=O) $+NH_2$	Diazepam
N-Dealkylation	$RNHCH_3 \rightarrow RNH_2 + CH_2O$	Diazepam, codeine, caffeine
2. Hydrolysis reactions	$R_1COR_2 \rightarrow R_1COOH + R_2OH$ (=O)	Acetyl-salicylic acid, clofibrate
	$R_1CNR_2 \rightarrow R_1COOH + R_2NH_2$ (=O)	Lidocaine
Phase II	**Reaction**	**Examples**
3. Conjugation reactions		
Glucuronation		Oxazepam, morphine

UDP- glacuronic acid

of: (a) the sorption behaviour of these substances towards sewage sludge and soil; (b) the distribution between water and octanol and finally (c) by a transformation test in water-sediment systems. According to the results obtained, additional analysis may be required. The pharmaceutical effect is also established by respiration inhibition tests, whereas the standard long-term toxicity analyses are performed in *Daphnia magna* fishes and aim to calculate the no-effect concentration ($PNEC_{water}$). The $PNEC_{water}$ is used to calculate the ratio $PEC_{surface\ water}$ versus $PNEC_{water}$. If the $PNEC_{water}$ value is lower than one, there is no additional necessity for ecotoxicological analyses for the aquatic compartment. However, if the obtained value is higher than one, additional analyses will be required on a second stage

(Tier B). The threshold recognized by the EMEA guideline is of 0.01 μg/L and may not be suitable for very specific and highly powerful pharmaceuticals such as synthetic hormones, which can have antagonistic effects in the environment at trace concentrations. These substances enter Phase II and are subject to a risk assessment taking into account the mode of action (Christen et al. 2010).

Similarly to others pharmacological compounds, psychiatric compounds occur in the environment in the range of ng/L to μg/L. However, although the concentrations in which they are found are below the levels considered to be harmful to humans, as well as causing acute or chronic toxicity to non-target organisms, it is vital to take into consideration that these compounds and their metabolites do not occur individually in the environment, but as complex mixtures. In this context, and due to their intrinsic biological activity that can 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 (Calisto and Esteves 2009). Since the potential adverse effects of steroids and other estrogens on the endocrine systems were discovered (Brooks et al. 2003a), little attention has been paid to non-steroidal pharmaceuticals that have the same ability to affect the neuronal system, to disrupt neuro-endocrine signaling and to cause perturbations on the reproductive behaviour (Gust et al. 2009), Table 2.4. One example is fluoxetine, an antidepressant that is suspected to be hormonally active (Kolpin et al. 2002).

In primary producers, invertebrates and fish, the mechanistic responses to SSRI, serotonin-specific reuptake inhibitors, are not completely clarified, however, several fish species were identified for the possession of serotonin receptors, making it possible to predict that SSRI can modulate serotonin levels in these animals (Brooks et al. 2005). An investigation conducted by Henry et al. (2004) regarding the chronic and acute toxicity of SSRI to *Ceriodaphnia dubia*, a water flea, acknowledged that the production patterns of *C. dubia* were affected by the exposure to SSRI. Pascoe et al. (2003) compared the acute and chronic toxicity of diazepam to an aquatic invertebrate sedentary organism (*Hydra vulgaris*) and described visible adverse effects such as deficient regeneration of polyps, at concentrations of 10 μg/L.

The majority of the studies concerning the impact, effect and fate of psychiatric pharmaceuticals in non-target organism are conducted in laboratory conditions, where most of the times, only one drug is analyzed at a time, thus not reproducing the actual and natural conditions of their occurrence in the environment, as well as all the interactions involved (Table 2.4).

The fluctuating concentrations of pharmaceuticals through time and space (this last one, due either to the location of pharmaceuticals facilities, domestic and hospital sewages, near natural hydric resources, but also to the dilution effect that pharmaceuticals suffer when enter the environment) are another important factor that must be considered in environmental and toxicity studies as well in ecotoxicological risk assessments. These studies should always consider the environmental effects of metabolites and transformation products, the impact and the short and long term effect of pharmaceuticals accumulation via food-chain, drug

Table 2.4 Effects of several psychiatric pharmaceuticals on non-target organisms (SAICM 2014)

Therapeutical group	Antidepressants			
Pharmaceutical	Fluoxetine			
Non-target organism	*Pseudokirchneriella subcapitata*	*Ceriodaphnia dubia*	*Ceriodaphnia dubia*	*Dreissena polymorpha*
Effects	Growth inhibition; cell deformities	Increase fecundity in neonates female	Reduce the number of neonates and broods per female; increase in mortality with increasing fluoxetine concentration	Induce spawning in male zebra mussels
Study type	Laboratory	Laboratory	Laboratory	Laboratory
Reference	Brooks et al. (2003b); Johnson et al. (2007)	Brooks et al. (2003b)	Henry et al. (2004)	Fong (1998)
Non-target organism	*Oryzias latipes*	*Elliptio complanata*	*Lampsilis fasciola*	*Lampsilis cardium*
Effects	Affect embryos development such as edema, curved spine, incomplete development (no pectoral fins, reduced eyes) and non-responsiveness; increase of steroids in females circulation; reduce growth	Induce parturition of nonviable larvae from female bivalves and release of spermatozeugmata in males; accumulation in mussel tissues and potential to disrupt reproduction in freshwater mussels	Stimulate lure display behaviour in female bivalves	Stimulate lure display behaviour in female bivalves
Study type	Laboratory	Wildlife	Wildlife	Wildlife
Reference	Brooks et al. (2003a, b)	Bringolf et al. (2010)	Bringolf et al. (2010)	Bringolf et al. (2010)
Non-target organism	*Potamopyrgus antipodarum*	*Valvata piscinalis*	*Rana pipiens*	*Xenopus*
Effects	Reduce the number of cumulated neonates per living adult; variation on the number of shelled embryos and the number of embryos in the brood pouch; loss of gonadal tissue	Decrease of the total number of eggs per living adult	Delay tadpole development	Tail flexure; faial malformations

(continued)

Table 2.4 (continued)

Therapeutical group	Antidepressants			
Pharmaceutical	Fluoxetine			
Study type	Laboratory	Laboratory	Laboratory	Laboratory
Reference	Gust et al. (2009)	Gust et al. (2009)	Foster et al. (2010)	Richards and Cole (2006)
Non-target organism	*Hyalella azteca*	*Morone saxatilis* × *Morone chrysops*	*Chironomus tentas*	*Mytilopsis leucophaeata*
Effects	Stimulate young female reproduction; growth inhibition	Reduce the ability to capture the prey	Reduce survival; reduce growth	Induce spawning in male zebra mussels and dark false mussels
Study type	Laboratory	450 L circular flow-through holding tanks	Laboratory	Laboratory
Reference	Brooks et al. (2003b)	Gaworecki and Klaine (2008)	Brooks et al. (2003a, b)	Fong and Molnar (2008)

Therapeutical group	Antidepressants			
Pharmaceutical	Fluoxetine	Sertraline		
Non-target organism	*Sphaerium striatinum*	*Xenopus*	*Pseudokirchneriella subcapitata*	*Oryzias latipes*
Effects	Reduce number of neonates	Tail flexure	Growth inhibition	Increase in mortality; disruption of larval locomotor behaviour
Study type	Laboratory	Laboratory	Laboratory	Laboratory
Reference	Fong (1998)	Richards and Cole (2006)	Johnson et al. (2007)	Chiffre et al. (2014)

Therapeutical group	Antidepressants			
Pharmaceutical	Fluvoxamine	Venlafaxine	Citalopram	
Non-target organism	*Dreissena polymorpha*	*Lymnaea stagnalis*	*Ceriodaphnia dubia*	*Oryzias latipes*
Effects	Induce spawning in male zebra mussels	Changes in immunocompetence (increased hemocyte count, ROS levels and phagocytosis, and decreased intracellular thiol levels)	Reduce number of neonates and increase mortality with increasing citalopram concentration	Increase in mortality; disruption of larval locomotor behaviour

(continued)

Table 2.4 (continued)

Therapeutical group	Antidepressants			
Pharmaceutical	Fluvoxamine	Venlafaxine	Citalopram	
Study type	Laboratory	Laboratory	Laboratory	Laboratory
Reference	Fong (1998)	Gust et al. (2013)	Henry et al. (2004)	Chiffre et al. (2014)

Therapeutical group	Antidepressants			
Pharmaceutical	Paroxetine			Fluvoxamine
Non-target organism	*Dreissena polymorpha*	*Xenopus*	*Dreissena polymorpha*	*Dreissena polymorpha*
Effects	Induce spawning in male zebra mussels and dark false mussels	Tail flexure	Induce spawning in male zebra mussels	Induce spawning in male zebra mussels
Study type	Laboratory	Laboratory	Laboratory	Laboratory
Reference	Fong and Molnar (2008)	Richards and Cole (2006)	Fong (1998)	Fong (1998)

Therapeutical group	Antidepressants			
Pharmaceutical	Venlafaxine	Norfluoxetine		
Non-target organism	*Lymnaea stagnalis*	*Daphnia magna*	*Mytilopsis leucophaeata*	*Sphaerium striatinum*
Effects	Changes in immunocompetence (increased hemocyte count, ROS levels and phagocytosis, and decreased intracellular thiol levels)	Decrease the offspring number	Induce spawning in male zebra mussels and dark false mussels	Reduce number of neonates
Study type	Laboratory	Laboratory	Laboratory	Laboratory
Reference	Gust et al. (2013)	Minguez et al. (2015)	Fong and Molnar (2008)	Fong and Molnar (2008)

Therapeutical group	Antidepressants		Anxiolytics	
Pharmaceutical	Citalopram		Oxazepam	Diazepam
Non-target organism	*Ceriodaphnia dubia*	*Oryzias latipes*	*Perca fluviatiis*	*Lymnaea stagnalis*
Effects	Reduce number of neonates and increase mortality with increasing citalopram concentration	Increase in mortality; disruption of larval locomotor behaviour	Altered behaviour and feeding rate	Changes in immunocompetence (increased hemocyte count, ROS levels and phagocytosis, and decreased intracellular thiol levels)

(continued)

Table 2.4 (continued)

Therapeutical group	Antidepressants		Anxiolytics	
Pharmaceutical	Citalopram		Oxazepam	Diazepam
Study type	Laboratory	Laboratory	Laboratory	Laboratory
Reference	Henry et al. (2004)	Chiffre et al. (2014)	Brodin et al. (2013)	Gust et al. (2013)

Therapeutical group	Anxiolitics			
Pharmaceutical	Diazepam		Carbamazepine	
Non-target organism	*Hydra vulgaris*	*Daphnia magna*	*Folsomia candida*	*Lymnaea stagnalis*
Effects	Deficient regeneration of polyps	Growth inhibition	Avoidance behaviour; decrease of acetylcholinesterase activity; peroxidative damages; glutathione *S*-transferase inhibition	Changes in immunocompetence (increased hemocyte count, ROS levels and phagocytosis, and decreased intracellular thiol levels)
Study type	Laboratory	Laboratory	Laboratory	Laboratory
Reference	Pascoe et al. (2003)	Lilius et al. (1995)	Oliveira et al. (2015)	Gust et al. (2013)

Therapeutical group	Mood-stabilizers			
Pharmaceutical	Carbamazepine			
Non-target organism	*Venerupis decussate*	*Venerupis philippirarum*	*Salmo salar*	*Dreissena polymorpha*
Effects	Decrease on lipid peroxidation levels; Glutathionse *S*-transferase activity stimulation; induction of glutathione reductase, superoxide dismutase and cytochrome P450 3A4 activities	Increase on lipid peroxidation levels; Glutathionse *S*-transferase activity decrease; induction of glutathione reductase, superoxide dismutase and cytochrome P450 3A4 activities	Induces differential transcriptome expression in brain	Increase in gills mRNA levels of hsp70 able to cause protein damage in gills
Study type	Laboratory	Laboratory	Laboratory	Laboratory
Reference	Almeida et al. (2014)	Almeida et al. (2014)	Hampel et al. (2014)	Contardo-Jara et al. (2011)

target-conservation on non-target organisms and establish and validate international analytical methods for the detection and quantification of drugs in different environmental matrices. Although considerable information regarding psychiatric pharmaceuticals occurrence and effects are currently available in the public domain, there are still a lot of gaps. Based on the literature review it is possible to advocate that over the past years, countless and different pharmaceuticals such as antibiotics, analgesics, anti-inflammatories, hormones, lipid regulators and psychiatric pharmaceuticals, have been detected in several environmental matrices. Psychiatric pharmaceuticals are of especially importance since they have the aptitude to directly affect the central nervous system, disrupt neuro-endocrine signaling and alter reproduction patterns in non-target organisms. Although the sources of psychiatric pharmaceuticals are well known, the environmental effects and fate of these compounds, as well as their metabolites, in natural and actual conditions are far from being fully studied and understood.

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