Pharmaceuticals and Their Metabolites in Sewage Sludge and Soils: Distribution and Environmental Risk Assessment

Juan Luis Santos, Julia Martín, Carmen Mejías, Irene Aparicio, and Esteban Alonso

Contents

Abstract Pharmaceutical compounds (PhCs) are continually discharged to sewer systems through human excreta. In wastewater treatment plants, these compounds are partially removed by biodegradation or retention onto the sludge generated during wastewater treatment. As a result, they can end up in the aquatic environment, through the discharge of wastewater effluents to the receiving waters, or to the soil, through the application of the sludge as organic amended, or by the irrigation with recycled water. Moreover, these compounds are partially metabolized after their consumption, and, as a result, PhCs and their metabolites are present in the environment. This chapter summarizes recent research on the occurrence of PhCs and their metabolites in sewage sludge stabilization processes and on sludge-amended soils. Recent studies have shown that antibiotics, non-steroidal anti-inflammatory drugs, antidepressants, and antidiabetics are the most abundant PhCs found in sludge matrices. Overall, attenuation of PhCs concentrations occurs during sludge stabilization, and particularly during anaerobic digestion and composting. The potential ecotoxicological risk associated with the presence of PhCs in amended soils is

J. L. Santos (✉), J. Martín, C. Mejías, I. Aparicio, and E. Alonso
Departamento de Química Analítica, Escuela Politécnica Superior, Universidad de Sevilla, Seville, Spain
e-mail: jlsantos@us.es

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medium-low for most PhCs. The most critical compounds found in sludge-amended soils are ciprofloxacin, 17α-ethinylestradiol, and 17β-estradiol.

Keywords Environmental risk, Metabolites, Occurrence, Sludge stabilization treatments, Sludge-amended soil

1 Introduction

In the last years, numerous studies have described the presence of pharmaceutical compounds (PhCs) in the environment [1]. These compounds are continually discharged to the sewer system through human excreta. In wastewater treatment plants (WWTPs), these compounds are partially removed by biodegradation or retention onto the sludge generated during wastewater treatment. As a result, they can end up in the aquatic environment, through the discharge of wastewater effluents to the receiving waters, or to the soil, through the application of the sludge as organic amended, or by irrigation with recycled water [2]. Moreover, veterinary pharmaceuticals used in livestock are excreted by the animals and end up in soils via grazing livestock or manure used as agricultural fertilizer [3]. Among PhCs frequently detected are anti-inflammatories like acetaminophen, ibuprofen, naproxen, or diclofenac [1, 4, 5]; antibiotics as sulfamethoxazole, trimethoprim, norfloxacin, or sulfonamides [4]; or antiepileptics as carbamazepine [6]. Moreover, these compounds are partially metabolized after their consumption [1, 2, 7]. Consequently, both pharmaceuticals and their metabolites have been detected not only in their sources, wastewater, and sludge [8, 9], but also in their main fates, surface waters [10], and soil [11, 12].

The amount of sewage sludge generated in WWTPs has increased strikingly in recent years. In the European Union, the most usual final destiny of these sludges is their use as organic amended in soil [5, 13]. For example, it is estimated that around 40% of the sludge produced in 2021 will be used as a source of organic matter and nutrients for agricultural purposes [5, 14], although different application rates are used among the Member States of the EU [14, 15]. The main stabilization processes applied to the sludge previously to their application onto the soil are anaerobic and aerobic digestion, composting, and, particularly in little municipalities, low-cost wastewater treatments, as lagooning [5, 14, 16]. However, several studies have described the persistence of PhCs along these treatments [2, 16–19].

In this chapter, a discussion is carried out on the main studies reported in the last years about the distribution of the most recurrent PhCs and their metabolites in sludges stabilization processes, and in soils amended with these sludges. Moreover, the risk associated with the presence of these compounds in sludge applied to the soil is discussed too.

2 Occurrence of PhCs and Metabolites Alongside Sludge Stabilization Treatments

The most usual sludge stabilization treatments are their digestion under anaerobic (in high-populated cities) and aerobic conditions (in low populated municipalities). In both processes, the sludge separated from influent wastewater in the primary sedimentation tank is concentrated in a gravity thickener (primary sludge) and mixed with the secondary sludge obtained from the secondary settler and concentrated in the flotation thickener. Mixed sludge is digested under anaerobic (in anaerobic stabilization plants) or aerobic (in aerobic stabilization plants) conditions. The final product of these treatments is usually subjected to composting processes carried out in the open air, forming piles in which the aeration is thermally controlled by turning [2].

In small municipalities, low-cost wastewater treatment is usually applied to wastewater treatment and sludge stabilization. The most usual treatment is lagooning, in which the sludge stabilization takes place at the bottom of a lagoon under anaerobic conditions [2].

In this chapter, the main findings included in more than 50 works published in the last 20 years about the presence and distribution of PhCs and their metabolites in sludge are evaluated (Fig. 1). About 70% of the published data have focused on compounds measured in the final product of the stabilization treatment (digested, dehydrated, or composted sludge). The studies about the distribution of metabolites in sludge stabilization treatments are even scarcer. Anti-inflammatories (36 papers, mainly about diclofenac, ibuprofen, naproxen, and ketoprofen), antibiotics (33 papers, mainly about ciprofloxacin, ofloxacin, enrofloxacin, norfloxacin, sulfamethoxazole, sulfamethazine, tetracycline, oxytetracycline, and trimethoprim), and antiepileptics (33 papers, mainly about carbamazepine) are the most studied therapeutic groups in sludge, followed by beta-blockers (22 papers, mainly about propranolol, metoprolol, atenolol), antilipemics (19 papers, mainly about bezafibrate and gemfibrozil), and stimulants (18 papers, mainly about caffeine).

Considering metabolites, the most studies have been focused on those derived from anti-inflammatories, antilipemics, or antiepileptics (mainly the metabolites of carbamazepine). On the contrary, the studies of the metabolites of antibiotics are very sparse.

Moreover, most of these studies evaluate the distribution on sludge stabilization treatments for only a few metabolites, as the ones from diclofenac [2], ibuprofen [2], carbamazepine [2, 15, 20], or sulfamethoxazole [20] (Fig. 1). This could be due to the complexity of the analysis of these samples and to the lack of commercial analytical standards that allow their determination.

Figures 2 and 3 show the concentrations of 180 PhCs, measured in sludge samples worldwide in the last 20 years, grouped by therapeutic group (data collected from [5]). Measured concentrations ranged from ng or μg per kilogram to even mg per kilogram, depending on the consumption, physicochemical properties of the compounds, and the characteristics of the sludge.

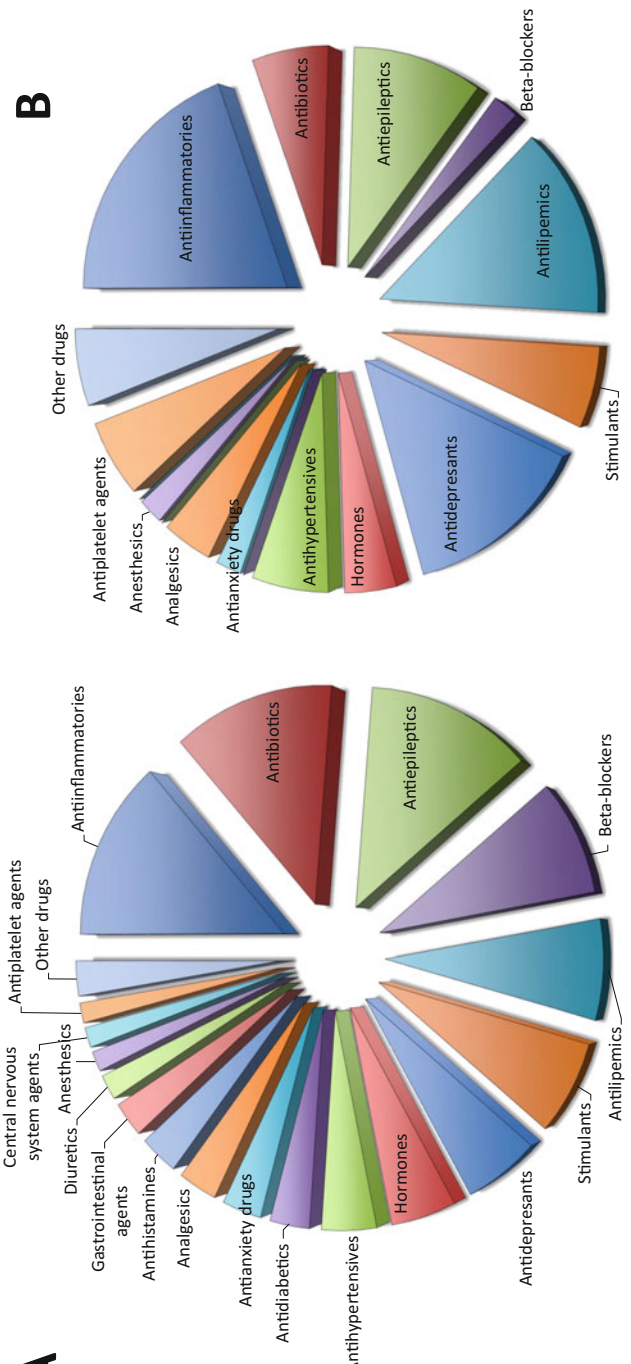

Fig. 1 Therapeutic groups studied in sludge in the last 20 years (Data from [5])

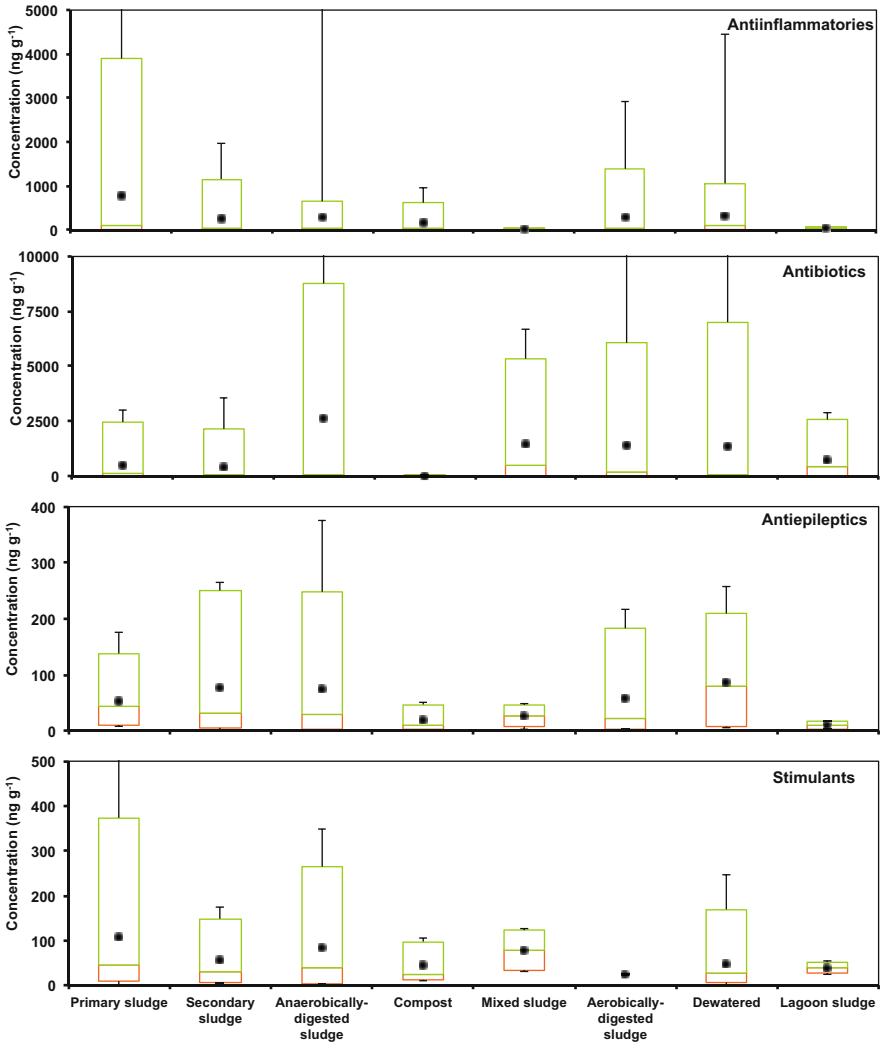

Fig. 2 Concentration of antibiotics, anti-inflammatories, antiepileptics, and stimulants measured alongside sludge stabilization processes. Raw sludge was considered as mixed sludge (Data collected from [5])

The higher concentrations in fresh sludge (primary, secondary sludge, and mixed) have been described in the case of antibiotics (in mixed sludge) and anti-inflammatories (mainly in primary sludge), followed by stimulants (mainly caffeine). The compounds more frequently measured and at the highest concentrations in these sludges are fluoroquinolones [14, 15, 20–22] as ciprofloxacin, norfloxacin, and ofloxacin (for example, concentrations of ciprofloxacin up to 12,858 ng g^{-1} were measured in raw sludge from France [22]), the anti-inflammatories diclofenac [2, 20, 22–26] (up to 7,020 ng g^{-1} measured in Germany) and ibuprofen [2, 24, 25]

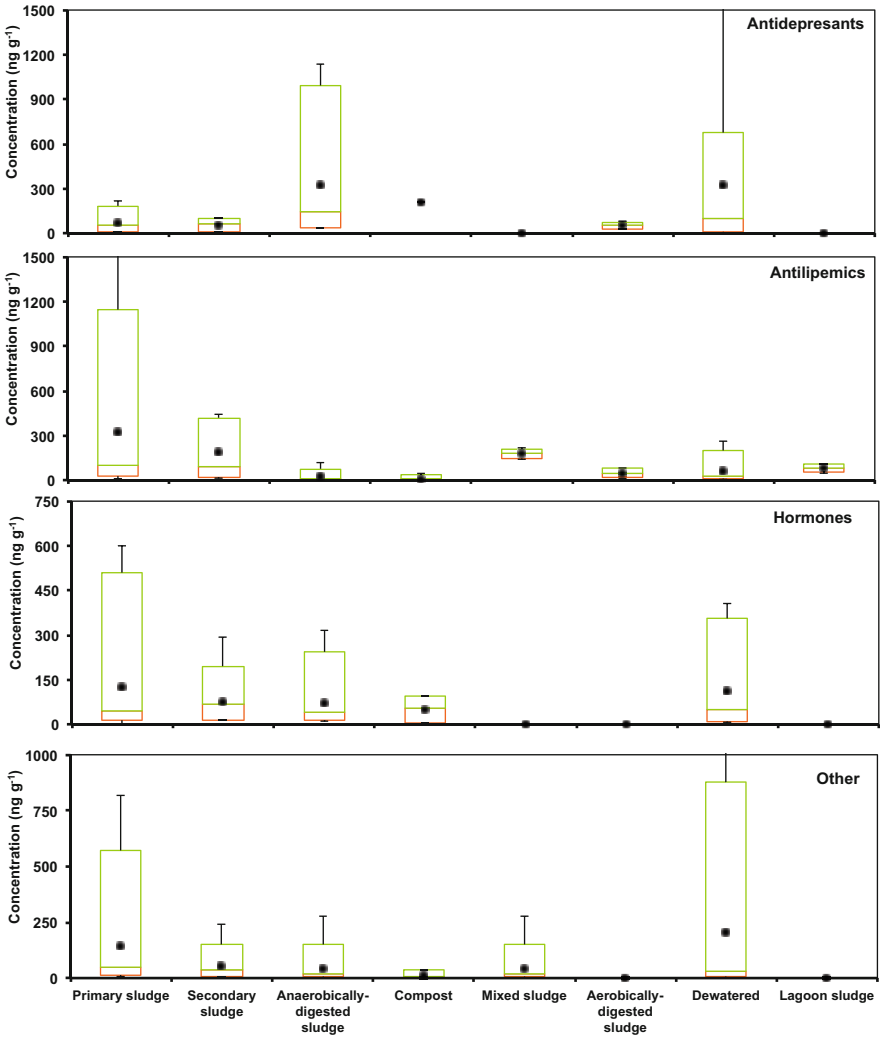

Fig. 3 Concentration of antidepressants, hormones, and other pharmaceuticals measured alongside sludge stabilization processes. Raw sludge was considered as mixed sludge (Data collected from [5])

(ranging from 11.1 to 4,105 ng g^{-1}), the antilipemic gemfibrozil (concentrations up to 2,026 ng g^{-1} have been measured in primary sludge from Spain [27]), the stimulant caffeine (up to 2,828 ng g^{-1} measured in Canada [28]) or hormones [22, 26, 28–31] (up to 599 ng g^{-1} dw and 421 ng g^{-1} dw in the case of 17-α-ethynylestradiol and estrone, respectively [31, 32]).

Other compounds, as sulfonamide or macrolide antibiotics, anti-inflammatory drugs as acetaminophen, naproxen or ketoprofen [5, 8, 27–31, 33–35], antidepressants as carbamazepine [19, 29, 31, 33, 36] or beta-blockers as propranolol and

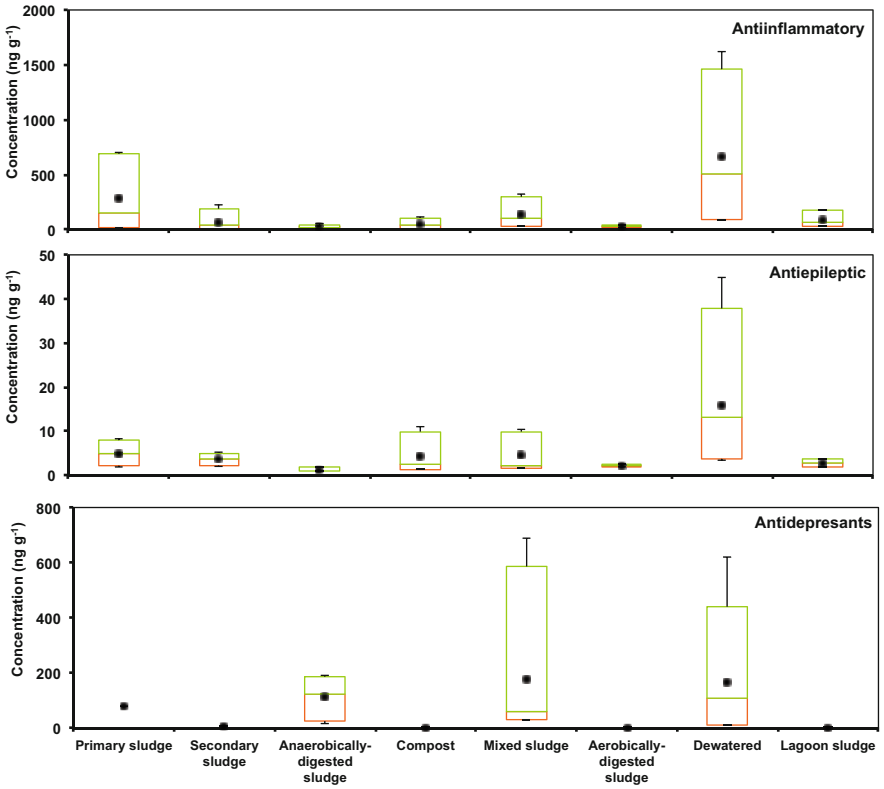

Fig. 4 Concentration of metabolites of anti-inflammatories, antiepileptics, and antidepressants measured alongside sludge stabilization processes. Raw sludge was considered as mixed sludge (Data collected from [5])

atenolol [8, 19, 20, 22, 27, 29, 31, 33] have been frequently detected, although at lower concentrations.

Considering pharmaceutical metabolites, the highest concentrations have been measured in the case of those derived from salicylic acid (concentrations up to 931 ng g^{-1} have been detected in sludge stabilization treatments from the south of Spain [8, 33]) and ibuprofen (up to 204 and 100 ng g^{-1}, in the case of carboxyibuprofen and 2-hydroxy ibuprofen, respectively [2]). Other compounds measured in fresh sludge (although at lower concentrations) are metabolites of antilipemics as clofibric acid [14, 26, 30], metabolite of clofibrate; N-desmethylcitalopram [37, 38] and norsertraline [19, 22, 37–39], metabolites of antidepressants, and paraxanthine (PX) [2], metabolite of caffeine. These metabolites have usually been found at lower concentrations than their parent compounds in fresh sludges (Figs. 2, 3, 4, and 5). This contrasts with the results obtained in aqueous environment, where some metabolites, as 2-hydroxyibuprofen (2OH-IBU) and carboxyibuprofen (CBX-IBU), have been measured at higher

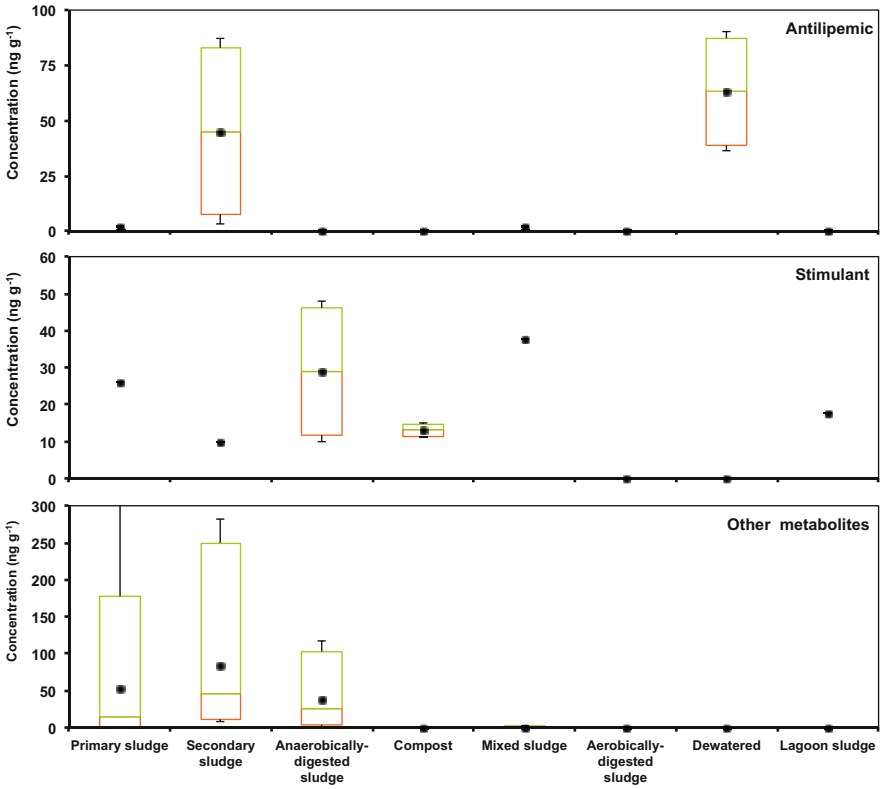

Fig. 5 Concentration of metabolites of antilipemics, stimulants, and other PhCs measured alongside sludge stabilization processes. Raw sludge was considered as mixed sludge (Data collected from [5])

concentrations than their parent compounds (specifically in wastewater samples). However, this could be explained by the high number of studies reporting the concentration of PhCs in sludge in relation to those reporting concentrations of their metabolites. On the contrary, Malvar et al. [2] found in sludge samples concentrations of 10-hydroxycarbamazepine (10OH-CBZ), 4-hydroxydiclofenac (4OH-DIC), 2OH-IBU and CBX-IBU higher than those measured for their parent compounds, as it was described for water samples. This shows the concentrations in influent wastewater as the main factor governing the concentration of these compounds in fresh sludge, in spite of the different sorption capacity of these compounds onto the sludge [5]. Moreover, the concentration of PhCs and metabolites in secondary and mixed sludges could be affected by the biodegradation of these compounds in secondary wastewater treatment. For example, recently Malvar et al. [2] related the concentrations of 10OH-CBZ, 2OH-IBU and CBX-IBU measured in secondary sludge (higher than those measured in primary sludge) with the biodegradation of ibuprofen during secondary treatment.

The PhCs and metabolites more frequently studied in fresh sludge and found at highest concentrations were the compounds most studied and detected in treated sludge: anti-inflammatory drugs, antibiotics, and antiepileptics, and, in less extension, antidepressants. Data published in the literature showed higher concentrations of antibiotics in treated sludge than those measured in fresh sludges, especially in the case of fluoroquinolone antibiotics, with concentrations up to 12,858 ng g^{-1} (ciprofloxacin), 6,049 ng g^{-1} (norfloxacin) and 6,712 ng g^{-1} (ofloxacin). The same behavior could be observed in the case of antiepileptics (mainly carbamazepine), which shows the high persistence of these compounds in the digestion processes. Other compounds, as anti-inflammatories, show a decrease of the concentrations measured in digested sludges with respect to those measured in fresh sludge (Fig. 2). In spite of that, concentrations up to 7,020 and 4,105 ng g^{-1} have been measured for diclofenac and ibuprofen, respectively. In the case of other PhCs, as stimulants, antidepressants or hormones, their behavior in sludge stabilization treatments seems to depend on the digestion process. Most of them showed lower concentrations in aerobic processes than those measured in sludge treated under anaerobic conditions. The differences in concentration pattern between aerobic and anaerobic stabilization processes have been previously described in the case of pharmaceuticals as azithromycin, irbesartan, sertraline, which are more frequently detected in aerobically digested sludge [15]. Other studies [40–42] showed a higher mitigation of the concentration of clarithromycin and azithromycin under anaerobic conditions, while caffeine showed a high persistence to the anaerobic treatment [8, 42], whereas under aerobic condition was widely removed. Moreover, several works have described the importance, not only of the anaerobic or aerobic conditions, but also of other parameters, such as temperature or treatment time. For example, 60% of diclofenac and diazepam were removed under mesophilic anaerobic conditions (38°C), while under thermophilic conditions (55°C) only 38% of diclofenac and 73% of diazepam were removed [43]. Other works have even showed an improvement in the removal of these compounds by the combination of the two conditions. For example, removals up to 90% have been measured in the case of diclofenac, oxazepam, ofloxacin, or propranolol using combined anaerobic and aerobic conditions [44, 45]. Regarding composting, in general the concentrations measured after the composting process are lower than those measured in digested sludge for the most of the PhCs. Some works showed the photodegradation of hydrosoluble PhCs, as well as mineralization and even the dilution due to the mixture with other products, as potential ways of removal [46].

Considering PhC metabolites, only one study has been reported in the literature [42], which shows the importance of performing a further investigation on this issue. The results obtained in this work described that the distribution of PhC metabolites depend on the compound and the conditions applied to the stabilization. Compounds as PX or the metabolites of ibuprofen showed high decrease of their concentrations alongside the sludge stabilization treatments, while other, as the metabolites of carbamazepine and diclofenac, were highly persistent to all treatments evaluated. Moreover, transformations between metabolites and parent compounds were only observed in the case of ibuprofen.

3 Distribution of PhCs and Metabolites in Soil

One of the main disposal options for the sludge generated during sludge stabilization treatments is its application to the soil as organic amended. As a result, organic contaminants in the sludge, among them PhCs and their metabolites, end up into the soil. In a study carried out in the Slovak Republic [15], it was estimated a total input load of up to 120 kg/year of fexofenadine disposed into the soil through the application of sewage sludge, together with other PhCs, including antihistamines, antidepressants, or antihypertensives. PhCs frequently detected and measured at highest concentrations in soil are antibiotics, as fluoroquinolones (up to 550 ng g^{-1}), tetracyclines (tetracycline and oxytetracycline, up to 63.8 and 101 ng g^{-1}, respectively) and sulfamethoxazole (47.9 ng g^{-1}) [47, 48], as well as other compounds as diclofenac [11, 49], ibuprofen [11], carbamazepine [11, 50], or caffeine [11].

Considering PhC metabolites, only a few data have been reported in the literature about their presence in soils. García-Galán et al. [51] evaluated the presence of several sulfonamide antibiotics and their metabolites in soils collected in rural areas from Catalonia (North East of Spain). Among the measured compounds were acetylsulfamethoxazole (up to 1.38 ng g^{-1}) and acetylsulfapiridine (up to 0.77 ng g^{-1}). Other metabolites as CBX-IBU [52] and 4OH-DIC [35] have been measured in soils at concentrations up to 46.1 and 3.3 ng g^{-1}, respectively.

In the soil, PhCs and their metabolites may undergo different routes, such as sorption/desorption processes [53, 54], transport by leaching [55], or degradation/transformation [2, 11]. The concentrations of PhCs and metabolites in the soil depend, in addition to the sludge application rates and frequency, on several factors, as soil properties, physicochemical characteristic of the compounds, precipitations or even land relief. Highly mobile compounds could contaminate surface water through runoff or groundwater by leaching. Highly adsorbed compounds could be accumulated into the soil [5]. In this way, several works have showed the mobility of ibuprofen, acetaminophen, or sulfamethoxazole [56, 57], which have been measured in leachates from sludge-amended soils, while other compounds as carbamazepine, diclofenac, trimethoprim, or propranolol showed high retention in the soil matrix [6, 56, 58]. Regarding PhCs metabolites, several works have shown, in laboratory experiments, the adsorption behavior of these compounds, mainly for carbamazepine [54, 55, 59]. These studies show different soil retention of PhC metabolites compared to those observed in the case of their parent compounds, what could be due to the different physicochemical characteristics of the metabolites. For example, Paz et al. [54] showed how the relative charge densities for metabolites of carbamazepine, due to the electronegative oxygen atoms, could contribute to the different adsorption behavior of these compounds.

Considering the degradation of these compounds in soils, only a few studies have assessed its dissipation in the edaphic environment. Some compounds as norfloxacin, ciprofloxacin or azithromycin have shown high persistence [60], while other as sulfamethoxazole, diclofenac or caffeine showed a high dissipation

in a few days [42]. Until now, only one study has been reported in the literature about the dissipation of metabolites of PhCs in soil [42]. In this work, batch experiments carried out with three different soils spiked with these substances showed differences between metabolites and parents compounds regarding their persistence in soil. For example, carbamazepine and epoxy-carbamazepine showed high persistence, while the metabolites 3OH-carbamazepine and 10OH-CBZ showed a rapid dissipation (up to 20 days). Other compounds, as caffeine and its metabolite PX and sulfamethoxazole and its metabolite acetylsulfamethoxazole, showed persistence between 20 and 60 days, depending on the soil characteristics. Only in the case of ibuprofen, transformation of ibuprofen in its metabolite 2OH-IBU could be considered.

4 Environmental Risk Assessment of Pharmaceuticals and Metabolites in Soil

The most common approach used to assess the environmental risk caused by the presence of PhCs and metabolites in soil is based on the European Medicines Agency Guideline [61] through the use of the risk quotient (RQ). The RQ is the relation between the measured (MEC) or predicted environmental concentrations (PEC) and the predicted no-effect concentrations (PNEC). To calculate the PNEC values, it is needed to use the lowest acute and chronic toxicity data in fish, *Daphnia magna,* or algae organisms and dividing them with an assessment factor of 1,000 or 100, respectively, to consider the worst-case scenario. Because of the lack of ecotoxicological data for terrestrial organisms, many authors usually take the values in aquatic organisms to estimate the $PNEC_{soil}$ through the equilibrium partition approach: $PNEC_{soil} = K_d \times PNEC_{water,}$ as suggested by the European Commission [8, 22, 33, 62]. Recently, Mejías et al. [5] recompiled the toxicity and K_{dsoil} data reported in the literature. This work draws attention as regards the lack of available data in the particular case of metabolites.

Once the RQ is estimated, the criteria proposed by Hernando et al. [63] is applied to evaluate the risk, considering low risk for $RQ < 0.1$, medium risk for RQ between 0.1–1 and a high risk when $RQ > 1$. Table 1 shows the minimum and maximum RQ values calculated based on the lowest and highest concentration levels found for PhCs and metabolites in digested sludge or compost, and the K_d compiled from the literature. The PEC values in soil were estimated according to the EC-TGD [62] by the equation:

$$PEC_{soil} = C_{sludge} \times APPL_{sludge}/DEPTH_{soil} \times RHO_{soil} \quad (1)$$

where C_{sludge} is the concentration measured in digested sludge or compost; $APPL_{sludge}$ is the dry-sludge application rate (0.5 kg m^{-2} year); $DEPTH_{soil}$ is the mixing soil depth (0.20 m), and RHO_{soil} is the bulk density of wet soil (1,700 kg m^{-3}).

Table 1 Risk quotient (minimum and maximum values) in soil amended due to PhCss and metabolites measured in digested sludge or compost in worldwide ($PNEC_{water}$ and K_d data taken from Mejías et al. [5])

Pharmaceuticals and metabolites	$PNEC_{soil}$ (ng g^{-1})	PEC_{soil} (min) (ng g^{-1})	PEC_{soil} (max) (ng g^{-1})	RQ (min)	RQ (max)
Ciprofloxacin	2.14	0.110	15.43	5.2E−02	7.2E+00
17α-ethinylestradiol	0.10	0.018	0.460	1.8E−01	4.6E+00
17ß-estradiol	0.03	0.062	0.062	1.9E+00	1.9E+00
Sulfamethoxazole	1.20	0.006	0.978	4.8E−03	8.1E−01
Sertraline	1.58	0.085	0.925	5.4E−02	5.8E−01
Tylosin	4.35	2.229	2.229	5.1E−01	5.1E−01
Carbamazepine	48.9	0.005	16.25	1.0E−04	3.3E−01
Diclofenac	34.2	0.016	6.233	4.6E−04	1.8E−01
Estrone	1.23	0.015	0.201	1.2E−02	1.6E−01
Fluoxetine	3.22	0.025	0.251	7.9E−03	7.8E−02
Atenolol	37.5	0.006	2.426	1.6E−04	6.5E−02
Ofloxacin	246	0.078	14.03	3.2E−04	5.7E−02
Oxytetracycline	213	0.002	10.83	7.6E−06	5.1E−02
Ketoprofen	140	0.012	6.553	8.4E−05	4.7E−02
Ibuprofen	46.5	0.071	1.686	1.5E−03	3.6E−02
Caffeine	10.3	0.011	0.365	1.1E−03	3.5E−02
Erythromycin	4.08	0.001	0.120	2.7E−04	2.9E−02
Tetracycline	146	0.006	3.493	4.3E−05	2.4E−02
Clarithromycin	6.72	0.008	0.147	1.1E−03	2.2E−02
Propranolol	40.6	0.015	0.545	3.7E−04	1.3E−02
Estriol	95.8	0.081	0.597	8.4E−04	6.2E−03
Naproxen	28.8	0.015	0.175	5.1E−04	6.1E−03
Simvastatin	68.9	0.382	0.382	5.6E−03	5.6E−03
Sulfamethazine	38.3	0.038	0.204	1.0E−03	5.3E−03
Trimethoprim	7.28	0.001	0.038	1.9E−04	5.3E−03
Metoprolol	146	0.009	0.588	6.3E−05	4.0E−03
Gemfibrozil	64.7	0.012	0.223	1.9E−04	3.5E−03
Acetaminophen	294	0.033	0.391	1.1E−04	1.3E−03
Sulfapyridine	173	0.036	0.178	2.1E−04	1.0E−03
Valsartan	365	0.038	0.221	1.0E−04	6.0E−04
Clofibric acid	113	0.012	0.054	1.1E−04	4.8E−04
Metformin	13,427	0.095	6.146	7.1E−06	4.6E−04
Bezafibrate	84.0	0.019	0.038	2.3E−04	4.6E−04
Salycilic acid	7380	0.027	2.390	3.6E−06	3.2E−04
Sulfathiazole	418	0.107	0.113	2.6E−04	2.7E−04
Irbesartan	273	0.071	0.072	2.6E−04	2.6E−04
Codeine	240	0.009	0.024	3.9E−05	9.8E−05
Norfloxacin	86,865	0.040	8.006	4.6E−07	9.2E−05
Azithromycin	40,964	0.032	1.232	7.9E−07	3.0E−05
Telmisartan	45,214	0.235	0.853	5.2E−06	1.9E−05

Although the estimated results showed an overall low risk for most of the compounds assessed, the evaluation of the environmental risks of ciprofloxacin (RQ 7.2) and estrogens (17α-ethinylestradiol (RQ 4.6) and 17β-estradiol (RQ 1.9)) should not be underestimated when the highest concentrations found are used.

Similar results have been reported by other authors [8, 22, 33, 64, 65]. Martín et al. [8, 33] indicated that 17β-estradiol, 17α-ethinylestradiol, ibuprofen, gemfibrozil, and sulfamethoxazole are among the most hazardous pharmaceuticals when performing a risk assessment in digested sludge and compost. Nevertheless, an important decrease in RQ was perceived when sludge is amended on soils, being 17β-estradiol the only substance showing some potential toxic effects. This practice caused a "dilution" effect, resulting RQ < 0.10. More recently, Gros et al. [65] and Bastos et al. [64] reported RQ > 1 for fluoroquinolones causing risk for soil life and crops. The scientific data available on the potential environmental consequences of sludge amendment to soils have increased the studies on the crop uptake of pharmaceuticals in last years [66]; however, there are gaps in the literature regarding the food chain and the risk to human health.

Finally, it is important to note that the use of highly sensitive organisms such as *H. attenuate* or *B. calyciflorus* in the study could have a high implication on the ecotoxicological risk assessment. In a near future, more research is needed to draw firm conclusions in (1) terrestrial organisms and type of crops and endpoints; (2) including metabolites; and (3) conducting these studies at lower environmentally relevant concentrations.

5 Conclusions and Future Trends

Many works have been published in the last 20 years about pharmaceutical compounds in the environment. Their distribution has been evaluated in their main sources, wastewater, and their main fates, surface waters. However, the studies reporting their distribution in sludge and, especially, their occurrence in sludge stabilization treatments are scarce. The few studies reported in the literature show that the decrease of the concentration of PhC and their metabolites in the sludge stabilization treatments depends not only on the compound but also on the conditions and the process applied to the sludge stabilization. In spite of these studies, there is a lack of information about the behavior of PhCs, and especially their metabolites (and not identified compounds), on both, wastewater and sludge treatment technologies.

Regarding the distribution of PhC and metabolites in soils, their adsorption onto the edaphic matrix as well as their degradation depends on the physicochemical characteristics of the compounds and the properties of the soil. However, for most of these pollutants, the mechanisms governing the occurrence of these compounds, the influence of their characteristics, and the properties of the soil are unknown.

On this basis, in-depth studies are necessary to elucidate the behavior of pharmaceuticals, and especially their degradation products, in different sludge

stabilization treatments, with different technologies, as well as there is a need to evaluate advanced technologies that allow their complete removal, especially in the case of sludges that are going to be applied to the soil. Moreover, further studies evaluating, not only the distribution in soil/water systems, but also their degradation in soils with different characteristics, are necessary.

Concerning the potential environmental risk of PhCs and their metabolites, in spite of the toxicological studies that are being carried out, more toxicological data, especially in the case of pharmaceutical metabolites, are necessary, in order to achieve a complete evaluation of environmental risks due to pharmaceutical compounds.

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