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Occurrence of pharmaceuticals and their metabolites in sewage sludge and soil: A review on their distribution and environmental risk assessment

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

Departamento de Química Analítica, Escuela Politécnica Superior, Universidad de Sevilla, Sevilla, Spain

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ABSTRACT

The recycling and recovery of organic matter and nutrients from sewage sludge for application in agricultural soils is gaining interest, while the presence of pharmaceutically active compounds (PhACs) in this matrix may have a great impact on the environment and human health. The aim of this review paper is to outline recent research on the occurrence of PhACs and their metabolites in sewage treatment lines. A total of 32 classes of therapeutic groups including 180 PhACs and 45 metabolites have been included. In a first part, a summary of the analytical methods with a critical overview of the extraction and determination techniques, quality control issues and methodological challenges for their determination is included. Subsequently, the study gives a snapshot of the concentration levels and distribution patterns found in primary, secondary, digested (aerobically and anaerobically), dehydrated and composted sludge. Data have been systematically summarized and categorized according to matrix type, treatment processes available for PhAC degradation in sludge, and geographical areas. Our literature review showed that antimicrobials, antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants and antidiabetics were the most abundant PhACs found in sludge matrices.Overall, attenuation of PhACs concentrations occurs during sludge stabilization, in particular during anaerobic digestion and composting. PhAC sorption onto sludge is strongly affected by the physicochemical properties, the sludge matrix and the operating and environmental conditions. Lastly, the paper discusses the impact of PhACs on sludge-amended agricultural land. The potential ecotoxicological risk associated with the presence of PhACs in amended soil is medium-low for most PhACs. The most critical compounds found in sludge-amended soil are ciprofloxacin, 17α-ethinylestradiol, 17β-estradiol, and triclocarban and triclosan.

1. Introduction

Pharmaceutically active compounds (PhACs) are anthropogenic contaminants that are continuously released into the environment and that may have a great impact on ecosystems and human health. Before their discharge in the environment, PhAC-rich influents are processed in wastewater treatments plants (WWTPs). The incomplete removal or degradation of PhACs in WWTPs results in the presence of these contaminants in wastewater effluents (ranging from ng/L to μg/L) and in biosolids (μg/kg to mg/kg) [1–3]. Based on mass balance studies, between 55 % and 100 % of norfloxacin, ciprofloxacin, ofloxacin and lomefloxacin (quinolone antibiotics), hydrochlorotiazide (antihypertensive), fenofibrate (a lipid-regulating agent), and propranolol (beta blocker) are removed in WWTPs being sorbed onto sewage sludge [3–9]. Their removal by activated sludge processes involves the formation of flocs by microbial activity, via electrostatic and hydrophobic interactions [6,7]. Other PhACs account for less than 20 % of the

Abbrevations: AeD, aerobic digestion; AnD, anaerobic digestion; APPL, dry-sludge application rate; d-SPE, dispersive solid phase extraction; d.m., dry matter; DEPTH, mixing depth of soil; EC, effect concentration; ESI, electrospray ionization source; GC/MS, gas chromatography with mass spectrometry detector; HF-LPME, hollow-fiber liquid phase microextraction; HILIC, hydrophilic interaction liquid chromatography; K_d, distribution or partition coefficients; LC–MS/MS, liquid chromatography with tandem mass spectrometry; LC, lethal concentration; MAE, Microwave assisted extraction; MEC, measured environmental concentration; MSPD, matrix solid phase extraction; NOEC, no observed effect concentration; NSAIDs, non-steroidal anti-inflammatory drugs; PEC, predicted environmental concentration; PhACs, pharmaceutically active compounds; PHWE, pressurized hot water extraction; PLE, pressurized liquid extraction; PNEC, predicted no-effect concentration; QA/QC, quality assurance/quality control; QqQ, triple quadrupole; QuEChERS, Quick, Easy, Cheap, Effective, Rugged and Safe; RHO, bulk density of wet soil; RQ, risk quotient; SPE, solid phase extraction; SPME, solid phase microextraction; SRT, sludge retention time; TOC, total organic carbon; TOF, time of flight; USE, ultrasonic solvent extraction; WWTPs, wastewater treatments plants.

* Corresponding author.
E-mail address: jbueno@us.es (J. Martín).

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amount in raw sewage [3,4], but because of the large amounts of sewage sludge generated, these compounds are also becoming a major global environmental problem [3,10].

In 2021, approximately 15 million tons of sludge (dry matter d. m.) will be produced in the European Union (EU) 28 [11,12]. Around 40 % of this sludge will be used as a source of organic matter and nutrients for agricultural purposes [13–15], but with large % variations in its application between the Member States of the EU (no application in countries like Malta, the Netherlands, Slovenia or Slovakia, and more than 50 % in Denmark, Spain, Ireland, and France) [11–14]. Land application of treated sewage sludge has also been widely used to reduce the sludge disposal cost component of sewage treatment in developed countries like the USA, Canada, Australia, New Zealand but particularly in developing countries [14].

EU Directive 86/278/EEC on the protection of the environment, and in particular of the soil, when sewage sludge is used in agriculture, was set to promote the application of sewage sludge to agricultural soils and to ensure its use does not harm the environment, humans or animals [16]. This Directive no longer fits the current needs and is currently under revision for its upgrade [14,17,18]. In 2010, the 3rd draft of the revision document on sludge proposed stricter limits for heavy metals and the possibility of analysing halogenated organic compounds in sludge [19]. In spite of everything, there are no regulations regarding the analysis of new emerging contaminants in sewage sludge [20]. The presence of PhACs in sewage sludge is becoming a matter of special concern because several studies have showed low-effect concentrations, crop transfer and multi-resistant pathogens [21–26].

Although PhAC concentrations in treated sludge are often related to their concentrations in wastewater influents [23,27,28], the physicochemical characteristics of the different PhACs can also influence their concentration [29], sludge matrix [28,30], and the operational parameters used for sewage treatment [31,32]. This paper reveals the necessity of introducing monitoring programs in sewage sludge with the aim of evaluating and reducing potential sources of PhACs that enter the environment through the common practice of using this biosolid as a fertilizer in agriculture. The review of the literature published in the last ten years provided us with data on the concentration of PhACs and their main metabolites found along different sludge treatment processes. The potential routes for their removal under aerobic and anaerobic conditions are discussed. Lastly, the paper examines the impact of PhAC-contaminated sewage sludge on land and the environmental risk assesment.

2. Analytical methods, quality control and challenges

Sewage sludge is a challenging matrix due to its complex nature and heterogeneous composition. This fact, along with the low concentrations of PhACs found in this matrix, makes the sampling, sample preparation and analytical determination critical steps that need to be carefully examined. Regarding the sampling procedure, a significant challenge in the PhAC analysis is to ensure representativeness, which is probably the main source of errors that often receives little attention. Adequate representativeness requires the collection of a number of random sub-samples which can then be pooled to obtain a representative composite. Martín et al. [33] collected 2 L of primary and secondary sludge and 1 kg of anaerobically digested dehydrated sludge and compost. Their analytical method involved sample homogenization, freeze drying and sieving and they used 1.0 g of primary or secondary sludge, 1.5 g of digested sludge or 2.0 g of compost aliquots for sample protocol.

Generally, sample preparation involves extraction, clean-up and pre-concentration steps [34–36]. The conventional ultrasonic solvent extraction (USE) is still widely applied for PhAC extraction in sewage sludge (more than a half of the publications) [34,37,38]. However, USE requires a manual manipulation of the extracts, long times as well as large consumption of reagents. In the last decade, a trend towards more environmentally friendy processes with lower cost, and automatization and miniaturization techniques [pressurized liquid extraction (PLE), matrix solid phase extraction (MSPD), Quick, Easy, Cheap, Effective, Rugged and Safe (QuEChERS), pressurized hot water extraction (PHWE), and others] have emerged [34,39–42]. Among these novel techniques, PLE with organic solvents or their mixture with an aqueous solvent is the most commonly applied extraction technique.

In most cases, the extraction procedure is not selective and a clean-up step is necessary. For sludge samples, solid phase extraction (SPE), with C18 or Oasis HLB sorbents, or dispersive-SPE (d-SPE), C18 and PSA sorbents, are commonly applied for clean-up [33,37,40]. However, compared to the extraction alone, this step significantly increases the analysis time and involves additional sample manipulation. In this regard, Rossini et al. [43] developed a combined approach of QuEChERS extraction with on-line SPE-liquid chromatography to tandem mass spectrometry (LC–MS/MS) in order to eliminate the d-SPE step of QuEChERS for the determination of non-steroidal anti-inflammatory drugs (NSAIDs) and their metabolites in sludge. Saleh et al. [42] applied for clean-up the novel hollow-fiber liquid phase microextraction (HF-LPME), after PHWE extraction, for the analysis of NSAIDs in sludge samples. When PLE or MSPD are chosen as extraction tecniques, the clean-up can be performed together with the extraction therefore reducing analysis time and tedious work [40,41]. Future efforts should be done to develop on-line coupling, automatic or semi-automatic protocols.

Given the wide range of psychochemical properties (including many polar and non-volatile compounds), the most suitable technique for the detection of PhACs and their metabolites is LC–MS/MS using reverse phase. In the last years, the use of hydrophilic interaction liquid chromatography (HILIC), which involves the use of a hydrophilic stationary phase and an aqueous-polar/organic solvent mobile phase, is gaining interest for the analysis of polar compounds, especially PhAC metabolites [34–36,41]. The triple quadrupole (QqQ) is widely considered as the most sensitive and selective analyzer for PhAC determination in sewage sludge samples. Nevertheless, recent advances in LC–MS have shown that time of flight (TOF) [44] or orbitrap [45] analyzers are a very suitable alternative to QqQ, allowing the screening of targeted and untargeted analytes [34–36].

Table 1 [33,37–44,46–51] shows a summary of multi-residue methods described in the literature for the determination of PhACs and their metabolites in different types of sludge samples. An important limitation of the reported studies is that most of them have been developed and validated for only one or maybe two types of sludge. However, to achieve a full assessment of PhAC distribution in WWTPs, measurements of PhAC concentrations need to be done in the different types of sludge from all the treatment stages, because some factors such as sample amount, reconstitution volumes and matrix effects could differ between sludge types. In addition, very few methods focus on the determination of PhAC metabolites, and those found are focused on a single PhAC [44,51], or on PhACs from the same therapeutic group [43,47]. Recently, Malvar et al. [40] have compared USE, PLE and QuEChERS for the determination of PhAC metabolites from different therapeutic groups (NSAIDs, antibiotics, antiepileptic drugs and central nervous system stimulants) in digested sludge and found that PLE was the most suitable extraction method because of its higher accuracy and sensitivity as well as the automatisation capacity for simultaneous sample extraction and clean-up.

Table 1
Analytical methods described in the literature for the determination of PhACs and their metabolites in different types of sludge samples.

Therapeutic group	Sample	Sample amount (g)	Extraction technique	Clean-up technique	Analytical determination	Recoveries (%)	Method detection limit (μg/kg dm)	Reference
NSAIDs and metabolites, antibiotics and metabolites, antiepileptic drugs and metabolites, nervous stimulant and metabolites	Digested sludge	2	PLE	–	LC-MS/MS	59–100	0.1–3.5	[40]
			USE	d-SPE (PSA and C18)		22–88	0.2–5.3	
			QuEChERS	d-SPE (PSA and C18)		25–78	0.2–11	
NSAIDs, antibiotics, antiepileptic, nervous stimulant, analgesics	Sludge	2	USE	SPE (C18)	GC/MS	50–89	0.1–1.7	[37]
	Soil	2				46–106	0.1–1.4	
NSAIDs and lipd regulators	Mixed sludge	0.8	MAE	SPME	GC/MS	30–70	<20	[39]
NSAIDs and metabolites, anesthetic drugs, antiepileptic drugs, β- blockers, lipid regulators, antidiabetics, antipsychotics, antidepressants	Sludge	2	MSPD	–	HILIC-MS/MS	45–122	1.25–1250	[41]
NSAIDs, antibiotics, antiepileptic, lipid regulators, antidepressants	Sludge	1	USE	QuEChERS and SPE (Oasis HLB)	LC/MS-MS	60–189	9.1–1230	[38]
	Soil	5				60–135	2.1–65.3	
NSAIDs and metabolites	Sludge	1	QuEChERS	SPE (on-line, Strata X)	LC/MS-MS	36–76	0.065–6.7	[43]
NSAIDs, antibiotics, antiepileptics, benzodiazepines, antipsychotics, antidepressants, illicit drugs	Digested sludge	0.1	USE	–	LC-MS/MS	50–110	0.9–10	[46]
Antibiotics and metabolites	Sludge	2	PLE	SPE (Oasis HLB)	LC/MS-MS		0.03–2.23	[47]
	Soil	5				60–130	0.01–0.55	
NSAIDs, Hormones, antibiotics, antidepressants, antipsychotics, antibacterials, antihistamines, proton pump inhibitors, anticoagulants, radiocontrast agents, anthelminthics, lipid regulators, anticancer agents, beta-blockers, diuretics, analgesics and metabolites	Treated sludge	2	QuEChERS	d-SPE (PSA)	LC/ToF-MS	33–135	1.0–2500.0	[44]
NSAIDs	Digested sludge	0.5	PHWE	HLPME	LC-MS/MS	23–30	0.4–3.7	[42]
NSAIDs, antibiotics, antiepileptic, β- blocker, nervous stimulant, estrogens, lipid regulators	Primary sludge	1	USE	SPE (Oasis HLB)	HPLC-UV-Fl	61–107	1.56–115	[33]
	Secondary sludge	1				47–97	1.55–112	
	Digested sludge	1.5				41–110	0.45–79.8	
	Compost	2				55–106	0.13–44.7	
	Sediment	2				42–103	0.36–50.5	
NSAIDs, antibiotics, β-blocker, nervous stimulants, lipid regulators	Primary sludge	1	PLE	–	LC/MS-MS	36.8–130	0.44–89.2*	[48]
	Secondary sludge					33.5–122	0.44–89.2*	
	Digested sludge					29.2–102	2.10–96.3*	
NSAIDs, antibiotics, antiepileptics, β- blocker, nervous stimulant, lipid regulators	Digested sludge	1	PLE	–	LC/MS	45–120	2–350 0.8–120	[49]
	Soil	2.7				50–110		
NSAIDs, antibiotics, β-blocker, nervous stimulants, lipid regulators	Sludge	5	PLE	–	LC/MS	72–109	14–32*	[50]
Antiepileptic drugs and metabolites	Untreated sludge	2.0–10.0	PLE	SPE (Oasis HLB)	LC-MS/MS	82–96	0.06–0.5	[51]
	Treated sludge					80–92	0.07–0.4	

GC/MS: gas chromatography with mass spectrometry detector; HILIC: hydrophilic interaction liquid chromatography; HLPME: Hollow fiber liquid phase microextraction; LC–MS: liquid chromatography with mass spectrometry detector; LC-ToF: Liquid chromatography–time-of-flight-mass spectrometry; MAE: Microwave assisted extraction; PHWE:Pressurized hot water extraction; PLE: Pressurized liquid extraction; SPE: Solid Phase Extraction; SPME: Solid Phase Microextraction; USE: Ultrasonication solvent extraction;*: Method quantification limits.

Finally, to guarantee reliable and precise results a quality assurance/quality control (QA/QC) protocol must be established. This protocol involves the use of control spiked samples, solvent injections, and procedural blanks into each analytical batch. Due to the lack of certified reference materials, in-house reference materials (prepared by spiking real samples) are used to check for accuracy during validation and QA/QC. One of the greatest drawbacks of PhAC analysis in sludge samples by LC–MS/MS when using the electrospray ionization source (ESI) is the perturbation of the signal by co-extracted substances coming from sludge matrix that may cause ion suppression or improvement of the analyte signal when compared with standards in solvent. Sludge matrix has a high content of organic components, which could increase the viscosity of the sample and the superficial tension of the droplets generated in the ESI source, which may decrease the evaporation efficiency of the target analytes. The presence of matrix effect in MS analysis can be evaluated by comparing the response obtained for standards directly injected in the mobile phase with the response for the same amount of standard added to the already extracted sample [44]. In practice, different ways can be used to reduce matrix effects: 1) the improvement of the clean-up of the extracts or the chromatographic separation (sometimes

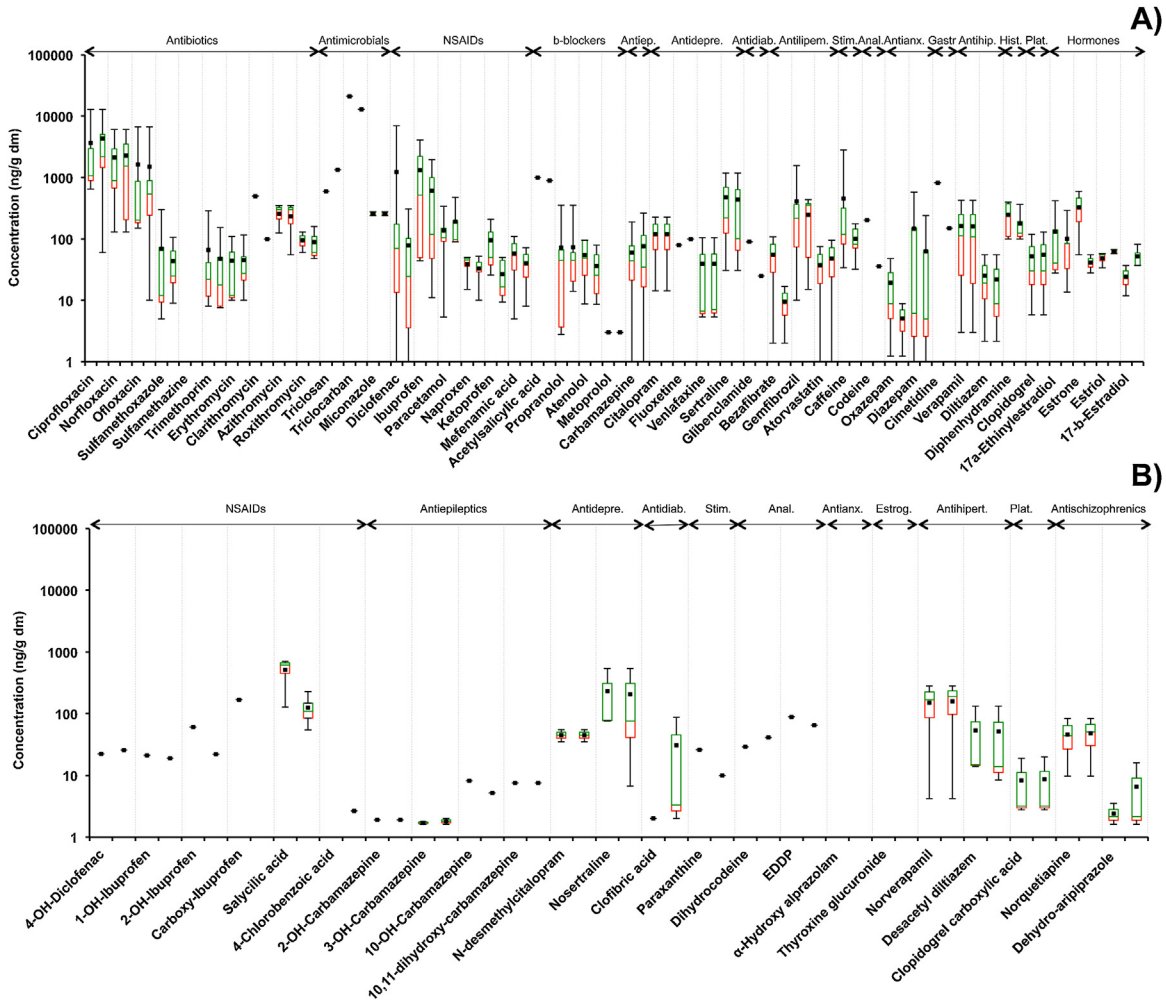

Fig. 1. Box-and-whisker plots on concentrations of PhACs (A) and metabolites (B) in primary (P, left box) and secondary (S, right box) sludge. (Antiep.: Antiepileptic drugs; Antidepre.: Antidepressants; Antidiab.: Antidiabetic drugs: Antilipem.: Antilipemic drugs; Stim.: Stimulants; Anal.: Analgesics; Antianx.: Antianxiety drugs; Gastr.: Gastrointestinal agent; Antihyp.: Antihypertensive; Hist.: Antihistamines; Plat.: Antiplatelet agents).

time consuming and can increase the risk of analyte losses); 2) sample dilution (decreases the amount of organic load entering the analyzer and improves the signal, but it can reduce the sensitivity); and 3) quantification using matrix-matched calibration curves as well as the use of isotopically labeled internal standards. The latter is the most common procedure, but it is costly and usually has limited commercial availability [40,47].

3. Occurrence of PhACs during sludge treatment

Typically, four types of sawage sludge [primary, secondary, aerobically or anaerobically digested, and dehydrated] can be identified in a WWTP (Table S1). A summary and comparison of the concentration levels of 180 PhACs and 45 metabolites detected in sewage sludge worlwide is shown in Tables S2 and S3, respectively. Concentrations vary substantially depending on the chemical, the usage, sludge matrix or geographical area, ranging from μg/kg to few mg/kg [27,51–54]. More than 70 % of published data determined concentrations often measured in the final product of the sewage sludge treatment (digested, dehydrated or composted sludge) [23,55–57] or concentrations obtained from laboratory studies or from pilot-scale WWTPs [58–60]. Only few studies have reported on the distribution of PhACs during the sludge stabilization treatment [53,61–63], and studies on metabolite distribution are even more lacking [52,64].

3.1. Untreated sludge: Primary and secondary sludge

Fig. 1 shows the concentration levels of PhACs and the metabolites more frequently detected in primary and secondary sludge as box-and-whisker plots. The five pharmaceutical classes most frequently measured and at higher concentrations were antimicrobials > antibiotics > NSAIDs > antidepressants > antidiabetics. The highest concentrations were found for the antimicrobial triclocarban (mean of 21,000 ng/g dm in primary sludge and 13,000 ng/g dm in secondary sludge). Fluoroquinolones were detected in a wide concentration range, reaching values of up to 12,858 ng/g dm for ciprofloxacin and 6712 ng/g dm for ofloxacine in France [61]. Together with fluoroquinolones, the presence of macrolide antibiotics in treated sludge represents an issue of concern related to the development of antibiotic resistance. Park et al. [65] found clarithromycin concentrations of 100−500 ng/g dm in a WWTP in Korea, while Mailler et al. [61] and Muriuki et al. [66] found higher concentrations for azythromicyn and sulfamethoxazole, up to 350 and 300 ng/g dm, in France and Kenia, respectively. Anti-inflammatory drugs such as diclofenac, ibuprofen and acetylsalicylic acid were also present in concentrations of 1228, 1332 and 1000 ng/g dm, respectively, in primary sludge, and 78, 611 and 900 ng/g dm in secondary sludge. The anticonvulsant carbamazepine is one of the most frequently studied and detected PhACs in sludge samples (Table S2), known for its persistence. Its

mean concentration ranged between 0.9 ng/g dm in China [67] to 256 ng/g dm in Spain [25]. Other frequently measured and quantified pharmaceutical groups include beta-blockers (propranolol and atenolol), antidepressants (citalopram and venlafaxine), stimulants (caffeine) and antilipemic drugs (gemfibrozil and bezafibrate), which can be attributed to their high consumption, although overall they were detected at lower levels.

High concentrations in primary sludge can be attributed to high concentrations (i.e. caffeine, ibuprofen or citalopram) in incoming or influent wastewater, or high partitioning to sludge because of their high hydrophobicity (i.e. triclosan or triclocarban). Depending on sewage sludge properties, the percentage of PhAC adsorption may vary [68]. Sorption occurs mostly through hydrophobic interactions between PhACs and the organic matter in sludge [31,69]. Hence, PhACs of hydrophobic nature such as triclocarban or triclosan (Log Kow values of 3.5–4.8) tend to heavily partition onto the particulate phase. However, not all PhACs detected in sludge are lipophilic compounds, many of them have polar functional groups (-NH2 or −COOH groups) and can adsorb onto organic matter or minerals via electrostatic interactions regardless of their lipophilicity. In this regard, high concentrations of hydrophilic chemicals such as norfloxacin (log Kow −1.03, up to 6049 ng/g dm [61]), acetaminophen (log Kow 0.46, up to 480 ng/g dm [70]) or atenolol (log Kow 0.16–1.95, up to 95 ng/g dm [65]) have been detected in primary and secondary sludge samples. At pH = 2.9 (isoelectric point [pI]) sludge surface will be negatively-charged in normal environmental conditions. Therefore, those PhACs that are normally neutral or positively-charged at pH 7 (tetracyclines, fluoroquinolones, beta-blockers and macrolides) are highly sorbed onto primary and secondary sludge [7,23,31,71–75]. In addition to electrostatic interactions, the formation of complexes can occur between PhACs and their metabolites, such as tetracyclines and metal cations (i.e. Mg2+, Ca2+, and Cu2+) present in sludge, which will also have an impact on their concentration [72–76].

There are others factors involved in the sorption of PhACs onto sludge [77] like the carbon content of sludge [31]. In this regard, Li et al. [69] found that sorption of antibiotics onto secondary sludge is positively correlated with the total organic carbon (TOC) content of sludges (7–45 % TOC). Zhang et al. [78] also found an increased sorption of 17α-ethinylestradiol with higher TOC contents (44–47 % TOC). However, other studies have not find these correlations [79,80].

Considering the large amounts of some PhACs that are metabolized in WWTPs, metabolites are also abundantly found in sludge samples (Fig. 1B). However, metabolites have been less studied than their parent compounds although sometimes they have been detected at higher concentrations. Salicylic acid and norsetraline are the compunds found at the highest concentrations in sewage sluge, up to 931 and 541 ng/g dm, respectively, in primary sludge (individual data in Table S3), despite their hydrophilicity (log Kow < 3.0) and the fact that they exist as anions under environmental pH. Some authors have explained this is a consequence of complex formation between the salycilic acid phenolic group (—OH) and Fe3+ present in the particulate matter of sludge [81]. Recently, Malvar et al. [52] reported that the detected concentrations of ibuprofen, carbamazepine and diclofenac metabolites were related to their metabolic ratios. They also found similar concentrations of metabolites in both primary and secondary sludge, but found significantly higher concentrations of 10-OH-carbamazepine, 2-OH-ibuprofen and carboxy ibuprofen in primary sludge than in secondary sludge, probably due to biodegradation of these compounds during secondary treatment [82]. For some compounds, the metabolite concentrations is higher in secondary sludge than in primary sludge, probably due to the presence of organic matter in sludge and to the higher hydrolysis of conjugates [13,14,76]. In this regard, Brown et al. [8] found a similar sorptive capacity of thyroxine and its metabolite glucuronide thyroxine, although the latter has a lower logK_{OW} (2.65 vs 4.15). Both compounds were detected at higher concentrations in secondary sludge than in primary sludge.

The concentrations reported for some compounds such as fluoroquinolones, diclofenac, ibuprofen, sertraline, gemfibrozil and caffeine significantly differ between studies, even up to three orders of magnitude (Fig. 1). These variations may be explained by the different prescribing habits related to human health conditions, sampling regions or climate conditions [23,27,83]. Moreover, some results were obtained by sampling only one or few WWTPs, which may not reflect the actual pollution status. Variations can be found not only between countries but also within them. For example, Chen et al. [23] found that PhAC concentrations in sludge from East China differed significantly from sludge from North or West China. Overall, studies on PhAC presence in sludge are mostly conducted in European countries, followed by the U.S. Canada and China. More investigations in the African continent are needed and expected to emerge soon (Fig. S1 in supplementary materials). Recently,Muriuki et al. [66] quantified antibiotics and antiretroviral agents in primary sludge using different technologies at concentration levels ranging from < limit of quantification (LOQ) to 31,555 ng/g dm.

3.2. Stabilization: anaerobically or aerobically digested sludge

Sludge is generally stabilized using anaerobic (AnD) or aerobic (AeD) digestion, which may play an important role on sludge contamination [11,58,84]. Each digestion process offers biodegradation pathways due to the distinct microbial communities. The concentrations of PhACs and metabolites in anaerobically or aerobically digested sludges are shown in Fig. 2 A and B, respectively, as box-and-whisker plots. The most studied and detected pharmaceutical classes in digested sludge correspond to those found in primary and secondary sludges: antibiotics, NSAIDs, antiepileptic and antidepressant drugs. PhACs detected at higher concentrations in digested sludge include triclocarban (up to 21,000 ng/g dm), ciprofloxacin (12,858 ng/g dm), ofloxacin (6712 ng/g dm), norfloxacin (6049 ng/g dm), diclofenac (7020 ng/g dm), ibuprofen (4105 ng/g dm), caffeine (2828 ng/g dm) and gemfibrozil (1562 ng/g dm). Studies involving the assessment and distribution of compounds during the sludge stabilization treatment show that attenuation occurs in their concentrations during AnD and AeD.

In most developed countries, sludge undergoes AnD stabilization (about 70 % of sewage sludge), therefore, comparison of PhAC concentrations in anaerobically or aerobically digested sludge is not normaly done [84]. Ivanova et al. [11] found that PhAC concentration patterns between AnD and AeD was significantly different. Telmisartan, sertraline, azithromycin, irbesartan were more abundantly detected in aerobically digestedsludge. In contrast, THC−COOH, fexofenadine, citalopram and N-desmethyl-citalopram concentrations were higher in anaerobically digested sludge. The results reported by Alenzy et al. [85] and Joss et al. [86] suggest that anaerobic microorganisms increase the removal of clarithromycin, erythromycin and estrogens, versus aerobic bacteria. In contrast, Ying and Kookana [87] detected triclosan at significantly lower concentrations in aerobically digested (220 mg/kg) than in anerobically digested sludge (5580 mg/kg). In laboratory-scale reactors dicloflenac, naproxen and roxithromycin were recalcitrant under anoxic conditions, but exhibited moderate-high removal (e.g. 14.9–60 %) under aerobic conditions [31,88,89].

Recently, several authors have reported enhanced PhAC degradation by combining two or more treatment conditions.

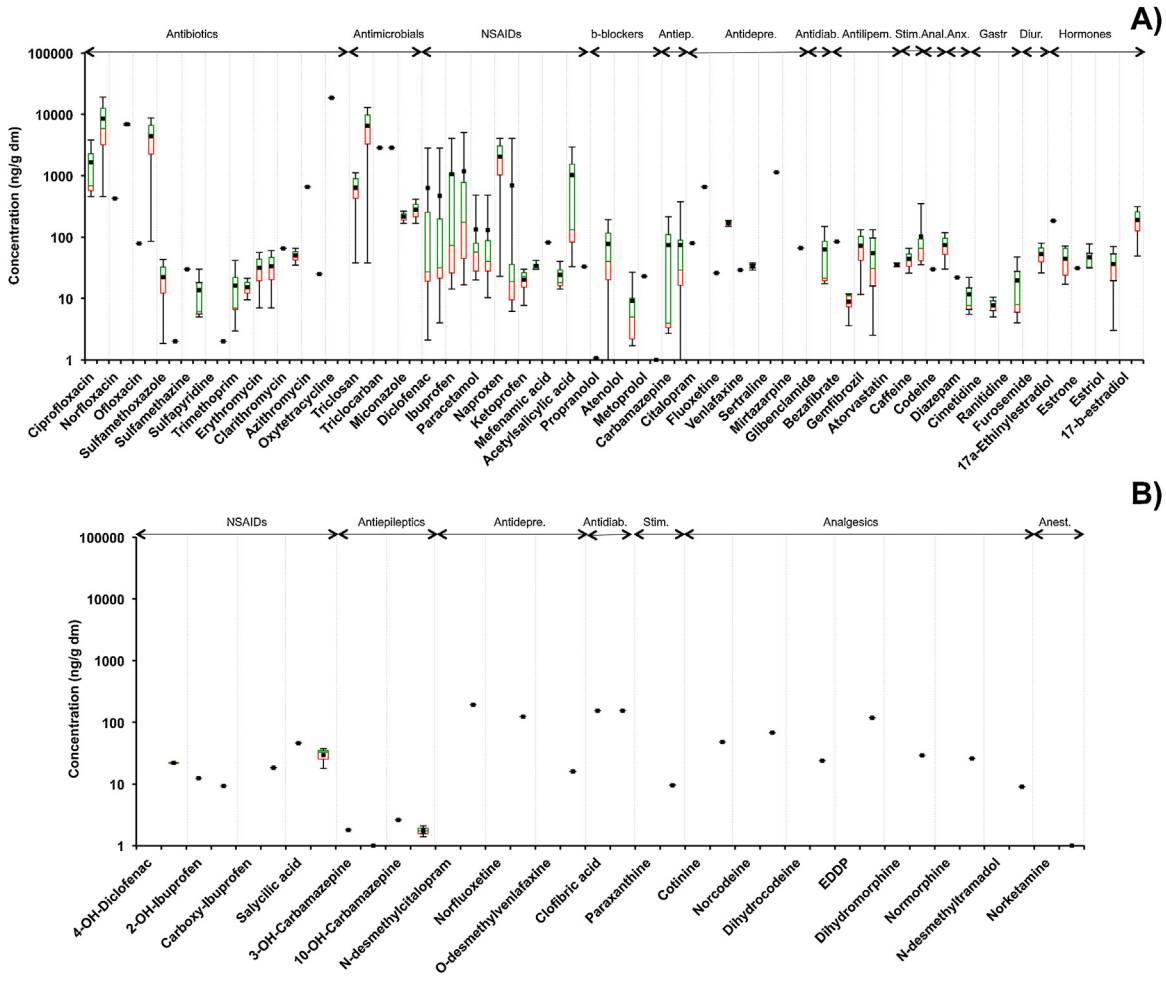

Fig. 2. Box-and-whisker plots on concentrations of PhACs (A) and metabolites (B) in aerobically digested sludge (left box) and anaerobically digested sludge (right box). (Antiepileptic drugs; Antidepre.: Antidepressants; Antidiab.: Antidiabetic drugs: Antilipem.: Antilipemic drugs; Stim.: Stimulants; Anal.: Analgesics; Anx.: Antianxiety; Gastr.: Gastrointestinal agent; Gastr.: Gastrointestinal agent; Diur.: Diuretic drugs; Anest.: Anesthetics).

For example, González-Salgado et al. [90] described moderate (diclofenac, 2OH-ibuprofen) to high (oxazepam, propranolol, ofloxacin) removal using an hybrid process involving a thermophilic aerobic reactor combined with mesophilic AnD, while removal rates higher than 90 % were found for caffeine and sulfamethoxazole regardless the process. Ahmad and Eskicioglu [59] observed that the sequential anaerobic/aerobic/anoxic digestion configurations improved PhAC removal (from 10 to 50 %) by either reducing their accumulation or enhancing their removal. Similar results were reported by Abbot and Eskicioglu[58] who found removal rates for triclosan and related compounds in digested sludge of up to 80 and 97 % using temperature cycling aerobic/anoxic digesters and sequential conventional mesophilic AnD + aerobic/anoxic processes, respectively, versus 40 % removal using single AnD. Longer sludge retention times (SRTs) also improved the removal of triclosan and organic matter across each type of digestion examined. Zhou et al. [91] reported that AnD integrated with mixed enzymolyses together with an ultrasonic irradiation pre-treatment and AnD integrated with mixed enzymolyses together with mechanical rotary disc post-treatment might improve PhAC removal.

In addition to PhAC properties and sludge characteristics, WWTP operation paratemeters also seem to be involved in compound removal [28,77]. Carballa et al. [92] reported removal > 80 % for naproxen, sulfamethoxazole, and roxithromycin at both mesophilic (37 °C) and thermophilic (55 °C) temperatures in anaerobic reactors. For diclofenac and diazepam, removal was associated with the temperature: 60 % for both compounds under mesophilic conditions, and 38 % for diclofenac and 73 % for diazepam under thermophilic conditions. In this study, the SRT (15 or 30 days) did not seem to influence PhAC removal. In another experiment in batch conditions, Heidler et al. [93] observed that triclocarban was not degraded during AnD after 19 days of incubation and, as a consequence, the treated sludge showed a higher concentration of this compound. Carbamazepine and diclofenac seem also recalcitrant during experiments with AnD [32,77]. While other compounds were time-dependent, bisoprol removal was 14 % after 161 days and naproxen removal 100 % after 14 days. Lastly, 6-O-Desmethylnaproxen was detected in sludge during anaerobic biodegradation of its parent compound [28,94].

Researchers have also suggested that the inhibition of methanogen bacteria by PhACs is correlated with their affinity to sorb onto anaerobic sludge and with their concentration levels [28,95–99]. Li et al. [94 found that a small addition of fluoroquinolones (2 mg/L) results in a slight increase of methane production, but a high addition (100 mg/L) resulted in no improvement or even in an 8% reduction of methane production. These results are consistent with the pioneering results obtained by Sanz et al. [96] that showed that erythromycin concentrations of up to 250 mg/L did not inhibit biogas production, while some antibiotics such as tylosine, doxycline, and neomycine partially inhibit biogas formation by interfering with the activity of

propionic-acid and butyric-acid degrading bacteria. In another study Fountoulakis et al. [97] observed a 50 % inhibition of methanogenesis at concentrations up to 400 mg/L of sulfamethoxazole and clofibric acid and 30 mg/L of propranolol. Recently, Silva et al. [100] observed different effects of PhACs (ciprofloxacin>17α-ethynylestradiol > diclofenac > ibuprofen) on the activity of acetogens and methanogens in anaerobic communities. None of these PhACs affected methanogenesis at low concentrations present in WWTP influents. A recent study by Alenzi et al. [85] demonstrated that long-term presence of PhACs induces process disturbances, which lead to volatile fatty acid accumulation. In contrast, anaerobic bacteria seem to improve the removal of clarithromycin and erythromycin over aerobic treatment.

Lastly, regarding the behaviour of metabolites during digestion processes we have found only one study about their occurrence in different sewage sludge stabilization treatments. This issue requires further investigation, as some metabolites might be present at high concentrations and contribute to toxicity. In this regard, Malvar et al. [52] revealed a high persistence of 3-OH-carbamazepine and 4-OH-diclofenac whereas paraxanthine, the main metabolite of caffeine, showed a high biodegradability. The hydroxylation and carboxylation of ibuprofen occur both under AeD and AnD.

3.3. Final product: dried and composted sludge

The concentrations of PhACs and metabolites in digested and dehydrated sludge and biosolid compost are shown in Table S2-S3 and summarized in Fig. 3. Comparatively, treated sludge (digested, dehydrated and composted) is the most frequently analyzed matrix as well as the matrix where more number of PhACs are analyzed (68 % of selected papers vs 31 % in primary and secondary sludge). A considerable attenuation in PhAC concentrations occurs during the drying and maturation or composting processes, probably because hydrosoluble PhACs present in sludge might undergo sunlight-driven photodegradation [101] as well as mineralization and dilution as a result of the mixing with other products occurring during composting. Arun et al. [68] reported two fold concentrations of fluoroquinolones in wet sludge versus dry sludge (environment temperature ≈28.6 °C). Similar results have been reported by Speltini et al. [102]. A small percentage of fluoroquinolones undergo photodegradation during the drying process.

As with other sludge matrices, there is much variation in PhAC concentrations and distribution between the different by-products of sludge treatment as well as within the same country, and therefore no clear tendency has been detected. The observed variations can be explained by differences in population density (rural versus urban), type of treatment process versus no treatment, and degree of PhAC consumption [103,104]. In a study carried out by Chen et al. [23] in dewatered sewage sludge from China, ofloxacin was the most abundantly detected PhACs with concentrations up to 24,760 μg/kg dm, followed by oxytetracycline at 5280 μg/kg dm, norfloxacin at 5280 μg/kg dm, and ketoprofen at 4458 μg/kg dm.

Bastos et al. [86] found that the concentration of PhACs in treated sludge is related to the maturation time and the type of treatment: lime sludge stabilization (7619 μg/kg dm, total concentration) > digested sludge (2364 μg/kg dm) > composted sludge (264 μg/kgdm). The authors observed that the longer the maduration of organic waste, the lower PhAC concentrations.

Kim et al. [105] investigated the mineralization of tetracyclines, sulfonamides, and macrolides during composting and found that after 5–6 weeks in batch reactors, PhAC concentrations declined below the relevant Korean guideline. This reduction is due to bacterial release of hydrolytic enzymes such as cellulase, protease, and lipase [106]. Chenxi et al. [107] showed that PhAC removal was compound- and time-dependent and found no removal for

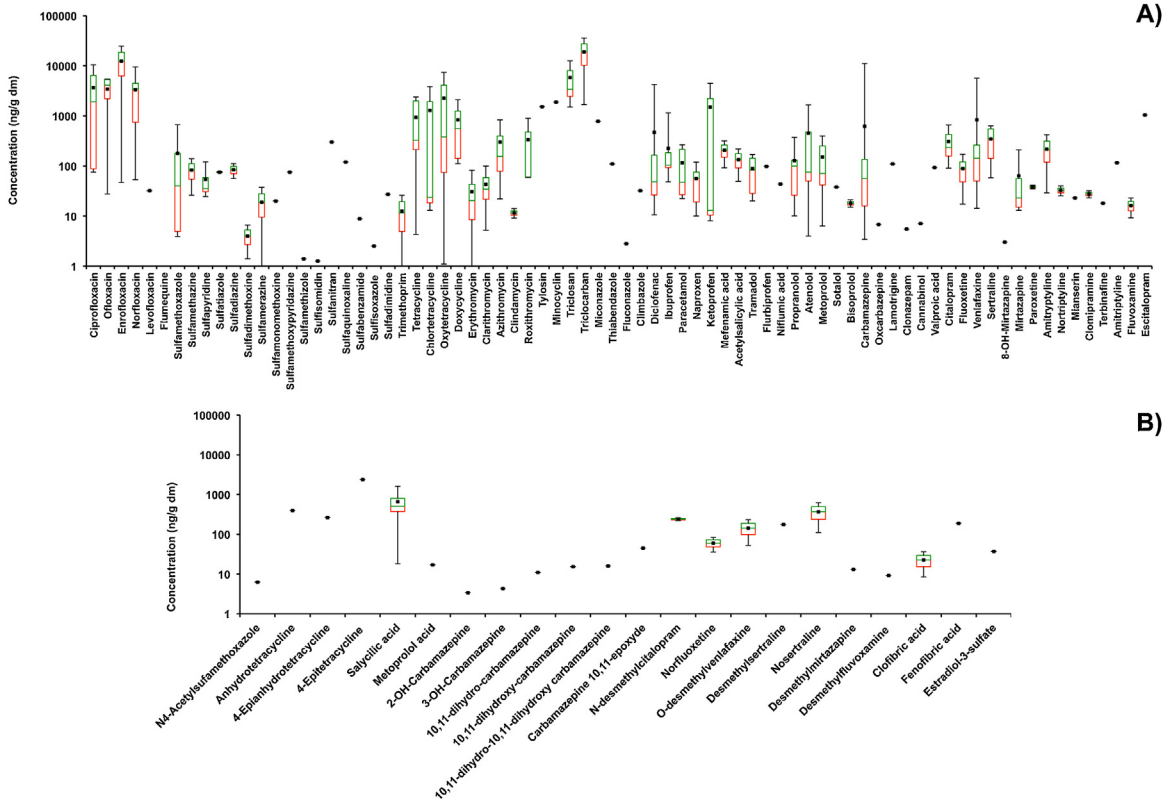

Fig. 3. Box-and-whisker plots on concentrations of PhACs (A) and metabolites (B) in dewatered sludge.

Table 2
Concentrations of PhACs in sewage sludge-amended soils.

PhAC	Measured concentration (ng/g dm)	Predicted concentration (ng/g dm)	Reference
Ciprofloxacin	350–400 after 8 months sludge application		[114]
	270–280 after 21 months sludge application		[114]
	450 (2.5 cm depth)		[115]
	542 (day 0) - 390 (day 994)		[116]
	<LOQ-8.7 (soil amended with composted sludge)	1.5–5.6	[117]
		0.17	[118]
Norfloxacin	320–290 after 8 months sludge application		[114]
	270–300 after 21 months application		[114]
	350 (2.5 cm depth)		[115]
	50 (day 0 in a mesocosms experiment)		[116]
	<LOQ-9.4 (soil amended with composted sludge)	0.8–5.5.	[117]
		0.36	[118]
Ofloxacin	470 (day 0) - 267 (day 994)		[116]
	5.3–8.6 (soil amended with composted sludge)	5.2–8.0	[117]
		0.23	[118]
Trimethoprim	0.64–2.15 (no amended experiment)		[119]
	n.d.–0.64		[120]
Azithromycin	30 (day 0 in a mesocosms experiment)		[116]
		0.39	[121]
Clarithromycin		0.18	[118]
Sulfamethoxazol		0.03	[25]
Tetracycline		0.28	[121]
	20 (day 0 in a mesocosms experiment)		[116]
		0.28	[118]
Oxytetracycline		0.23	[121]
Doxycycline	15 (day 0 in a mesocosms experiment)		[116]
		0.26	[121]
Triclosan	1715 (day 0)		[116]
	833		[120]
	10,900		[122]
	14,000		[123]
Triclocarban	2715		[116]
	4940		[122]
	8000		[123]
Diclofenac		0.37	[124]
Paracetamol		0.27	[118]
	18.7		[122]
	24		[123]
Ibuprofen		0.57	[124]
	63.5		[122]
	750		[123]
Naproxen		8	[124]
	6		[122]
	470		[123]
Acetylsalicylic acid		0.36	[121]
Salicylic acid		0.52	[118]
Propranolol		0.069	[118]
Metoprolol		0.12	[118]
Carbamazepine	6 (day 0 in a mesocosms experiment)		[116]
	<LOQ-0.2 (soil amended with composted sludge)	0.1–0.3	[117]
	0.7–1.4 (no amended experiment)		[125]
	183		[122]
	9		[123]
		0.08–0.15	[25]
		0.17	[121]
Sertraline		0.26	[118]
Fluoxetine	10 (day 0 in a mesocosms experiment)		[116]
Venlafaxine		0.15	[118]
Miconazole	60 (day 0 in a mesocosms experiment)		[116]
Diphenhydramine	40 (day 0 in a mesocosms experiment)		[116]
	<LOD-40 (sludge amended field)		[120]
Metformin		0.35	[118]
Gemfibrozil	30 (day 0 in a mesocosms experiment)		[116]
	57		[122]
	24		[123]
Caffeine		0.14	[118]
		0.16–0.48	[25]
		0.14	[118]
17alfa-Ethynilestradiol		0.03–0.08	[25]
17 beta-estrdiol		0.12–0.47	[25]
Estriol		0.01	[25]
Estrone	0.25–0.41 (sludge amended soils)		[126]
Diethylstilbestrol	<LOD-0.4 (sludge amended soils)		[126]
Mestranol	0.10–0.21 (sludge amended soils)		[126]
Dienestrol	0.98–3.3 (sludge amended soils)		[126]

ciprofloxacin, carbamazepine, and triclosan after either aerobic or anaerobic treatments. Tetracycline and doxycycline needed 77 days to be slightly removed and erythromycin and clarithromycin were removed relatively fast. Authors also reported a significant relation between aeration and erythromycin and tetracycline removal. Similar results were reported by Iranzo et al. [108] who found a 50 % removal for azithromycin but only 10 % removal for citalopram. Fluoxetine was completely biodegraded in 15 days. Authors identified 11 different strains of microorganisms that degraded specific PhACs using them as carbon and nitrogen sources. More recently, Zheng et al. [109] have described that triclosan can be successfully removed by aerobic composting, with slightly higher degradation related to an increase in aeration. In addition, composting promotes microbial activity and increases the relative abundance of microorganisms related to triclosan degradation. Lastly, photodegradation has been found to have a low impact on PhAC removal [110].

Over the last few years, authors have investigated the potential use of emerging technologies such as hydrothermal carbonization, biodrying, and hydrothermal liquefactionprior to the application of sewage sludge to agricultural land and they have also tried to improve sludge disposal. Eyser et al. [111] investigated the removal of twelve PhACs in sewage sludge by hydrothermal carbonization and found removal rates between 39 % for metoprolol and 97 % for carbamazepine. In contrast phenazone concentration increased, which could indicate that additional metabolites present in the native sewage sludge might degrade to phenazone during the treatment. Pilnacek et al. [112] highlighted the pretreatment with biodrying, which uses the heat produced in the thermophilic phase of composting to produce a biowaste-based product, for antibiotic biodegradation. Silva Thomsen et al. [113] showed that hydrothermal liquefaction is a suitable technology for sewage sludge treatment and for the the removal of 9 out of 30 PhACs and 5 out of 7 biocides investigated (over 98 % removal). Citalopram was found to be moderately recalcitrant at 300 °C (87 % removal) and it was removed at temperatures >325 °C (>99 % removal).

4. Occurrence of PhACs in soil after sludge application

Given the concentration levels of some PhACs found in treated sludge, sludge disposal cannot be neglected, in particular when applied to soil. Information on PhAC occurrence in soils amended with digested or composted sludge is scarce (see Table 2) [25,114–126]. The groups of PhACs detected at higher concentrations were antimicrobials (triclosan and triclocarban) at 1200−3000 ng/g dm and antibiotics (fluoroquinolones) at 50−550 ng/g dm. Other antibiotics frequently detected include oxytetracycline (100.9 ng/g), tetracycline (63.8 ng/g), and sulfamethoxazole (47.9 ng/g) [68,127]. Ibuprofen, diphenhydramine, diclofenac, fluoxetine, fluoxetine, gemfibrozil, miconazole and azithromycin, have been deteted at lower concentrations (6−60 ng/g dm) [128]. Fluoroquinolones, ibuprofen and naproxen have been detected at different concentration ranges, which supports that a number of factors such as sludge application frequency, soil conditions and characteristics, precipitation and runoff may influence their occurrence [27,129]. Based on the estimated annual load after sludge application in the Slovak Republic, the total load of PhACs in soils ranged between hundred grams to low hundreds of kilograms. The highest input load was found for fexofenadine (120 kg/year), verapamil (28 kg/year), citalopram (21 kg/year), telmisartan (16 kg/year), and diclofenac (12 kg/year). The metabolites of these compounds also contributed to the total load in soil (9.8 %) [11].

PhAC behaviour in soil is a complex process that depends on several factors affecting mass transfer such as the nature of the aqueous solution and the physicochemical properties of both the compound and soil [130]. Strongly sorbing PhACs tend to accumulate in soil, whereas those highly mobile tend to leach to groundwater and can be transported with groundwater flow, drainage water, and surface runoff to surface waters [64]. In soil-column experients, Lachasagne et al. [131] reported that the leaching potential, and consequently the risk of groundwater contamination, is mainly related to the sludge source and found ibuprofen and diclofenac in the leachates of urban sludge amended soil and salicylic acid and paracetamol only in the leachates of hospital sludge-amended soil. Other PhACs including ciprofloxacin, carbamazepine, ketoprofen, econazole, and atenolol were found in soil but not in leachates. Similar results were also reported by Shao et al. [132] and Chefetz et al. [133] who found that diclofenac and carbamazepine exhibited low mobility in soils with high organic matter levels [103]. Barron et al. [130] concluded that some bound PhACs to topsoils migh leach (salbutamol, bezafibrate, sulphamethazine, sulphamethoxazole or ketoprofen), while others (trimethoprim, indomethacin, propranolol, metoprolol and carbamazepine) showed significant retention in soils and were therefore more prevalent. Recently, Wang et al. [134] found different behaviours of PhACs in soils amended with lime-stabilized sludge. For example, erythromycin and naproxen increased their mobility by 21.7 % and 33.8 %, respectively, carbamazepine, triclosan, and fluoxetine reduced their mobility by 100 % after 63 days. The authors also reported that pH effects on PhAC hydrophobicity and speciation were highly correlated with the mobility of erythromycin and fluoxetine, but these effects were slighly correlated with the mobility of the rest of compounds.

Several authors have also assessed the dissipation or persistance of PhACs with time. Walters et al. [116] used an outdoor mesocosms experiment with sludge-amended soil and found no noticiable loss of triclocarban, diphenhydramine, and fluoxetine over the three-year monitoring period. In contrast norfloxacin, azithromycin, and ciprofloxacin exhibited moderately high half-lives (t1/2) (from 990 to 3466 days). Triclosan showed lower persistence (t1/2 182–193 days), which is consistent with other studies reporting that triclosan concentration decreased up to 80 % after one year of sludge application [128,129]. Golet et al. [115] found ciprofloxacin and norfloxacin at concentrations between 270−300 ng/g dm and between 290−400 ng/g dm in topsoil after 21 and 8 months of sludge application, respectively. Butler et al. [129] reported that triclosan concentration in soil slightly decreased during the first eight months after sludge application to three different soil types. One year after the application, the reduction was about 80 %. They explain that the reduction is related to triclosan biodegradation to methyl triclosan, which was found at 0.4 mg/kg. Clotrimazole desorption from sludge-amended soil was negligible, whereas fluconazole desorption was rapid. Clotrimazole was more persistent than fluconazole in dry soil, whereas the contrary occurred in wet soil [135].

Other studies have also explored the relations between compound properties, soil characteristics, and their interactions. Srinivasan et al. [136] observed that sulfamethoxazole sorption to six dairy farm soils was positively related to TOC. However, higher TOC % was correlated with higher cation exchange capacity and specific surface [8]. Similarly, correlation studies have shown that t1/2 of carbamazepine and triclosan was positively related to TOC, while t1/2 of the two PhACs was negatively related to pH. Positive correlations between sorption coefficients and TOC have been also observed for trimethoprim and carbamazepine [137]. Similarly, Leal et al. [138] investigated the sorption of FQs and sulphonamides in amended soils and found that the most important factors affecting the sorption were soil texture and cation exchange capacity. Kodešová et al. [137] explored the effects of different soil properties on PhAC sorption/desorption. Sorption of ionizable compounds was highly affected by soil pH.Moreover, positive

correlations between sorption coefficients and clay content were found for clarithromycin, clindamycin, atenolol, and metoprolol. According with their results, clarithromycin exhibited the highest sorption followed by trimethoprim, metoprolol, atenolol and clindamycin. While carbamazepine and sulfamethoxazole exhibited the lowest sorption and therefore higher mobility in soils, which may result in contamination of groundwater and accumulation in plants. Other authors have highlighted that the dissolved organic matter (DOM) increases the apparent solubility of the solute, therefore enhancing its mobility [103,133], but DOM can also reduce the mobility due to cumulative sorption and co-sorption to the soil's solid phase. Le Guet et al. [139] have also reported on these different effects of DOM on PhAC sorption capacity (increase or decrease).

5. Ecotoxicological effects and risks in sludge-amendeded soils

The risk quotient (RQ), ratio between measured (MEC) or predicted environmental concentrations (PEC) with predicted no-effect concentrations (PNEC), is the most common approach to identify high- or low-risk ecotoxicological situations associated with the presence of PhACs in the terrestrial environment, especially in soil [140]. PNECs are usually calculated using the lowest acute (lethal concentration (LC) or effect concentration (EC)) and chronic toxicity data (no observed effect concentration (NOEC)) in model organisms (fish, Daphnia magna and algae) and dividing them by an assessment factor, between 1000 and 10, respectively, to consider the worst-case scenario [25–27,141]. Because of the lack of acute toxicity data for some terrestrial organisms such as earthworms, plants and soil microorganisms, few studies use the PNEC values in soil to estimate the risk [117,118]. Instead, an equilibrium partition approach through the distribution or partition coefficients (K_d) is usually used to obtain $PNEC_{soil}$ from $PNEC_{water}$ [25–27,142]. Table 3 shows the ecotoxicological data and K_d values reported in the literature together with the calculated $PNEC_{soil}$ [15,20,27,28,30,68,130,143–166]. It should be noted that the toxicity data selected correspond to the most sensitive species among those most commonly used in toxicity studies. It also reveals the lack of data, for both ecotoxicological and K_d data, available for metabolites.

The criteria usually applied to evaluate the risk using the RQ model are those proposed by Hernando et al. [167] who classifies

Table 3
Ecooxicological data and predicted no-effect concentration (PNEC) of measured PhACs in digested and dehydrated sludge or compost.

Pharmaceutical compound	Ecotoxicological study			Reference	$PNEC_{water}$ (ug/L)	K_d (L/kg)	$PNEC_{soil}$ (ng/g dm)
	Species	Test	Ecotoxicity (mg/L)				
Ciprofloxacin	*M. aeruginosa* (cianobacteria)	EC_{50}	0.005	[143]	0.005	427	2.135
17a-Ethinylestradiol	*S. purpuratus* (invertebrate)	EC_{50}	0.03	[144]	0.03	3.35	0.1005
Triclosan	fish	chronic toxicity	0.005	[145]	0.05	127	6.35
Triclocarban	fish	chronic toxicity	0.00116	[145]	0.058	438	25.404
17ß-Estradiol	*S. purpuratus* (invertebrate)	EC_{50}	0.01	[146]	0.01	3.3	0.033
Sulfametoxazole	*P. subcapitata* (algae)	EC_{50} (96 h)	0.15	[146]	0.15	8	1.2
Sertraline	*D. magna* (crustacean)	EC_{50} (21 d)	0.066	[147]	0.066	23.95*	1.5807
Tylosin	*M. aeruginosa S.* (algae)	EC_{50}	0.034	[147]	0.034	128	4.352
Carbamazepine	*H. attenuate* (invertebrate)	EC_{50} (96 h)	3.76	[148]	3.76	13	48.88
Diclofenac	*V. pezeri* (bacteria)	EC_{50} (5 min)	3.8	[149]	3.8	9	34.2
Estrone	*T. battagliai* (invertebrate)	LC_{50} (10 d)	0.1	[150]	0.1	12.3	1.23
Fluoxetine	*P. subcapitata* (algae)	EC_{50} (120 h)	0.024	[147]	0.024	134	3.216
Atenolol	*D. rerio* (fish)	LC_{50} (96 h)	2.5	[151]	2.5	15	37.5
Ofloxacin	*S. leopolensis* (algae)	EC_{10} (7 d)	0.206	[152]	0.206	1192	245.552
Oxytetracycline	*M. Aeruginosa* (algae)	EC_{50} (72 h)	0.207	[147]	0.207	1030	213.21
Ketoprofen	*V. fischeri* (bacteria)	EC_{50} (15 min)	15.6	[153]	15.6	9	140.4
Ibuprofen	*H. attenuata (cnidarian)*	EC_{50} (96 h)	1.65	[148]	1.65	28.2	46.53
Caffeine	*S. Proboscideus* (crustacean)	LC_{50} (24 h)	0.409	[154]	0.409	25.12	10.27408
Erythromycin	*P. subcapitata* (algae)	EC_{50}	0.06	[155]	0.06	68	4.08
Tetracycline	*M. aeruginosa* (algae)	EC_{50}	0.09	[147]	0.09	1620	145.8
Claritromicin	*A. flos-aquae* (cianobacteria)	EC_{50}	0.0056	[156]	0.0056	1200*	6.72
Propranolol	*D. subspicatus* (algae)	EC_{50} (48 h)	0.7	[157]	0.7	58	40.6
Estriol	*S. purpuratus* (invertebrate)	EC_{50}	1.52	[144]	1.52	63*	95.76
Naproxen	*H. attenuata (cnidarian)*	EC_{50} (96 h)	2.62	[148]	2.62	11	28.82
Simvastatin	*N. spinipes* (copepod)	LC_{50} (96 h)	0.81	[147]	0.81	85	68.85
Sulfamethazine	*D. magna* (crustacean)	EC50 (21 d)	4.25	[147]	4.25	9	38.25
Trimetoprim	*V. pezeri* (bacteria)	EC_{50} (30 min)	0.28	[158]	0.28	26	7.28
Metoprolol	*D. subspicatus (algae)*	EC_{50}	7.3	[147]	7.3	20	146
Gemfibrozil	*H. attenuata (cnidarian)*	EC_{50} (96 h)	1.18	[148]	1.18	54.8*	64.664
Paracetamol	*D. magna* (crustacean)	EC_{50} (48 h)	9.2	[154]	9.2	32	294.4
Sulfapyridine	*H. attenuata (cnidarian)*	EC50 (96 h)	21.61	[147]	21.61	8	172.88
Valsartan	Algae	–	3.94	[159]	3.94	92.75*	365.435
Clofibric acid	*L. minor* (duckweed)	EC_{50} (7 d)	12.5	[147]	12.5	9	112.5
Metformin	*D. subspicatus* (algae)	LC_{50} (4 d)	320	[160]	320	41.96*	13427.2
Bezafibrate	Fish	EC_{50}	6	[161]	6	14	84
Salycilic acid	*V. fischeri* (bacteria)	EC_{50} (30 min)	90	[147]	90	82	7380
Sulfathiazole	*D. magna* (crustacean)	EC50 (96 h)	85.4	[147]	85.4	4.9	418.46
Irbesartan	*D. magna* (crustacean)	LC_{50} (48 h)	0.29	[162]	0.29	940*	272.6
Codeine	*D. magna* (crustacean)	EC_{50}	16	[160]	16	15	240
Norfloxacin	Algae	EC_{50}	15	[163]	15	5791	86,865
Azitromicin	Algae	EC_{50} (96 h)	19	[164]	19	2156*	40,964
Telmisartan	*D. magna* (crustacean)	LC_{50} (48 h)	7.813	[162]	7.813	5787*	45213.831
Lidocaine	*B. rerio* (fish)	LC_{50} (4 d)	106	[160]	106	52.79*	5595.74
Loratadine	*L. macrochirus* (fish)	LC_{50} (4 d)	0.4	[160]	0.4	31,425*	12,570
Fluconazole	*O. Latipes*	LC_{50} (4 d)	100	[147]	100	21.57*	2157

K_d data in soil taken from [20,27,68,130,165]; *: K_d data in sludge taken from [28,30,166].

the risk into: low risk (RQs < 0.1), medium risk (RQs between 0.1–1) and high risk (RQs > 1). An environmental risk assessment in soil amended with digested and dehydrated or composted sludge was conducted using the PhAC concentrations gathered from our literature review. PEC_{soil} values were stimated one year after one sludge-dose application to agricultural soil using the equation 1 provided by the European Commission Technical Guidance Document on Risk Assessment [25]:

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

where C_{sludge} is the contaminant concentration in digested or composted sludge; $APPL_{sludge}$ is the dry-sludge application rate (0.5 kg/m^2 year); $DEPTH_{soil}$ is the mixing depth of soil (0.20 m) and RHO_{soil} is the bulk density of wet soil (1700 kg/m^3). The minimum and maximum RQ values were estimated using the minimum and maximum concentrations of PhACs in soils (Fig. 4). The most critical compounds found in sludge-amended soil and that pose the highest ecotoxicological risk were the fluoroquinolone ciprofloxacin, the estrogens 17α-ethinylestradiol and 17β-estradiol and the antomicrobials triclocarban and triclosan. The presence of sulfamethozaxole, sertraline, tylosin, carbamazepine, diclofenac and estrone was related to a medium but not insignificant risk, and the metabolites salycilic acid and clofibric acid, two of the few for which data are available, were associated to a low risk.

Using this same approach, Martín et al. [25,26] reported that sulfamethoxazole, ibuprofen, gemfibrozil, 17β-estradiol and 17α-ethinylestradiol were the most relevant compounds when assessing the risks in digested and composted sewage sludge. However, RQ dramatically decreased after sludge application to soils, with 17β-estradiol being the only PhACs exhibiting some potential toxic effects. The authors selected toxicity data most commonly used in toxicity studies and reported that to the most sensitive organisms, such as *H. attenuate* or *B. calyciflorus*, the analysis of other PhACs could have also resulted in ecotoxicological risk. In the study conducted by Thomaidi et al. [118] and Gros et al. [168] triclosan and norfloxacin represent a risk for soil life and crops. More recently, Bastos et al. [103] reported RQ > 1 for trimethoprim, ciprofloxacin and norfloxacin with acute and chronic effects in soils amened with limed or digested sludge but RQ < 0.10 was found in soils amended with organic wastes, which was a result of a "dilution" effect suggesting low environmental risks. Lachassagne et al. [131] reported that the estimated RQ for acute and chronic effects of PhACs in soils amended with limed and digested sludge was related with medium risks, mainly due to the presence of sulfamethixazol.

Recent studies have also demonstrated that PhAC occurrence in soils can result in changes in the microbial communities by modifiying their ability to metabolize different carbon sources. Pino-Otín et al. [169] reported that NSAIDs and antibiotics had the lowest and highest risk of ecotoxicity, respectively, while lipid regulators and β-blockers exhibited intermediate toxicity. The most known health risk related to the presence of antibiotics in soil and related environmental samples are associated to the risks that promote the ocurrence and spread of antibiotic resistance in pathogenic bacteria [68]. Several studies have reported on the presence of genes related to antibiotic resistance in soil bacteria [127,170]. Lastly, it has been reported that the presence of antibiotics at subinhibitory concentrations in soil might act as signaling molecules and can lead to the development of spontaneous mutations in bacterial DNA, which is also associated with different antibiotic resistance mechanisms [171,172].

6. Conclusions

The detection of PhACs at concentration from μg/kg to mg/kg dm in sludge matrices is an indication that more monitoring of detected PhACs is required. Such monitoring should also be extended to metabolite analysis. Thirty-five classes of therapeutic groups, including 180 PhACs and 45 metabolites, have been analyzed in sludge from different countries. The most studied classes of PhACs include antibiotics, NSAIDs, antiepileptic and antidepressant drugs. Regarding the spatial distribution, Europe and Asia are the two continents with more published studies about the occurrence and effects of PhACs on sewage sludge. Despite advances in sludge stabilization, many compounds and their metabolites are not removed by sludge treatment. It is difficult to determine the specific conditions that will reduce PhAC accumulation in sludge as there are many factors involved. Promising results have been reported when using AnD in combination with other treatments. Information regarding the stabilization of PhACs in aerobic versus anaerobic conditions is scarce as well as regarding the behaviour and characterization of their metabolic pathways.

Amendment of agricultural soils with treated sludge may be an optimal way of sludge disposal. When sludge is mixed with soils, this causes a "dilution" of contaminants, which reduces their concentrations. Hydrothermal carbonization, biodrying or hydrothermal liquefaction have been recently investigated as potential technologies that can be used prior to sludge application to agriculture land in order to reduce the load of PhACs. In any case, the use of treated sludge as fertilizers should be done with caution because of the potential ecotoxicological risks associated with its use. Available literature suggests that this risk is medium-low for most PhACs, with the exception of triclocarban, triclosan,

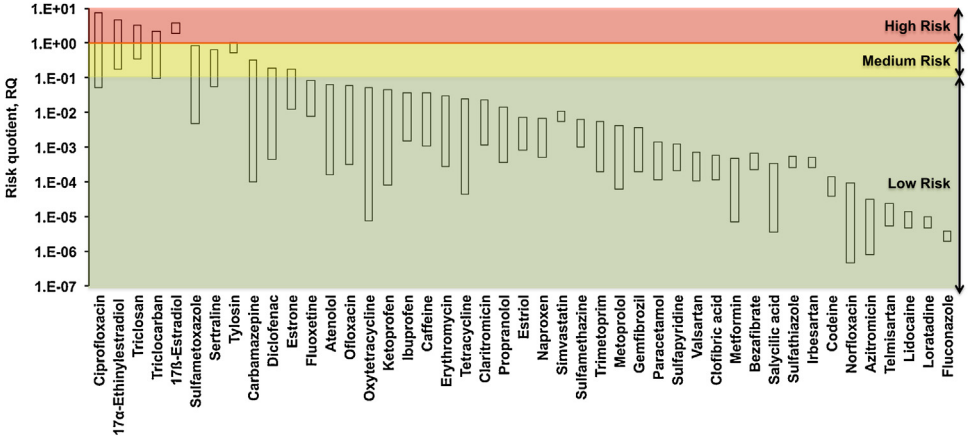

Fig. 4. Calculated risk quotient in case of sludge-amended soil due to PhACs measured in digested and dehydrated sludge or compost in literature.

ciprofloxacin and 17α-ethinylestradiol, which can be considered as critical compounds (RQ > 1). Nevertheless, improvements in environmental risk assessment are highly recommended, particularly the investigation into PNEC. Ecotoxicological data are mainly obtained from aquatic organisms, but the information regarding the effect of PhACs on terrestrial organisms is scarce. These differences are particularly evident for PhAC metabolites, with the added lack of K_d data from both soil and sludge matrices, which consequently complicates the environmental risk assessment for most metabolites.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.teac.2021.e00125.

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