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Review

Assessment of the occurrence of 455 pharmaceutical compounds in sludge according to their physical and chemical properties: A review

Anastasia Sellier^{*}, Somar Khaska¹, Corinne Le Gal La Salle¹

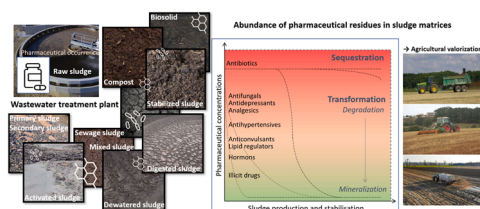
CHROME Détection, évaluation, gestion des risques CHRONiques et éMErgents (CHROME) / Université de Nîmes, 30021 Nîmes Cedex 01 - FRANCE



HIGHLIGHTS

- This review provides a holistic approach of the issue of 305 quantified pharmaceuticals in amendable sludge matrices.
- Significant variability of pharmaceutical concentrations in sludge matrices was evidenced.
- Stabilization processes contribute to the attenuation of pharmaceutical contents, but relevant residual levels persist.
- Sorption of pharmaceuticals to sludge is controlled by the synergistic action of both physical and chemical mechanisms.

GRAPHICAL ABSTRACT



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ABSTRACT

Sludge agronomical reuse is of major interest due to the beneficial contribution of nutrients. However, it implies the introduction of unregulated pharmaceuticals into amended-soils and creates a controversial issue about sludge management. To limit their dissemination, it is essential to identify the compounds of interest and understand their attenuation mechanisms through the sludge processes. This paper summarizes the knowledge on 455 investigated pharmaceuticals among 32 therapeutical categories in amendable sludge matrices. It contributes to enlarging the list of commonly quantified compounds to 305 residues including 84 additional compounds compared to previous reviews. It highlights that sorption appears as the main mechanism controlling the occurrence of pharmaceuticals in sludge matrices and shows the considerable residual levels of pharmaceuticals reaching several mg/kg in dry weight. Antibiotics, stimulants, and antidepressants show the highest concentrations up to 232 mg/kg, while diuretics, anti-anxieties or anticoagulants present the lowest concentrations reaching up to 686 µg/kg. Collected data show the increase in investigated compounds as antifungals or anti-histamines, and underline emerging categories like antidiabetics, antivirals, or antiarrhythmics. The in-depth analysis of the substantial database guides onto the pharmaceuticals that are the most likely to occur in these amendable matrices to assist future research.

Abbreviations: PhCs, Pharmaceutical compounds; WWTP, Wastewater treatment plant; dw, dry weight; LCA, Life Cycle Assessment; OM, Organic matter.

^{*} Correspondence to: 29 Rue du Pignon blanc, 49250 La Ménitré, France.

E-mail addresses: anastasia.sellier@unimes.fr (A. Sellier), somar.khaska@unimes.fr (S. Khaska), corinne.legallasalle@unimes.fr (C. Le Gal La Salle).

¹ **Full postal address:** Site GIS - Parc scientifique et technique Georges Besse - 150, Rue Georges Besse 30035 Nîmes Cedex 01 - FRANCE

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1. Introduction

Increasing population lead to growing pressure on terrestrial resources. The conservation of a safe environment results in the recycling intensification of the urban liquid and solid effluents. The reuse of WWTP outputs raises questions on the fate of pharmaceuticals compounds (PhCs), which are not restricted by guidelines in wastewater treatment plants outputs (WWTP). Indeed, as the current WWTP objective is to mostly reduce organic matter (OM) and a set of mineral and organic compounds contents before discharge into the natural environment, incomplete treatment effectiveness on pharmaceuticals is noticed (Boeglin, 2018). The elimination rates vary widely from 0% to more than 90%, according to the properties of the target molecule, regardless of the treatment processes (Miège et al., 2009; Dulio and Morin, 2009; Petrie et al., 2013; Luo et al., 2014; Mansouri et al., 2021). Hence, persistent compounds may be found in the liquid and solid matrices as non-negligible concentrations in the residual sludge, in the range of $\mu\text{g/L}$ to mg/L , and $\mu\text{g/kg}$ of dry weight (dw) to occasionally reach up mg/kg , respectively.

Management of WWTP sludge and the improvement of treatments technologies have become a major concern for members of water treatment industries (European Directive 91/271/EEC of 20/05/91). Indeed, the total sewage sludge production reports growing to approximately 103 million tons worldwide and approximately 15 million tons (dw) in the European Union (Ivanová et al., 2018a; Eurostat, 2021; Mateo-Sagasta et al., 2015).

Agricultural recycling emerges as the most economical option for high volumes of sludge disposal based on life cycle assessment studies (LCA) (Kelessidis and Stasinakis, 2012; Christodoulou and Stamatelatos, 2016; Fijalkowski et al., 2017; Clarke and Smith, 2011). The high OM content of sewage sludge about 53% increases the total organic carbon content of soils (Ghirardini and Verlicchi, 2019; Hamdi et al., 2019). Nutrients positively impact the biological properties of soils by improving microbial biomass and providing additional enzymatic activity (Hamdi et al., 2019). However, the sludge recycling field remains an environmental issue and helpful scientific discussion will contribute to draw conclusions depending on societal perception and LCA studies limited by environmental, political and economic aspects (Kelessidis and Stasinakis, 2012; Christodoulou and Stamatelatos, 2016; Sharma et al., 2017; Seleiman et al., 2020).

Regulations on sludge recycling are put into practice to limit environmental and socio-economic risks. Requirements have been established for disruptive and hazardous substances in the sludge (e.g. pathogens, metallic trace elements) based on European Directive 86/278/EEC of 12/06/86 and Part 503 Environmental Protection Agency of the United States (Seleiman et al., 2020; Martín-Díaz et al., 2020; Öberg and Mason-Renton, 2018). Faced with these restrictions, composting represents a more tolerant societal, economic and ecological alternative to sludge amendment as it allows biological decomposition and dilution with green waste products, recognized as a recycling practice of sludge valorization (Eurostat, 2021; Buta et al., 2021).

The increasing reuse of the unavoidable WWTP by-product in agricultural practices creates nevertheless growing concern about the continuous exposure to emerging organic contaminants, as more than a thousand organic contaminants have already been identified in sludge matrices (Meng et al., 2016). Pharmaceutical residues are not yet regulated (Keefer, 1947), however reviews identify critical organic compounds and highlight pharmaceuticals at similar or even higher concentrations than other regulated organic compounds (Fijalkowski et al., 2017; Clarke and Smith, 2011; Lü et al., 2021a; Díaz-Cruz et al., 2009; Harrison et al., 2006).

Recent paper review summarized the PhCs contents in sludge by matrix type and their potential risk on environment by quotient risk calculation from predictive no-effect concentration. Verlicchi et al., 2015 brings up 152 PhCs and metabolites in sludge matrices panning 23 therapeutical categories, from 59 references covering 2002–2015)

(Verlicchi and Zambello, 2015). More recently, Meijas et al., 2021 highlights up to 225 PhCs and metabolites quantified in sludge matrices, among 53 references covering 2003–2021 (Meijas et al., 2021). These reviews make a comprehensive presentation of the 45 pharmaceutical residues for which a risk study was performed. These risk assessments calculations are made after field application (leading to dilution effect), hence focusing on the short-term effect of a single application (Clarke and Smith, 2011; Walters et al., 2010; Martín et al., 2012a; Yan et al., 2014; Bourdat-Deschamps et al., 2017a). Other paper reviews focus exclusively on the efficiency of stabilization process as digestion or composting (Clarke and Smith, 2011; Lü et al., 2021a, 2021b; Dubey et al., 2021; Ezzariai et al., 2018). Overall, they found relatively variable removal rates from one study to another, regardless of the processes studied and the target PhCs. The initial concentrations of sludge entering the process is identified as one of the main factors governing residual PhCs levels. Also, the operating conditions and the properties of both PhCs and sludge are suggested to mainly impact on sorption mechanisms. Although composting should be one of the most promising solutions to PhCs biodegradation or mineralization, significant residual concentrations are quantified in stabilized sludge, qualifying some of them as recalcitrant to these processes (e.g. carbamazepine, antibiotics). Therefore, reviews suggest that vigilance in assessing the significance and implications of contaminants in sludge is needed to ensure the long-term sustainability of agronomic reuse.

This review answers a multifaceted concern that addresses several aspects. There is a need to strengthen existing knowledge by updating the current reviews on the occurrence of PhCs in sludge matrices. This represents the first aim of this paper. To our knowledge, this is the first review which evaluate the importance of PhCs occurrence in sludge by listing 455 investigated pharmaceutical residues through 32 therapeutical categories, of which 305 were detected. This review expands on current knowledge with an additional 84 PhCs not listed in the previous literature reviews and expose undetected compounds up to now. Then, to highlight the most persistent compounds, PhCs are organized according to their quantification frequencies and observed concentration range. To underline the compounds that potentially requiring more attention by experts, the number of studies associated with each compound are highlighted. Moreover, to ensure the most relevant pharmaceuticals susceptible to contaminate the environment among sludge-amended soils, this review article aims to underline the mechanisms that control the occurrence of persistent pharmaceuticals in sludge. Finally, this paper investigates deeper the relationship between the residual levels of hundreds pharmaceutical residues and their physico-chemical properties, which is not sufficiently addressed in the literature for such a large panel of compounds. This exhaustive review, of currently investigated pharmaceutical compounds, provides a substantial data base allowing to canvas long-term perspectives and regulations for pharmaceutical residues in all type of sludge with respect to agricultural amendments.

2. Representativeness of collected data

2.1. Identification and characterization of sludge matrices

A *sludge* is a semi-solid material produced through wastewater treatment processes. The total suspended solid particles is mostly composed of organic and inorganic materials and pathogenic microorganisms, such as bacteria (*Salmonella*, *E. Coli*), viruses (*Clostridium perfringens*), protozoa or eggs of parasites (Seleiman et al., 2020; Dubey et al., 2021). The type of sludge depends on the water treatment process and stabilization techniques (Fig. 1).

Various sludge matrices are produced by WWTP, with varying characteristics due to the several implemented WWTP steps:

- (i) raw sludge, issued from the screening and filtering of the raw water inputs. It contains suspended solids.

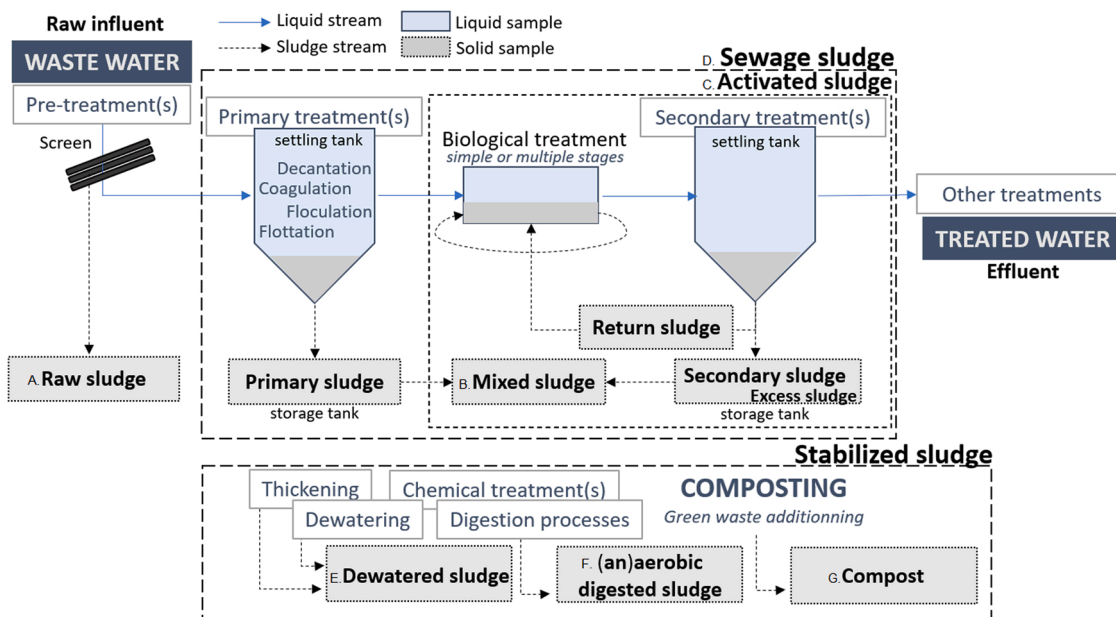


Fig. 1. Schema of the different types of sludge identified in literature studies. The liquid and solid fluxes are represented through blue and grey colors respectively, detailing the major type of sludge found under the reviewed papers. Raw sludge and sewage sludge globalize the matrices sampled between the WWTP input (wastewater) and the WWTP output (treated wastewater). Stabilized sludge, resulting from several stabilizing processes detailed by blue stickers, can be reuse through three main destinations.

- (ii) primary sludge: they result from a more involved treatment of raw wastewater, including clarification processes such as flocculation and decantation, and are also composed mostly of decantable organic and inorganic particles.
- (iii) secondary sludge: they are generated by biological treatment, mostly aerated, and put away into the biological systems (return sludge).
- (iv) mixed sludge: they represent the mixture of primary and the excess part of secondary sludge. Literature studies distinguish raw sludge and other sludge as sewage sludge because of the treatments involved, but also differentiate primary sludge and the other type of sludge (activated sludge) by their global composition and particle sizes.

Despite the several numerous production processes implemented, sewage sludge may further undergo conditioning treatments to reduce the moisture content by reducing their amount of water from 1%–10% to 2%–20% (dw) as mechanical (thickening, dewatered by settling, centrifugation, filter press). Other thermal techniques could be applied to reduce the amount of sludge, as pyrolysis. This kind of process allows mainly the recovery of the produced energy content (Sharma et al., 2017; Dubey et al., 2021; Tarpani et al., 2020; Zhang et al., 2017). Although pyrolysis is considered as a stabilization process by reducing the organic contamination (Meijas et al., 2021), the “biochar” matrix is more considered as a landfilling waste than a regulated product for agricultural valorization (Tarpani et al., 2020) and as such is not considered in this paper review.

According to regulations objectives of destructing pathogenic germs, stabilization processes as chemical (liming) or biological (aerobic and anaerobic digestion under mesophilic $\sim 37^\circ\text{C}$ and thermophilic $\sim 55^\circ\text{C}$ conditions) are implemented (Boeglin, 2018). Composting, a practice of mixing sludge and green waste (>45% dw), is another type of stabilization process implying OM decomposition with regularly aerated matter and temperatures going up to 80°C . The digested or composted products are included in this review.

In numerous studies the sludge production processes are not clearly documented. The studies comparison gets complicated with existence of several nomenclature in the management and regulations of semi-solid

residues, depending on the country. The term “sewage sludge” describe a by-product of wastewater that is not suitable for reuse in agricultural application (Christodoulou and Stamatelatu, 2016; Öberg and Mason-Renton, 2018). The term “biosolid” is generally found in North American legislatures (US EPA503, 1994) and currently used in Europe. This term would have been introduced in the USA as a definition of stabilized sludge in order to promote societal acceptability through agriculture reuse. The “biosolid” is also found in Europe to describe a solid product mixed with green wastes, making this term the subject of discussion on its categorization. By this way, the specification of the involved processes for sludge treatment remaining often imprecise.

Reviewed studies investigated a relatively even distribution over 155 types of sludge with 82 sewage sludge (22 raw sludge, 20 secondary sludge, 8 mixed sludge, 32 sewage sludge) and 73 stabilized sludge (16 dewatered sludge, 34 digested sludge, 11 composts and 12 biosolids) (Fig. 1). The collected data are generally based on a sampling campaign, introducing more than a single sample. The use of sludge as fertilizer is beneficial by improving soil quality through composition and physical structure, also Table 1 shows the current knowledge of agronomical criteria and physical-chemical characteristics that qualifies each type of sludge. The nutrient content varies greatly depending on the characteristics of wastewater input and the applied treatment (Seleiman et al., 2020), but present fertilizing nutrients such as nitrogen (N), phosphorus (P), potassium (K) and calcium (Ca) up to 25% (Harrison et al., 2006; Costa et al., 2017; Suh and Rousseaux, 2002). Most studies on the PhCs occurrence in sludge matrices do not mention the sludge’s physical nor chemical properties while they may have an impact on the fate of pharmaceutical compounds.

2.2. Overview and analytical quality of target pharmaceuticals

Without an official list of PhCs to monitor, studies often focus mainly on the contaminants previously identified in wastewater and persisting in sludge. The compiled screening lists are directed by parameters governing the occurrence of contaminants in liquid matrices without considering parameters related to the presence of suspended solids with high OM content leading to select target PhCs mostly restricted to soluble compounds, based on observation such as national consumption or

Table 1

Summary table of agronomical criteria, and physical-chemical characteristics of several types of sludge collected from the literature (Boeglin, 2018; Seleiman et al., 2020; Harrison et al., 2006; Verlicchi and Zambello, 2015; Meijas et al., 2021; Costa et al., 2017; Suh and Rousseaux, 2002; Golet et al., 2003; Hörsing et al., 2011; Hyland et al., 2012; Jelic et al., 2012; Huang et al., 2014; Liu et al., 2019; Ferhi et al., 2016; Cao et al., 2016; Gonzalez-Gil et al., 2016; Bourdat-Deschamps et al., 2017b; Khadra et al., 2019; Drillia et al., 2005; Carballa et al., 2007; Gao et al., 2012). TS. Total solid. - N. nitrogen - OM. Organic matter – C. Carbon - P. phosphorus, K. potassium - Ca. calcium. CEC. Cation exchange capacity – CODt, CODs. Total and soluble dissolved organic carbon, respectively.

<u>Agronomical criteria</u>							
	Primary	Secondary	Mixed	Sewage	Dewatered	Digested	Stabilized
TS (g/L)	50–145	10–35	29–110	15–40	36	18–25	18
pH	5.7–7.9	5.7–8.0	5.4–7.1	6.0–7.9	6.7	5.8–7.9	7.9
OM (% dw)	65–68	81–86	59–80	55–65		24–67	
C (% dw)	32–70	7–72	44.9			14–30	
N (% dw)	0.9–2.7	3.3–6.9	3.5–4.5	1.4–5		0.7–5.7	
P (% dw)	< 0.1	0.1–5.0	1.1–2.5	0.3–2.0	0.3	0.1–4.4	
K (% dw)	0.3–3	1.2–1.3	0.2–0.7	0.2–0.5		0.2–1	
Ca (% dw)	5.3–5.9	1.6–3.1	4.8–10.0	3.5–10.0		5.0–10.0	
<u>Physical-chemical characteristics</u>							
	Primary	Secondary	Mixed	Sewage	Dewatered	Digested	
CEC (meq/100 g)		54–75	31.6				
CODt (g/L)	45–120		30–110	10–50			
CODs (g/L)	1–8		1–8	1–7			
Alkalinity (mg/L)				9070	1316	2077	14224

solubility (Östman et al., 2017; Y. Chen et al., 2013; Z.F. Chen et al., 2013; Patel et al., 2019; Verlicchi et al., 2012; Beausse, 2004). The two-thirds of established PhCs lists are mostly reduced to less than 20 compounds and sometimes approach a broad range of PhCs until 148 molecules.

These studies are generally restricted to specific therapeutical categories and extend to others with the increasing number of surveyed PhCs. Antibiotics are of major interest due to new concerns about their occurrence, impacts on the environment and potential spread of antibiotic resistance on the ecosystem after progressive contamination of the aquatic and terrestrial ecosystem (Prosser and Sibley, 2015; Wu and Zhu, 2016; Bondarczuk et al., 2016). Previous reviews (Verlicchi and Zambello, 2015; Ezzariai et al., 2018) and sludge PhCs studies (Yan et al., 2014; Östman et al., 2017; Ashfaq et al., 2017; Chen et al., 2013) point out antibiotics as the most studied category and the main source of pharmaceutical contaminants. Hormones are generally included in these studies because of their impact on aquatic environments affecting fish physiology and reproductive development of animals (Lapen et al., 2008; Xu et al., 2009). Regarding antifungals, anti-inflammatories and analgesics, the reason for their research is their high toxicity potential in amended soils with WWTP matrices (Wilkinson et al., 2017).

It is essential to assess the accuracy, reliability and quality of existing data from sampling steps, sample preparations, extraction protocols and analytical methods (Keefer, 1947; Pérez-Fernández et al., 2017; Pérez-Lemus et al., 2019; Martín-Pozo et al., 2019; Cieslik et al., 2015; Jones-Lepp and Stevens, 2007; de Oliveira et al., 2020; Larivière et al., 2017). Indeed, high OM content in sludge generates high matrix effect for mass spectrometry analysis, leading to potentially underestimated concentrations if no labelled standards are rise in the analytical protocol (Pérez-Lemus et al., 2019). A description of the analytical method (extraction techniques, cleaning procedures, instrumentations) used for the evaluation of PhCs occurrence, and that associated quality control need to be included to understand analytical limits.

The detection and quantification limits of the reviewed methods (MDL and MQL, respectively) show significant variabilities due to a lack of a standardized method for sludge extraction and analysis. Some papers already highlight the abundance and heterogeneity of protocols used for the PhCs study of complex matrices as sludge (Díaz-Cruz et al., 2009; Pérez-Fernández et al., 2017; Larivière et al., 2017; Hamid and Eskicioglu, 2012; Vieno et al., 2006; Gomes and Lester, 2004). This review confirms that approximately 50% of the reviewed papers do not specify the necessary information's to assess the representativeness and comparison of the lowest quantified levels. Consequently, a wide range of method limits are listed with values ranging from a few µg/kg to

several mg/kg (dw) for a single compound, detailed in [Supplementary material](#) (Tab. SM1). Therefore, the literature review takes all values as data “at face value” and the minimum measured concentrations are associated to the lowest quantification limits of the reviewed studies.

Based on a keyword search in SCOPUS, PubMed and MDPI (“waste-water treatment plant”, “sewage-sludge”, “compost”, “biosolid”, “pharmaceutical”, “amendment/amended soils”), [Table 2](#) lists the 110 reviewed papers, according to the considered type of sludge, and the analytical methods. This document includes references from 2002 to 2021 showing the emerging interest in studies on the occurrence and fate of pharmaceutical residues (Meng et al., 2016; Ezzariai et al., 2018; Fu et al., 2010; Ahnert and Krebs, 2021), as well as the improved analytical performance allowing multi-residue analysis of complex matrices (Pérez-Fernández et al., 2017; Pérez-Lemus et al., 2019; Larivière et al., 2017). This table, organized by the increasing number of investigated PhCs, from 2 to 148 compounds through the 455 searched for, summarizes the [supplementary material](#) (Tab.SM1) to highlight the disparities from the PhCs occurrence in sludge matrices. The literature PhCs cover over 32 therapeutical categories, which those investigated are explained for each study. All literature figures are from the following references showing contents among European countries (e.g., Spain, Germany, France), Asia (China) and America (Canada, USA) within the limitations listed above.

3. Occurrence of pharmaceutical compounds in sludge

3.1. Overview of the investigated PhCs

Among the 455 investigated PhCs, a panel of compounds frequently appears in the established list of target PhCs PhCs (e.g., carbamazepine, sulfamethoxazole, ibuprofen, ketoprofen, diclofenac, ciprofloxacin, norfloxacin, ofloxacin, tetracycline, trimethoprim, naproxen, gemfibrozil, bezafibrate caffeine, acetaminophen, fluoxetine, atenolol, propranolol) (Tab.SM1). PhCs categories are presented among the most studied therapeutical categories regrouping PhCs referenced from more than 15% of papers and concentrate in all studies. The most studied categories include 252 detected compounds among 345 investigated through 12 main studied categories as antibiotics (53% of articles; 102 investigated compounds), anti-inflammatories (42%; 35), anticonvulsants (42%; 17), antihypertensives (41%; 32), lipid regulators (36%; 11), stimulants (31%; 8), hormones (27%; 29), antidepressants (26%; 30), analgesics (26%; 7), antihistamines (23%; 12), antifungals (23%; 10), and illicit drugs (16%; 52). Novel categories as the 20 remaining categories issued from less than 10% of papers are emerging through the

Table 2

List of the reviewed studies showing the type of studied sludge, the number of investigated compounds according to the extraction protocols and instrumental analysis. *References in bold are studied several types of sludges during the production and stabilization processes.* Studied sludge: A. Raw sludge – B. Mixed sludge – C. Activated sludge – D. Sewage sludge – E. Dewatered sludge – F. Digested sludge – G. Compost – H. Biosolid (presented in Fig. 1) Extraction protocol: PLE. Pressurized liquid extraction – SLE. Solid liquid extraction - UAE. Ultrasonication assisted extraction – MAE. Microwave assisted extraction – QuEChERS. Quick, Easy, Cheap, Rugged and Safe extraction. (d)SPE – (Dispersive) solid phase extraction – MSPD. Matrix solid phase dispersion. Instrumental analysis. LC. Liquid chromatography – GC. Gas chromatography – MS². Mass spectrometry (tandem) – DAD. Diode array detection – Fluo. Fluorimetry.

Number of investigated PhCs		Type of studied sludge								Extraction Instrumental		References
<i>Detail of investigated therapeutic PhCs</i>		A	B	C	D	E	F	G	H	protocol	analysis	
2	2antiarrhythmics.				X		X			MSPD – SPE	LC-MS ²	(Montes et al., 2015)
3	3antibiotics.				X					UAE	LC-UV	(Arun et al., 2020)
	3antifungals.				X	X				UAE - SPE	LC-MS ²	(Huang et al., 2012)
						X				QuEChERS - dSPE	LC-MS ²	(Masiá et al., 2015)
4	3hormones.		X	X	X	X				UAE - SPE	LC-MS ²	(Gabet-Giraud et al., 2010)
	4anti-inflammatory.				X					MAE - SPE	GC-MS	(Dobor et al., 2010)
		X			X					UAE - SPE	GC-MS	(Samaras et al., 2011)
						X				UAE - SPE	GC-MS	(Stasinakis et al., 2013)
	4antifungals.	X				X				UAE - SPE	LC-MS ²	(Peng et al., 2012)
	4hormones.		X							UAE - SPE	LC-MS ²	(Ashfaq et al., 2018)
					X					PLE - SPE	LC-MS ²	(Muller et al., 2008)
					X					UAE - SPE	LC-MS	(Nie et al., 2009)
						X				UAE - SPE	LC-MS ²	(Ternes et al., 2002)
	2antihypertensives – 1antibiotic – 1antidepressant.					X				LC-MS ²		(Ruan et al., 2019)
5	2hormones - 1analgesic – 1antihypertensive.	X								LC-MS ²		(Brown and Wong, 2018)
	5antibiotics.				X					SLE - SPE	LC-UV	(Kimosop et al., 2016)
							X			PLE - SPE	LC-MS ²	(Salvia et al., 2015)
					X	X				UAE - SPE	LC-MS ²	(Tang et al., 2012)
	5antifungals.				X					UAE - SPE	LC-MS ²	(Huang et al., 2010)
	4hormones – 1antineoplastic.				X					SLE - SBSE	GC-MS	(Tan et al., 2008)
6	1antibiotic – 1anticonvulsant - 1antidepressant – 1anti-inflammatory – 1lipid regulator								X	MAE-SPE	LC-MS	(Wang et al., 2018)
	6antifungals.	X								UAE	LC-MS ²	(García-Valcárcel and Tadeo, 2011)
		X					X	X		UAE - SPE	LC-MS ²	(Lindberg et al., 2010)
	6hormones.					X				UAE - SPME	GC-MS	(Vakondios et al., 2016)
	5anticonvulsants – 1stimulant.			X					X	PLE - SPE	LC-MS ²	(Miao et al., 2005)
	2anti-inflammatory - 1antibiotic - 1anticonvulsant - 1lipid regulator – 1antibacterial.				X					PLE - SPE	LC-MS ²	(Dong et al., 2016)
7	7antifungals.						X			SLE - MSPD	LC-MS ²	(Casado et al., 2015)
	7antibiotics.		X						X	PLE - SPE	LC-MS ²	(Khadra et al., 2019)
							X			PLE - SPE	LC-MS ²	(Lillenberg et al., 2009)
	7hormones.				X					PLE	LC-MS ²	(Nieto et al., 2008)
	3lipid regulators – 4anti-inflammatory.							X		UAE	LC-MS ²	(Luque-Muñoz et al., 2017)
	Number of investigated PhCs	Type of studied sludge								Extraction Instrumental		References
	<i>Detail of investigated therapeutic PhCs</i>	A	B	C	D	E	F	G	H	protocol	analysis	
8	8hormones.		X							MAE - SPE	GC-MS	(Huang et al., 2014)
							X			MAE - SPE	LC-MS ²	(Vega-Morales et al., 2013)
	8antibiotics				X					UAE-SPE	LC-MS ²	(An et al., 2015)
							X			PLE - SPE	LC-MS ²	(Pamreddy et al., 2013)
	7hypnotics – 1anticonvulsant.				X					PLE	LC-MS ²	(Arbeláez et al., 2014b)
	4antibiotics – 3anti-inflammatory – 1lipid regulator.							X	X	UAE	LC-MS ²	(García-Rodríguez et al., 2014)
	5antibiotics – 3antivirals				X					UAE	LC-MS ²	(Muriuki et al., 2020)
9	8illicit drugs – 1stimulant.				X					PLE	LC-MS ²	(Arbeláez et al., 2014a)
	4hormones – 3lipid regulators – 2anti-inflammatory.						X			UAE - SPE	GC-MS	(Zhang et al., 2016)
	5anti-inflammatory – 3lipid regulators – 1antibiotic.							X		UAE - dSPE	LC-MS ²	(Tavazzi et al., 2013)
	3anti-inflammatory – 2antibiotics – 1analgesic – 1anticonvulsant – 1antidepressant – 1lipid regulator.			X						PLE - SPE	LC-MS ²	(Petrie et al., 2014)
10	9antihypertensives – 1bronchodilator.			X			X			PLE - SPE	LC-MS ²	(Scheurer et al., 2010)
	8antibiotics – 1antihistamine – 1antiulcer.				X					PLE	LC-DAD	(Nieto et al., 2007)
	5hormones – 3antihypertensives – 2anticonvulsants.					X				UAE - SPE	LC-MS ²	(Yu et al., 2011)

(continued on next page)

Table 2 (continued)

Number of investigated PhCs	Detail of investigated therapeutical PhCs	Type of studied sludge								Extraction Instrumental		References
		A	B	C	D	E	F	G	H	protocol	analysis	
11	5anti-inflammatories – 2lipid regulators – 1analgesic – 1anticonvulsant – 1hormone.				X					UAE - SPE	GC-MS	(Yu and Wu, 2012)
	3antidepressants – 2antibiotics – 2antihypertensives – 1anti-inflammatory – 1antifungals – 1antipsychotic.			X						SLE	LC-MS ²	(Iranzo et al., 2018a)
	11antibiotics.				X					PLE - SPE	LC-MS ²	(Díaz-Cruz et al., 2006)
	10antibiotics – 1antifungal.						X			UAE	LC-MS ²	(Lindberg et al., 2005)
12	3anti-inflammatories – 3hormones – 1antibiotic – 1anticonvulsant – 1antihypertensive – 1lipid regulator – 1stimulant.	X				X	X	X		UAE - SPE	LC-DAD	(Martín et al., 2012a)
	11antibiotics – 1antifungal.				X					SLE - SPE	LC-MS ²	(Bajkacz et al., 2020)
13	4anticonvulsants – 4anti-inflammatories – 2antibiotics – 2stimulants						X	X		SPE-dSPE	LC-MS ²	(Martín et al., 2021)
	13anti-inflammatories.					X				QuEChERS - SPE	LC-MS	(Rossini et al., 2016)
14	13illicit drugs.			X						PLE - SPE	LC-MS ²	(Senta et al., 2013)
	8antibiotics – 2anti-inflamatories – 1anticonvulsant – 1antidepressant – 1lipid regulator.				X	X	X			UAE - SPE	LC-MS ²	(Ferhi et al., 2016)
					X			X		UAE - dSPE	LC-MS ²	(Bourdat-Deschamps et al., 2017a)
	4antibiotics - 3anti-inflamatories - 3hormones - 2hypnotics - 1anticonvulsant – 1antidepressants.		X	X	X	X	X	X		UAE - SPE	GC-MS ²	(Gonzalez-Gil et al., 2016)
15	6anti-inflammatories – 4anticonvulsants – 2antibiotics – 2stimulants	X	X	X		X	X	X		UAE-dSPE	LC-MS ²	(Luis Malvar et al., 2020)
	11hormones – 3anti-inflammatories – 1antineoplastic.		X							MAE	LC-MS ²	(Guedes-Alonso et al., 2016)
16	12antibiotics - 1analgesic – 1anticonvulsant – 1stimulant.			X		X			X	PLE - SPE	LC-MS ²	(Ding et al., 2011)
	7antibiotics – 2anti-inflammatories – 1anticonvulsant – 1antihypertensive – 1bronchodilator – 1lipid regulator – 1stimulant – 1vasodilator.	X	X							UAE - SPE	LC-MS ²	(Okuda et al., 2009)
	14antidepressants – 2anticonvulsants.	X					X	X		UAE - SPE	LC-MS ²	(Lajeunesse et al., 2012)
	5anti-inflammatories – 4hormones – 2antibiotics – 2lipid regulators - 1anticonvulsant – 1antihypertensive – 1stimulant.	X		X			X			UAE - SPE	LC-DAD	(Luis Malvar et al., 2020)
Number of investigated PhCs						X				UAE - SPE	LC-DAD	(Martín et al., 2010)
	Detail of investigated therapeutical PhCs	A	B	C	D	E	F	G	H	Extraction protocol	Instrumental analysis	References
16	7anti-inflammatories – 3lipid regulators – 1analgesic – 1anticonvulsant – 1antidepressant – 1antigout – 1antihypertensive – 1stimulant.								X	SLE - MSPD	GC-MS ²	(Albero et al., 2014)
	5illicit drugs – 2antibiotics - 2antidepressants – 2anti-inflammatories – 1anticonvulsant – 1 antihistamine – 1antihypertensive – 1hormone – 1lipid regulator.				X					PLE	LC-MS ²	(Langford et al., 2011)
17	17antibiotics.							X		MAE - dSPE	LC-MS ²	(Dorival-García et al., 2015)
					X					UAE - SPE	LC-MS ²	(Huang et al., 2013)
18	5antidepressants – 5antihypertensives – 4hormones – 1analgesic – 1antihistamine – 1bronchodilator – 1stimulant.							X		MAE - SPE	LC-MS ²	(Evans et al., 2015)
	19antibiotics.	X		X				X		UAE - SPE	LC-MS ²	(Jia et al., 2012)
20	3antihistamines – 3stimulants – 2antibiotics – 2antifungals – 1anticoagulant – 1analgesic – 1anticonvulsant – 1antidepressant – 1antihypertensive – 1hormone 1lipid regulator – 1illicit drug – 1vasodilator.								X	PLE - SPE	GC-MS	(Kinney et al., 2006)
	17illicit drugs – 2hypnotics – 1stimulant.					X	X			PLE - SPE	LC-MS ²	(Mastroianni et al., 2013)
21	11antibiotics – 2anti-inflammatories – 2lipid regulators – 2stimulants – 1anticonvulsant – 1antihistamine – 1antihypertensive.								X	UAE - SPE	LC-MS ²	(Spongberg and Witter, 2008)
	4anti-inflammatories – 3antifungals – 2antihelminthics – 2antihypertensives – 2lipid regulators – 1antiarrhythmic – 1anticonvulsant – 1antidepressant – 1antidiabetic – 1antipsychotic – 1hypnotic – 1vasodilator.			X						SLE	LC-MS ²	(Cerqueira et al., 2018)
	9anti-inflammatories – 3hormones - 2antibacterials – 2antihypertensives – 1analgesic – 1antibiotic – 1anticonvulsant – 1antiprotazoal – 1lipid regulator.				X					MAE - SPE	GC-MS	(Azzouz and Ballesteros, 2012)
	10antibiotics – 5lipid regulators – 2antihypertensives – 2anti-inflammatories – 1analgesic - 1anticonvulsant.						X			UAE - SPE	LC-MS ²	(Yan et al., 2014)
22	22antibiotics.			X						UAE - SPE	LC-MS ²	(Gao et al., 2012)
					X					PLE - SPE	LC-MS ²	(García-Galán et al., 2013)
23	5antibiotics - 5anti-inflammatories – 4hormones – 3lipid regulators – 2antihypertensives – 1analgesic – 1anticonvulsant – 1stimulant.	X				X	X			PLE - SPE	LC-MS ²	(Li et al., 2013)
	5antibiotics – 5hormones – 2analgesics – 2antihypertensives – 1antiarrhythmic – 1antibacterial – 1anticonvulsant – 1antidepressant – 1antidiabetic – 1antiemetic – 1antifungal – 1antihistamine.	X						X	X	UAE - SPE	LC-MS ²	(Martín et al., 2015)
	5antihypertensives – 4hormones - 3antidepressants – 3anti-inflammatories – 2antibiotics – 1anticoagulant – 1anticonvulsant – 1antifungal – 1diuretic – 1hypnotic – 1stimulant.		X							QuEChERS - dSPE	LC-MS ²	(Mailler et al., 2017)
	1antidepressant – 1antidiabetic – 1antiemetic – 1antifungal – 1antihistamine.			X						UAE	LC-MS ²	(Malmberg and Magnér, 2015)
24	4anti-inflammatories – 3anticonvulsants – 3antihypertensives – 3antipsychotics – 2antibiotics 1antidepressants – 1analgesic – 1antianxiety – 1antihistamine – 1antiulcer – 1diuretic – 1hypnotic – 1lipid regulator - 1stimulant.	X								UAE - SPE	GC-MS ²	(Yang et al., 2016)
	18antibiotics – 3antihypertensives – 1antibacterial – 1anticonvulsant – 1lipid regulator – 1stimulant.		X							UAE - SPE	LC-MS ²	(Yuan et al., 2014)

(continued on next page)

Table 2 (continued)

Number of investigated PhCs	Type of studied sludge								Extraction Instrumental		References
	A	B	C	D	E	F	G	H	protocol	analysis	
<i>Detail of investigated therapeutic PhCs</i>											
8antibiotics – 3anti-inflammatories - 2antihypertensives - 1analgesic – 1anticonvulsant – 1antihistamine – 1stimulant – 1vasodilator	X								QuEChERS	LC-MS ²	(Park et al., 2020)
27 10antidepressants – 6hypnotics - 5antihypertensives – 2antiplatelets - 1anticonvulsant – 1antihistamine – 1antineoplastic – 1stimulant.		X							UAE - SPE	LC-MS ²	(Subedi and Kannan, 2015)
30 19antibiotics – 5anti-inflammatories – 2lipid regulators – 1analgesic – 1anticonvulsant – 1antihypertensive – 1stimulant.					X				UAE - SPE	LC-MS ²	(Subedi et al., 2013)
8antidepressants – 6antihypertensives - 4antibiotics- 2antifungals – 2anti-inflammatories – 2antiplatelets – 2stimulants - 1analgesic – 1antihistamine – 1illicit drug – 1lipid regulator.			X						PLE - SPE	LC-MS ²	(Y. Chen et al., 2013; Z.F. Chen et al., 2013)
				X					UAE - SPE	LC-MS ²	(Subedi et al., 2017)
Number of investigated PhCs	Type of studied sludge								Extraction Instrumental		References
<i>Detail of investigated therapeutic PhCs</i>	A	B	C	D	E	F	G	H	protocol	analysis	
31 7anti-inflammatories - 5antibiotics - 5antihypertensives – 5lipid regulators – 3antihistamines - 2antidepressants - 1analgesic – 1anticonvulsant – 1antidiabetic – 1antiulcer.	X					X		X	PLE - SPE	LC-MS ²	(Radjenović et al., 2009)
32 7antihypertensives – 6lipid regulators - 5anti-inflammatories - 4antibiotics – 4antihistamines – 2hypnotics – 1anticonvulsant – 1antidiabetic – 1antifungal – 1diuretic.				X					PLE - SPE	LC-MS ²	(Jelic et al., 2011)
34 8antibiotics – 8anti-inflammatories – 4antihypertensives – 2analgesics – 2antifungals – 2lipid regulators - 1anticonvulsant – 1antidressant – 1antihistamine – 1antiulcer – 1bronchodilator – 1hypnotic – 1illicit drug – 1vasodilator.					X				SLE – MSPD	LC-MS ²	(Li et al., 2016)
35 9antihypertensives – 5anti-inflammatories – 4antidepressants – 4hormones – 4hypnotics – 3bronchodilators – 2antibiotics – 1analgesic – 1antihistamine – 1lipid regulator – 1stimulant.				X					UAE - SPE	LC-MS ²	(Soulier et al., 2011)
36 10antihypertensives - 5antidepressants – 5hormones – 4anti-inflammatories – 3diuretics – 2antidiabetics - 1analgesic – 1antianxiety – 1antiarrhythmic – 1antibiotic – 1anticoagulant – 1lipid regulator – 1vasodilator				X					SLE-SPE	LC-MS ²	(Huber et al., 2016)
40 24antibiotics – 10hormones - 3antihypertensives – 1lipid regulator – 1anticonvulsant – 1stimulant.				X					UAE - SPE	LC-MS ²	(Ben et al., 2018)
12antibiotics – 9anti-inflammatories – 4antihypertensives – 2analgesics – 2antifungals 2lipid regulators – 1anticonvulsant – 1antidepressant – 1antidiabetic – 1antineoplastic – 1antiulcer – 1bronchodilator – 1hypnotic – 1stimulant – 1vasodilator.		X							UAE - SPE	LC-MS ²	(Ashfaq et al., 2017)
41 17antibiotics – 6anti-inflammatories – 4antihypertensives - 2anticonvulsants – 2antineoplastics – 2bronchodilators – 2lipid regulators – 1analgesic – 1antihistamine – 1antiulcer – 1diuretic – 1stimulant – 1vasodilator.					X				UAE - SPE	LC-MS ²	(Zhou et al., 2012)
43 8antibiotics - 8antihypertensives – 7anti-inflammatories – 6lipid regulators - 4antihistamines - 2analgesics – 2diuretics – 2hypnotics – 1anticonvulsant – 1antidiabetic – 1antifungal – 1bronchodilator.						X			PLE - SPE	LC-MS ²	(Jelić et al., 2009)
44 18antibiotics – 8anti-inflammatories – 3antiarrhythmics – 3bronchodilators – 2antibacterials – 2lipid regulators – 2anticonvulsants – 2diuretics – 1stimulant – 1antineoplastic – 1antiulcer – 1antipsychotic.					X	X			UAE - SPE	LC-MS ²	(Narumiya et al., 2013)
47 14illicit drugs - 10antidepressants – 6antihypertensives – 6hypnotics - 4antibiotics – 2anti-inflammatories - 1anticonvulsant – 1antifungal – 1antihistamine – 1antiplatelet – 1stimulant.		X							UAE - SPE	LC-MS ²	(Subedi et al., 2015)
59 16antibiotics – 7antidepressants – 4anti-inflammatories – 4hormones - 3anticonvulsants – 3antihypertensives – 3antipsychotics - 2analgesics – 2antiarrhythmics – 2antibacterials – 2antifungals – 2antihistamines – 2illicit drugs - 1anticoagulant – 1antidiabetic – 1antiemetic – 1antihelminthic – 1contrast media – 1hypnotic – 1stimulant.				X					PLE - SPE	LC-MS ²	(Ait-Aissa et al., 2014)
60 4illicit drugs - 7antidepressants – 7antihypnotics – 2analgesics – 2stimulants – 1vasodilator.			X						PLE - SPE	LC-MS ²	(Baker and Kasprzyk-Hordern, 2011)
68 48antibiotics - 2antiarrhythmics – 2antifungals – 2hypnotics - 2anti-inflammatories - 2stimulants - 2analgesic – 1anticoagulant – 1anticonvulsant – 1antidepressant – 1antidiabetic - 1antihistamine – 1bronchodilator – 1hormone – 1lipid regulator.				X					UAE - SPE	LC-MS ²	(McClellan and Halden, 2010)
69 46antibiotics - 4antihistamines – 3stimulants - 2antibacterials – 2antifungals – 2anti-inflammatories - 1analgesic – 1antiarrhythmic – 1anticoagulant – 1anticonvulsant – 1antidepressant – 1antidiabetic – 1antihypertensive – 1illicit drug – 1lipid regulator – 1vasodilator.								X	UAE - SPE	LC-MS ²	(U.S. EPA, 2009)
80 21illicit drugs - 9antidressants – 7antihypertensives – 7stimulants - 6antibiotics – 4analgesics – 4antihistamines – 4anti-inflammatories – 4antineoplastics - 3antidepressants – 3hormones - 2antidiabetics - 2lipid regulators – 1antihistamines - 1contrast media – 1hypnotic – 1illicit drug.						X			MAE - SPE	LC-MS ²	(Petrie et al., 2016)
94 18illicit drugs - 14antibiotics – 13anti-inflammatories - 12antidepressants – 6antihistamines - 5anticonvulsants – 4lipid regulators – 3stimulants - 2antiarrhythmics – 2antidepressants – 2antiparkinsons – 2antipsychotics – 2hypnotics - 1analgesic – 1anticholinergic – 1antidiabetic – 1antifungal – 1anti-inflammatory – 1antineoplastic – 1antiviral – 1bronchodilator – 1diuretic.					X	X			UAE	LC-MS ²	(Ivanová et al., 2018b)
127 32antibiotics – 13anti-inflammatories – 13hormones - 8antidepressants – 6antihistamines – 6antipsychotics - 5antibacterials – 4antihypertensives – 4antineoplastics – 4contrast medias – 4illicit drugs – 4lipid regulators - 3anticonvulsants – 3antifungals – 3hypnotics - 2analgesics – 2antiarrhythmics – 2antihelminthics – 2antiulcers - 1anticoagulant – 1antidiabetic – 1antiemetic – 1bronchodilator – 1diuretic – 1stimulant – 1vasodilator.					X	X	X		QuEChERS - dSPE	LC-MS ²	(Peysson and Vulliet, 2013)

(continued on next page)

Table 2 (continued)

Number of investigated PhCs	Detail of investigated therapeutic PhCs	Type of studied sludge										Extraction Instrumental		References
		A	B	C	D	E	F	G	H	protocol	analysis			
148	40antibiotics - 23illicit drugs - 15hypnotics - 13anti-inflammatories - 8anticonvulsants - 6antipsychotics - 5antihypertensives - 4lipid regulators - 3antibacterials - 3diuretics - 3stimulants - 2analgesics - 2antihistamines - 1antianxiety - 1antiarrhythmic - 1antidiabetic - 1antifungal - 1antiprotozoal - 1antitumor - 1bronchodilator - 1hormone.					X						UAE	LC-MS ²	(Gago-Ferrero et al., 2015)

improvement of analytical techniques and the expansion of the list of target compounds. These categories are considered as the relatively less studied categories with 53 detected compounds among 110 investigated, including bronchodilators (11%; 6), antidiabetics (11%; 3), antineoplastics (9%; 11), vasodilators (9%; 5), antibacterials (8%; 8), antiarrhythmics (8%; 6), antiulcers (8%; 3), antipsychotics (7%; 14), diuretics (7%; 7), anticoagulants (5%; 2), antiplatelets (4%; 2), antihelminthics (3%; 4), contrast media (3%; 4), antianxieties (2%; 21), antiprotozoals (2%; 2), antivirals (1%; 4), antigout (1%; 1), and antiemetic (1%; 1). The categories anticholinergics (1%; 1), and antiparkinsons (1%; 2) were not detected in sludge matrices.

Fig. 2 shows the proportion of each PhCs category throughout the total number of investigated compounds. The labels describe, for each category, the number of detected compounds relative to the total search for. The relatively less studied categories include 3 times less compounds than the most studied categories.

3.2. Main processes affecting the occurrence in sludge

3.2.1. Sorption mechanisms in sludge production processes

The mass balance studies investigated in this review highlight that a PhC quantity in the solid phase above 20% represents a strong affinity to the sludge solid phase compared to liquid phase (Ferhi et al., 2016; Petrie et al., 2014; Yang et al., 2016; Phan et al., 2018; Zhang and Li, 2018). Sludge characteristics (e.g., pH of the solution, the oxidation reduction potential, organic matter content, cation exchange capacity) are identified as factors affecting the partitioning of PhCs (Meijias et al., 2021; Hörsing et al., 2011; Chen et al., 2013). These variables can impact on their occurrence, through a similar type of sludge from 20% to 95%, and also correspond to concentrations of a few µg/kg (Östman et al., 2017; Lindberg et al., 2010; Jia et al., 2012).

Absorption and adsorption are considered as major interactions governing the PhCs partition between the aqueous and the solid phase of the wastewater (Verlicchi et al., 2012). Electrostatic interactions are more significant than hydrophobic interactions due to their high protein content of extracellular substances of organic matter (e.g. biomass implying lipophilic cellular membrane). This predominance is notable in sludge resulting from biological treatments than for high lipidic matrices as raw and primary sludge. In addition, other interactions occur, such as ion exchange, surface complexation with inorganic particles, metallic trace elements and divalent cations, and are considered as negligible (Golet et al., 2003; Tran et al., 2016; Schaffer and Licha, 2015).

The variable lipidic phase and biomass content of sludge may explain the variable PhCs partition on the solid phase in the different types of sludge, related to the implemented production and stabilization processes (Verlicchi and Zambello, 2015; Martín et al., 2012b; Phan et al., 2018; Östman et al., 2018). Fig. 3 schematically describes how the physical-chemical properties of both sludge and compounds can control the interactions between compounds and solid matrices: - The lipidic phase contributes to the affinity of hydrophobic compounds by absorption processes. - The organic matter plays a significant role, with protein content and associated aromaticity, increasing the adsorption of ionic PhCs on sludge and dissolved particles through major electrostatic interactions.

Biomass is known to be degradable with a residual fraction considered as refractory to biological processes. The availability of organic matter to change into stable humus under aerobic and anaerobic processes is schematically describe by coloring from green to red. Then, the increasing of fermentable character of sludge biomass implies modifications of the prevailing sludge properties and physical-chemical properties, which involve changes in sorption interactions. The modification of the fermentable sludge characteristics. Residual particulates, which are considered as the most refractory matter, always result from treatments, and constitute also the non-extractable fraction of sludge.

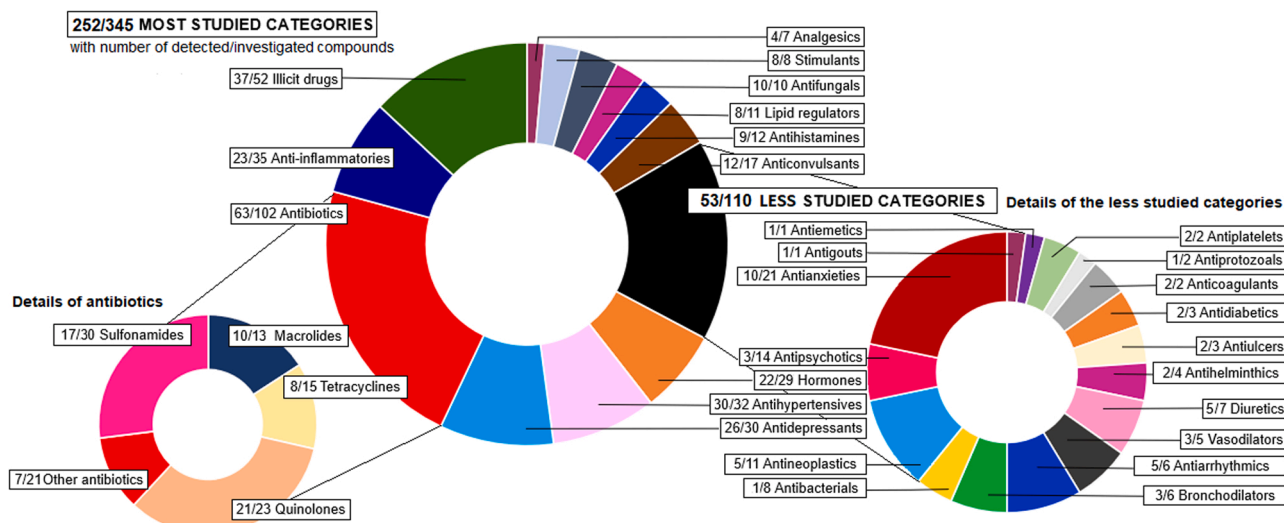


Fig. 2. Overview of detected therapeutical compounds in sludge detailing the ratio between the number of detected PhCs and the total number of investigated pharmaceuticals. The represented distribution of detected compounds in each category is given detailing the antibiotics and the relatively less studied categories. See references and data (Table 2, Tab.SM1).

3.2.1.1. *Absorption.* Hydrophobic interactions on suspended particles spontaneous occurs generally with non-polar or neutral PhCs (neutral aliphatic and aromatic groups) (Hyland et al., 2012), or with specific functional groups (e.g., halogens, heterocyclic aromatic groups with nitrogen, aromatic amines and amides) (Yan et al., 2014; Fernandez-Fontaina et al., 2016) (Fig. 3).

– Sludge properties.

Sludge composition can modify the sorption proportion of PhCs because of the hydrophobic interactions between PhCs and non-charged organic matter (lipophilic cell membrane of microorganisms, bacterial lipid structure) and the fatty fraction of the sludge (McClellan and Halden, 2010; Östman et al., 2018). The lipid content

of the primary sludge is quite comparable to that observed in the raw wastewater, whereas the lipid fraction decreases considerably in the secondary sludge. Therefore, PhCs absorption tends to decrease in secondary sludge with respect to primary sludge (Verlicchi and Zambello, 2015; Jelic et al., 2012; Ternes et al., 2005). Phan et al. 2018 confirm a strong positive correlation between the hydrophobicity of the compounds and their sorption onto primary sludge (Phan et al., 2018).

– PhCs properties.

The absorption capacity of non-ionic hydrophobic PhCs in sludge can be assessed based on the PhCs hydrophobicity through the octanol/water partition coefficient ($\log K_{ow}$). Sorption affinity can be estimated and classified in three categories according to the K_{ow} :

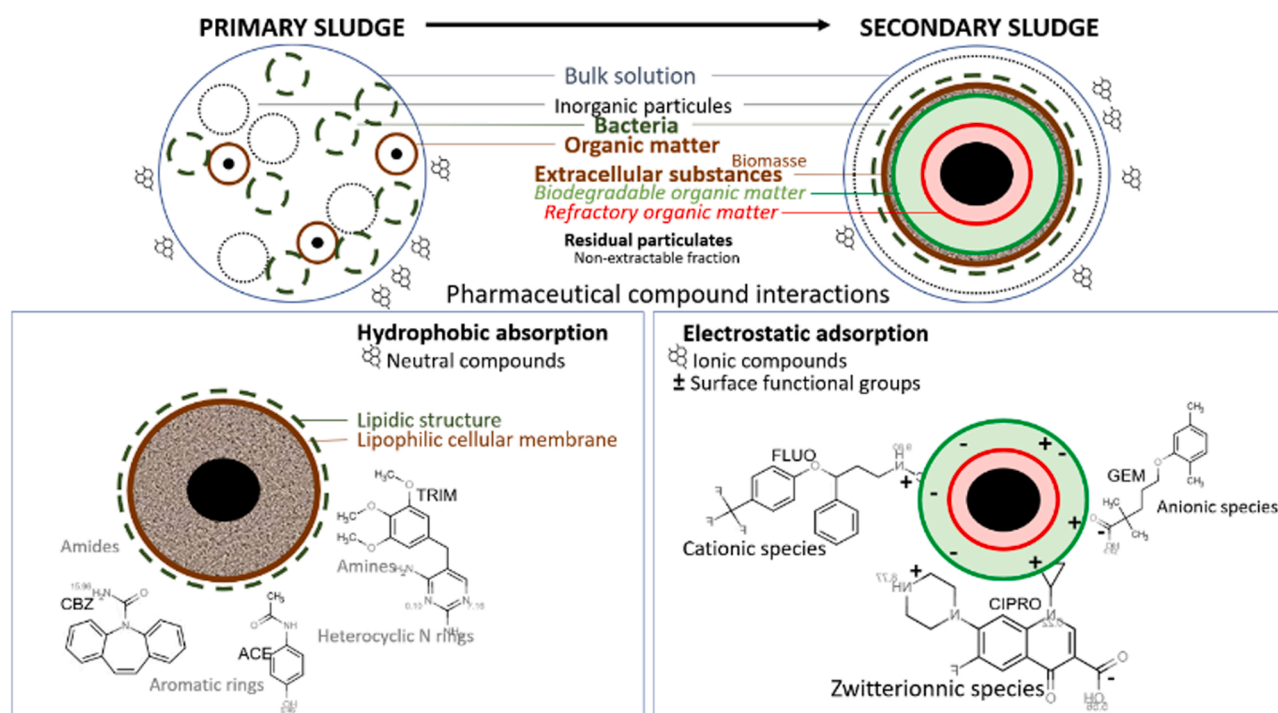


Fig. 3. Schematic sorption mechanisms explained through sludge composition. The concentricity presented is qualitative giving an order of magnitude on the evolution of the OM degradability and describing schematically the components in the primary and secondary sludge.

- Compounds with a high $\log K_{ow} \geq 4.0$ would tend to have a high sorption potential on suspended solids, such as most antifungals (e.g., miconazole, clotrimazole, econazole,) and antidepressants (Malmborg and Magnér, 2015; Gago-Ferrero et al., 2015).
- Compounds with a $\log K_{ow} \approx 2.5-4$ show moderate affinity to sludge such as estrogens type hormones (Nie et al., 2009; Nieto et al., 2008). Anti-inflammatories, showing such $\log K_{ow}$ variability, tend to kind heavily partition onto the particulate phase, explaining their levels higher in primary sludge than in other types of sludge (Martín et al., 2015).
- Compounds with a $\log K_{ow} \leq 2.5$ would often show a low or negligible sorption potential, as in the case of antihypertensives as beta-blockers, and analgesics (Vieno et al., 2007). A low $\log K_{ow}$ would explain the low concentrations of illicit drugs observed in sludge.

3.2.1.2. Adsorption. Electrostatic and Van Der Waals interactions with biomass increase the compounds affinity with the solid phase (Verlicchi et al., 2012; Jia et al., 2012; Göbel et al., 2007) (Fig. 3), mostly through their ionic state linked to pH-dependent functional groups (Hörsing et al., 2011; Kodešová et al., 2016). Also, the dissociation constant of functional groups (acidity constants as pK_{a1} , pK_{a2} etc) express the fraction of ionizable compounds in the considered sludge phases, whatever the variations of the WWTP conditions (Section 2.1, $pH=6.0-8.0$).

- Sludge properties.

The extend of electrostatic interactions are linked to the composition of organic matter, which define the nature of functional groups present on the sludge surface. Each functional surface group show a range of pK_a value independent on the type of biological sludge studied and its biomass composition (Lachassagne, 2015). The carboxyl groups (R-COOH) are found on protein compounds (proteins and amino acids), humic substances (humic and fulvic acids) and uronic acid. Their pK_a values remain within the same orders of magnitude ($pK_{a1}=2.5-4.6$, $pK_{a2}=4.7-5.6$). Phosphoric groups (R-POOH), generally associated with bacterial membranes, show higher pK_a values ($pK_{a3}=6.3-7.28$). The bacterial proteins and polysaccharide structures, which compose the organic fraction of sludge, present the respective functional amine groups R-NH₂ and hydroxyl groups R-OH with pK_{a4} in the range of 8.0–11.8 (Seleiman et al., 2020; Ternes et al., 2005; Lachassagne, 2015). Also, the isoelectric point pH_{zpc} (pH for which the positive and negative charges linked to the proteins are equivalent and the sum of electric charge is zero) is evaluated from 2.4 to 4.7 (Wang et al., 2015). Then, the high proportion of carboxyl and phosphoric groups involve a sludge surface negatively charged at sludge pH. It is important to note that predominance of negatively charged surface does not exclude positively charged surface associated with amine and hydroxyl groups.

- PhCs properties.

Studies also highlight the impact of the functional chemical groups of PhCs that play a major role in adsorption, regardless of their lipophilicity absorption capacity. Indeed, many PhCs can adsorb onto organic matter via electrostatic interactions though their several ionic state depending on their pK_a and the sludge pH (Schaffer and Licha, 2015). Therefore, positively charged PhCs (e.g., tetracyclines, quinolones, beta-blockers and macrolides – basic compounds) are highly adsorbed on the negatively charged surface of sludge (Ivanová et al., 2018a; Martín et al., 2015; Soulier et al., 2011; Wang et al., 2017). Moreover, PhCs mainly present in zwitterionic compounds (e.g., quinolones) or several forms tend to be strongly adsorbed by multiplying the interactions with functional groups of sludge matrices (Jia et al., 2012; Díaz-Cruz et al., 2003; Stevens-garmon et al., 2011). Negatively charged PhCs (e.g., sulfonamides, anti-inflammatories, lipid regulators, antihypertensives – acidic compounds) present fewer adsorption capacity due

to possible electrostatic repulsions with the mostly negative charge surface of sludge (Yan et al., 2014).

3.2.2. Biodegradation efficiency of sludge stabilization processes

In general, the observed PhCs concentrations in remaining sludge suggest their low degradability according to the biodegradation process capacity. Indeed, PhCs which present refractory degradable characteristics tend to be relatively low degradable through biomass activity and persist in matrices (Meijas et al., 2021). Although the main objective is to reduce the organic contaminant contents by mineralization, these stabilization processes generally allow to minimise the PhCs contents and then increase the treatments efficiencies.

The rates of PhCs biodegradation from the literature differ from the type of biomass and the physical-chemicals properties of target PhCs, modifying the concentrations into the liquid and the solid phases (Hörsing et al., 2011; Hyland et al., 2012; Stasinakis et al., 2013; Jia et al., 2012; Fernandez-Fontaina et al., 2016). Interestingly, sorption onto sludge of hydrophobic compounds ($\log D_{ow} > 1.5$) tends to inhibit biodegradation processes (Phan et al., 2018). The biodegradation effectiveness of hydrophobic compounds is varying from no efficiency, 0–80% while it exceeds 80% for hydrophilic compounds ($\log D_{ow} < 1.5$). This difference could be explained by the implication of sulfur or nitrogen in functional groups of the chemical structure, which tend to moderate their susceptibility to biodegradation.

Antibiotics are poorly degraded under sludge stabilization treatments due to their bactericide activity; nevertheless, antibiotics sub-categories, such as sulfonamides (sulfamerazine, sulfamethazine, sulfamethizole, sulfamethoxazole) and macrolides (clindamycin, erythromycin) are more susceptible to the biodegradation pathways, as illicit drugs, hypnotics, anticoagulants, analgesics (Ivanová et al., 2018a; Gao et al., 2012; Yang et al., 2019). Moreover, the presence of metabolites quantified in sludge and their progressive apparition during the monitoring of stabilization processes verified their susceptibility to degradation processes. Indeed, it appears for instance that antidepressants metabolites are more detectable in stabilized sludge (>60%) than in sewage sludge (6–75%) (Tab.SM1).

Meijas et al., 2021 resumes that specific microbial communities are responsible for compound degradation depending on PhCs functional groups, which can be more susceptible to degradation processes than other groups that are considered as recalcitrant (Meijas et al., 2021). Depending on the sludge treatment process, and associated prevailing conditions, biodegradation would be more or less efficient. This process is described below.

3.2.2.1. Digestion stabilization. Thickening and dewatering stabilization methods seem not to significantly affect the PhCs content in sludge (Semblante et al., 2015), even if they would provide aerobic conditions favorable to the degradation of the compounds (Garcia-Rodríguez et al., 2014). Contrasting with thickening and dewatering processes, stabilization by digestion reduce PhCs concentrations for most compounds (Ivanová et al., 2018a; Verlicchi and Zambello, 2015; Ashfaq et al., 2017; Garcia-Rodríguez et al., 2014; Martín et al., 2012b, 2015; Radjenović et al., 2009). The process of stabilization by digestion contributes to the reduction of particle size, allowing a better PhCs biodegradation from the microorganisms communities (Golet et al., 2003). The biodegradation efficiencies of sludge treatment by digestion differ depending on the aerobic or anaerobic conditions (Ivanová et al., 2018a; Venegas et al., 2021; Joss et al., 2005; Falas et al., 2016). Literature suggests that treatment processes under aerobic conditions (aeration tank, aerobic digestion and composting) promote the PhCs removal by biological degradation (Martín et al., 2012a; Semblante et al., 2015). Nevertheless, some antibiotics such as fluoroquinolones-type (e.g., ciprofloxacin, norfloxacin, ofloxacin) appears to remain resistant to stabilization processes (Verlicchi and Zambello, 2015; Ezzariai et al., 2018; Chenxi et al., 2008; Iranzo et al.,

2018b). Under anaerobic conditions, Gonzalez-Gil et al., 2016 showed biotransformation efficiency higher than 50% for fluoxetine, citalopram, and antibiotics as roxithromycin, sulfamethazine, trimethoprim (Gonzalez-Gil et al., 2016). However, literature considered biodegradation as reduced process under anaerobic conditions leading to increase sorption processes (Martín et al., 2012b; Semblante et al., 2015; Boix et al., 2016).

3.2.2.2. Composting. Placed among the most promising treatments, sludge composting allows further biological hygienization by the action of microorganisms on organic matter and permit amendment on agricultural soil (Suh and Rousseaux, 2002; Apedaile, 2001). The contaminant removal are based on the differences in concentrations measured in the initial and final compost mixtures and express the removal due to the composting process only (Lü et al., 2021a; Ezzariai et al., 2018; Martín et al., 2015), but effectiveness could also be compared to WWTP sludge output. In that last case, the contribution of carbonaceous structures needs to be considered in the material balances to correctly consider the effectiveness of the process by the dilution effect of organic waste addition. Though effectiveness depends on target compounds variation in composting materials and method used, most of the PhCs would remain present in the matrix with residual concentrations ranging hundreds of $\mu\text{g}/\text{kg}$ (dw) (Verlicchi and Zambello, 2015; Martín et al., 2012a; Sheng et al., 2021). The storage time, or maturation, would be the most significant factor to reduce PhCs contents and allowing mineralization through microbial activity (Arun et al., 2020; Chenxi et al., 2008; Camotti Bastos et al., 2020). The total PhCs degradation would take place over both (i) short timescales, over 0–15days for 43% removal, for clarithromycin for instance, and (ii) longer time scale, over 35–120days for 36% and 75% removal for lincomycin and tetracycline, respectively (Khadra et al., 2019). Moreover, concentrated compounds in sludge such as antibiotics present degradation effectiveness up to 98% for fluoroquinolones, ranging from 70% to 99% for tetracyclines and a lesser extend for sulfonamides and macrolides, with highly variable rates of 45–95% and 25–48%, respectively (Ezzariai et al., 2018; Malmberg and Magnér, 2015; Yang et al., 2016; Semblante et al., 2015).

To summarize, PhCs removal from sludge may be carried out by different techniques with variable degree of efficiency depending on the

physical-chemical properties of target compounds, time, and treatment method. Partial removal can be achieved through suspended solids stabilization processes that promote biodegradation of compounds. A microbial activity inhibition was observed due to the PhCs persistence, at low concentrations or long term (Meijas et al., 2021), which could lead to residual concentrations of many therapeutical PhCs (e.g., antibiotics, antidepressants, anti-inflammatories, antihypertensives) in the order of mg/kg (Gao et al., 2012; Verlicchi et al., 2012; Petrie et al., 2014; Pomies, 2013). Also, sequestration, release or stabilization by organic fractions of PhCs over the long term is poorly discussed in the literature (Lü et al., 2021a; Aemig et al., 2019), as the formation of non-extractable residues is briefly identified or raised by questions about the bioavailability limit of compounds.

3.3. Variability of PhCs concentrations in sludge

The multiple socio-economic factors can influence the PhCs concentrations, and important contrast can be observed at a different scale. Indeed, the use of pharmaceuticals differs among countries according to the health care practices and the economic level. Moreover, seasonal variations in the PhCs use may occur, specifically for antibiotics; the consumption impacts the subsequent concentration levels in wastewater and thus the presence in the solid phase (Gao et al., 2012; Martín et al., 2012b). Finally, the PhCs concentrations also depend on the compound's metabolization and excretion rates varying between individuals (e.g., age, lifestyle). Hence, the origin of the influents and the different applied treatment processes (wastewater treatments, sludge production and stabilization processes) constrain PhCs concentrations in sludge, ranging from analytical method limits to several mg/kg (dw).

This section is based on a treatment of all the collected data and presents the information in several ways to first provide an overview of all data, integrated in therapeutical categories and showing their overall detection frequencies and concentration medians observed in sludge. Hence, this section provides a solid foundation for identifying the compounds most likely to persist in sludge by detailing the variability of concentrations ranges for all quantified compounds, based on the number of matrices studied. In addition, an in-depth analysis of the characteristics of the compounds that may explain their affinity in

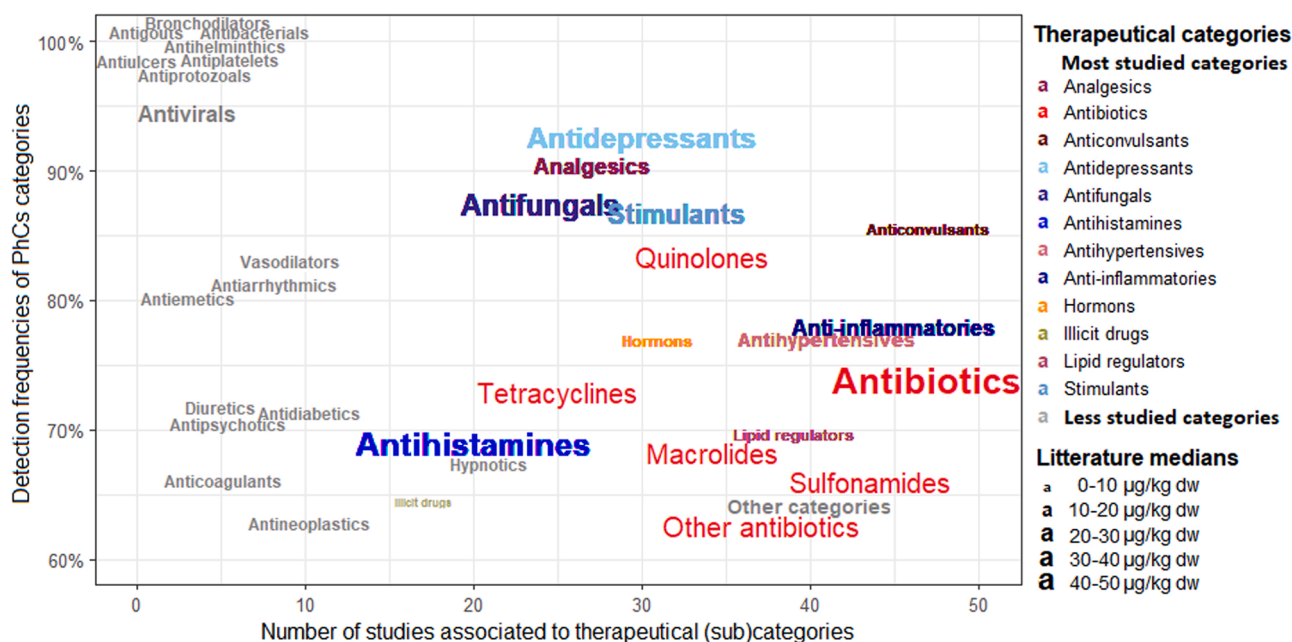


Fig. 4. Overview of detection frequencies of therapeutic categories and subcategories in sludge matrices, according to the number of studies and depending on the detected pharmaceuticals from the literature collected data. This assessment describes the sludge detection frequencies of each detected therapeutic category with placement depending on the number of studies referring them, and size corresponding of their estimated medians from pharmaceuticals search for.

sludge and their residual occurrence in those environmental matrices is presented.

3.3.1. Overall occurrence of pharmaceuticals

Fig. 4 gives a synthetic global appreciation of the 32 detected categories in the reviewed studies according to the overall PhCs detection frequencies. These detection frequencies in sludge matrices, for each therapeutic category, are calculated by the ratio of the overall number of detections by the number of investigations given across all studies. Each category is represented in a specific color for the most studied categories and in grey for the overall relatively less studied categories. The size of the category name gives an idea on prevalence occurrence of some categories by their size corresponding to a range of the overall median concentrations in $\mu\text{g}/\text{kg}$ (dw). This assessment gives the current state of knowledge considering the potential bias due to the representativeness of over-investigated PhCs in sludge. Then, all the detected categories present detection frequencies over 60% in sludge.

This representation highlights that the categories which are more studied do not present the highest detection frequency nor the highest median concentrations. Indeed, by this figure it can be noted that antidepressants need more attention with detection frequencies above 90% with median around $\sim 43 \mu\text{g}/\text{kg}$, or antifungals and stimulants at 88%, with respectively $\sim 47 \mu\text{g}/\text{kg}$ $\sim 37 \mu\text{g}/\text{kg}$ (dw). Antihistamines, although less detected, would have median levels (69%, $\sim 50 \mu\text{g}/\text{kg}$) higher than other categories such as analgesics (90%, $\sim 24 \mu\text{g}/\text{kg}$), anti-inflammatories (78%, $\sim 24 \mu\text{g}/\text{kg}$), antihypertensives (77%, $\sim 20 \mu\text{g}/\text{kg}$) or anticonvulsants (86%, $\sim 12 \mu\text{g}/\text{kg}$). On the other hand, lipid regulators and hormones have similar median levels to anticonvulsants ($\sim 13 \mu\text{g}/\text{kg}$) with lower detection frequencies of 70% and 77%, respectively. Illicit drugs represent the least detected and least concentrated category (65%, $\sim 6 \mu\text{g}/\text{kg}$). In general, the relatively less studied categories are at the same level of detection as the generally most studied categories. Their median content is equivalent to around $15 \mu\text{g}/\text{kg}$. In this way, Fig. 4 makes explicit the lack of data related to the relatively less studied pharmaceutical categories, represented on the left side of the figure with less than 20 references, for which the detection frequencies are close to 100% due to their detection in the limited studies that address them.

Fig. 4 provides, on the grounds of current knowledge, a grading of

each therapeutic category based on the frequencies of quantification and the number of associated studies. This highlights the compounds that may require further attention by experts.

3.3.2. Reviewed concentrations ranges

The following sections provide summaries of the concentration range of the quantified pharmaceuticals in sludge, with completion of detection frequencies from the studies, when literature values are available. Tab.SM1 summarizes findings for each compound throughout the reviewed papers. PhCs are detailed by their concentration ranges through their minimum, maximum, and median concentrations in all studied sludge, according to Figs. 5–8. These reviewed concentrations are shown by a vertical line between the lowest MQL and the highest observed concentrations, for each compound classified by their therapeutic category. High concentrations values can be due either to layouts or exceptional concentrations quantified during specific pollution peak or specific sampling site. To minimize the weight of outliers, medians are compiled and shown by a horizontal line. Also, descriptions of reviewed PhCs are completed by specified detection frequencies for each type of sludge, if applicable (Clarke and Smith, 2011; Tarpani et al., 2020; Zhang et al., 2017; Costa et al., 2017; Suh and Rousseaux, 2002; Golet et al., 2003; Hörsing et al., 2011; Hyland et al., 2012; Jelic et al., 2012; Huang et al., 2014; Liu et al., 2019; Ferhi et al., 2016; Cao et al., 2016; Gonzalez-Gil et al., 2016; Bourdat-Deschamps et al., 2017b; Khadra et al., 2019; Drillia et al., 2005; Carballa et al., 2007; Gao et al., 2012).

Among the 305 quantified PhCs, 84 pharmaceuticals were not mentioned in previous literature reviews. They are identified on Figs. 5 to 8 by an asterisk (*) in front of their acronyms. These PhCs with concentrations that range from close to the detection limits up to several mg/kg (dw) include 12antibiotics (Fig. 5), 2 antifungals, 1 antidepressant, 9 anti-inflammatories, 2 antihistamines (Fig. 6), 6antihypertensives, 10 hormones, 1 lipid regulator, 1 anticonvulsant (Fig. 7), 19 illicit drugs and 19 relatively less studied pharmaceuticals as 4 antianxieties – 2 antiarrhythmic – 1 antibacterial – 1 anticoagulant – 1 antigout – 2 antihelminthics – 2 antineoplastics – 1 antiprotozoal – 1 antipsychotic – 1 antiulcer – 2 diuretics – 1 vasodilator (Fig. 8).

3.3.2.1. Antibiotics. Fig. 5 represents concentration ranges of quantified

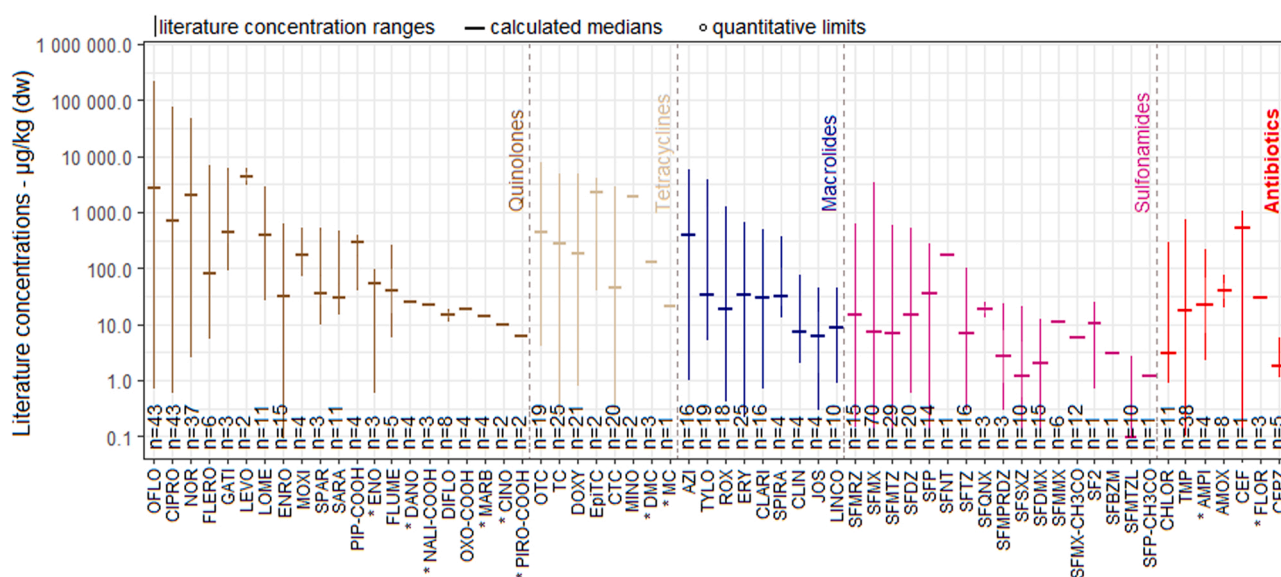


Fig. 5. Sludge concentrations of 62 quantified antibiotics among 21 quinolones, 8 tetracyclines, 9 macrolides, 17 sulfonamides and 7 other antibiotics. Variability of PhCs concentrations is presented from the least to the highest quantified concentration (|), showing the calculated median concentrations (-) from the overall literature studies. In addition, the number of sludge matrices studied over the studies is specified (n = x). See references and data (Table 2, Tab.SM1). The asterisk (*) indicates PhCs identified for the first time in a literature review.

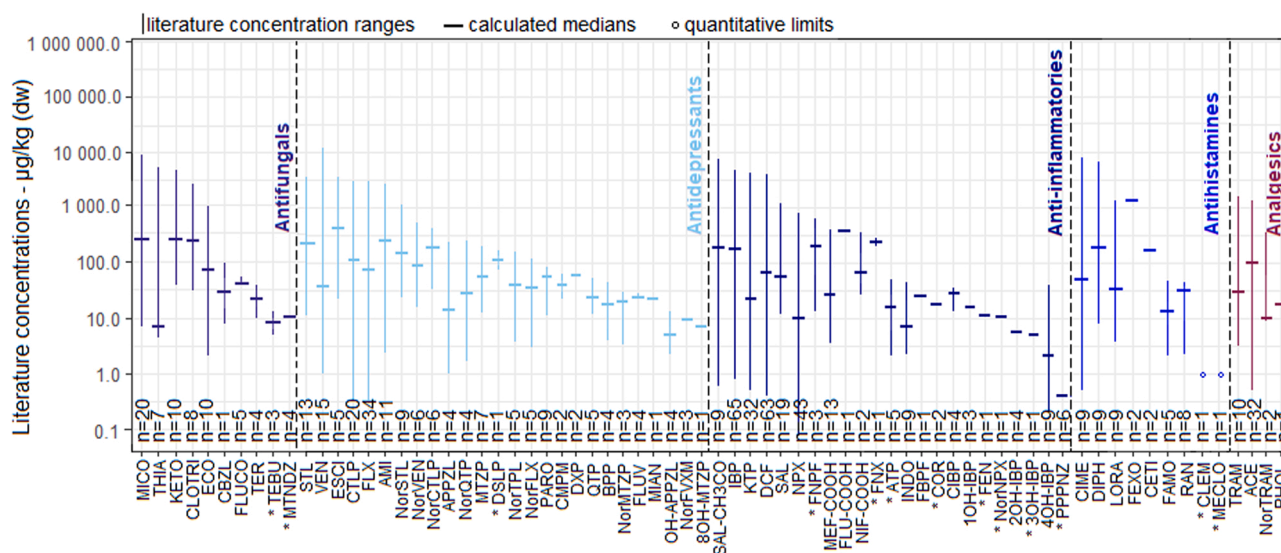


Fig. 6. Sludge concentrations of 10 antifungals, 26 antidepressants, 23 anti-inflammatories, 9 antihistamines and 4 analgesics. Variability of PhCs concentrations is presented from the least to the highest quantified concentration (\square), showing the calculated median concentrations (-) from the overall literature studies. In addition, the number of sludge matrices studied over the studies is specified ($n = x$). See references and data (Table 2, Tab.SM1). The asterisk (*) indicates PhCs identified for the first time in a literature review.

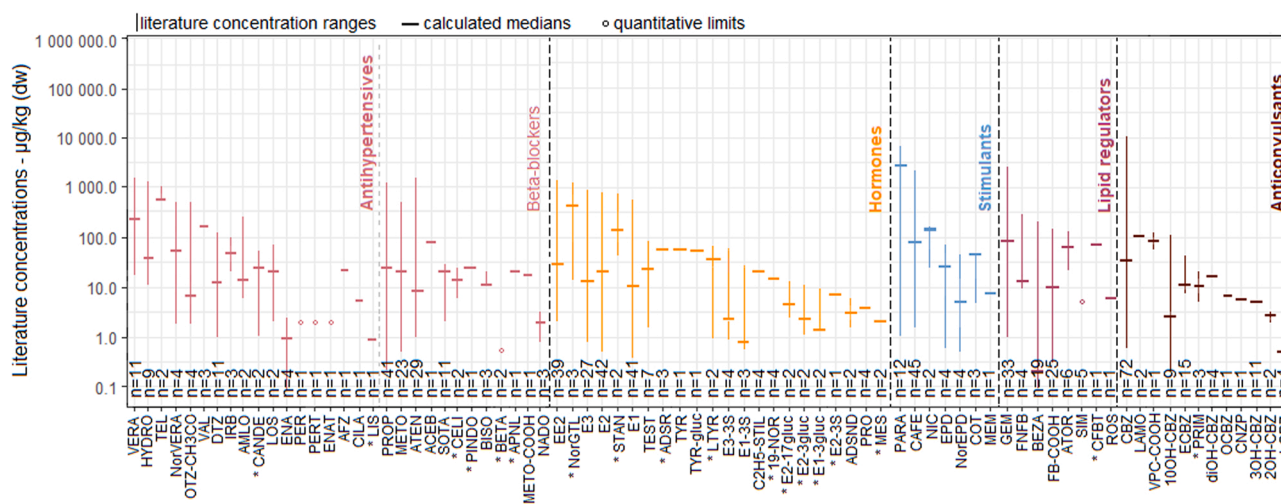


Fig. 7. Sludge concentrations of 30 antihypertensives including 12 beta-blockers, 22 hormones, 7 stimulants, 8 lipid regulators, and 12 anticonvulsants. Variability of PhCs concentrations is presented from the least to the highest quantified concentration (\square), showing the calculated median concentrations (-) from the overall literature studies. In addition, the number of sludge matrices studied over the studies is specified ($n = x$). See references and data (Table 2, Tab.SM1). The asterisk (*) indicates PhCs identified for the first time in a literature review.

antibiotics, the most studied category, which show the highest concentrations in sludge matrices varying widely from 3 to over 5 orders of magnitude. Antibiotic concentrations range generally from the MQLs of a few $\mu\text{g}/\text{kg}$ to tens of mg/kg (dw). Quinolones show the highest observed concentrations reaching occasionally hundreds of mg/kg . Tetracyclines and macrolides present concentration varying over 4 orders of magnitude, with the highest concentrations reaching a few mg/kg . Sulfonamides and other antibiotics show concentrations one order of magnitude lower with the highest concentrations in the range of hundreds of $\mu\text{g}/\text{kg}$ (dw). Given the large number of compounds identified in the sludge, a detailed description of antibiotics, the omnipresent therapeutic category is given (Fig. 5, Tab.SM1).

Regarding the quinolones, ofloxacin (OFLO), ciprofloxacin (CIPRO), and norfloxacin (NOR) show the highest concentrations (dw) up to 232 mg/kg , 82 mg/kg , and 50 mg/kg respectively with medians of 1–3 mg/kg . These compounds are the most studied and show non-

negligible concentrations through more than 35 matrices and detection occurrence of 75% in studied matrices. High differences between raw sludge and sewage sludge appears for CIPRO, NOR and OFLO, for which concentrations tend to increase of at least 2 orders of magnitude (Okuda et al., 2009; Jia et al., 2012). Stabilization processes greatly impact CIPRO with reduced concentrations from 2 to 7 times the initial levels (Ferhi et al., 2016; Tang et al., 2012; Jia et al., 2012) while other studies suspect no impact with concentrations above the hundreds of $\mu\text{g}/\text{kg}$ to tens of mg/kg (dw) (Martín et al., 2015; Mailler et al., 2017). NOR and OFLO are quantified as constant whatever the involved stabilization process, also presenting concentrations in the same orders of magnitude. The concentrations of fleroxacin (FLERO), gatifloxacin (GATI), levofloxacin (LEVO), lomefloxacin (LOME) reach up to a few mg/kg (dw). Their median concentrations are in the order of a few hundreds of $\mu\text{g}/\text{kg}$ considerably lower than for OFLO, CIPRO, and NOR. These compounds are studied in less than 10 matrices. LEVO present a

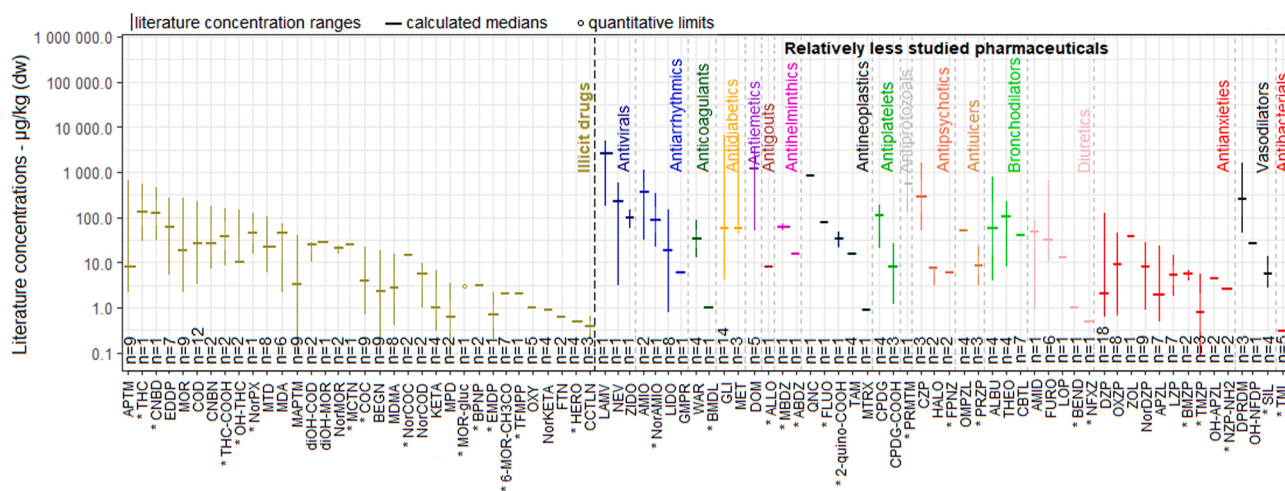


Fig. 8. Sludge concentration of 34 illicit drugs and 51 other PhCs considered as less studied (3 antivirals, 4 antiarrhythmics, 2 anticoagulants, 2 antidiabetics, 1 antiemetic, 1 antigout, 2 anthelmintics, 5 antineoplastics, 2 antiplatelets, 1 antiprotozoal, 3 antipsychotics, 2 antiulcers, 3 bronchodilators, 5 diuretics, 11 anti-anxieties, 3 vasodilators, 1 antibacterial). Variability of PhCs concentrations is presented from the least to the highest quantified concentration (\square), showing the calculated median concentrations (-) from the overall literature studies. In addition, the number of sludge matrices studied over the studies is specified ($n = x$). See references and data (Table 2, Tab.SM1). The asterisk (*) indicates PhCs identified for the first time in a literature review.

much lower concentration variability compared to the other 4 compounds as it was searched in only 2 sewage sludge matrices. The 13 other quinolones, which are studied in less than 10 sludge matrices, are usually observed in concentration below 1 mg/kg (dw). The 6 newly identified quinolones in sludge were quantified at levels reaching a hundred of $\mu\text{g}/\text{kg}$ for enoxacin (ENO) and a few to a twenty $\mu\text{g}/\text{kg}$ (dw), for danofloxacin (DANO), nalidixic acid (NALI), marbofloxacin (MARB), cinoxacin (CINO), and priomidic acid (PIRO-COOH). The most concentrated quinolones are the most detected (67–100%) in sewage sludge, while those showing lower concentrations, below 1 mg/kg, are poorly detected (9%–44%), in sewage sludge, but for enrofloxacin (ENRO) which still show a high detection frequency of 27–100% (Fig. 5 brown, Tab.SM1). Quinolones with concentrations in the range of mg/kg (dw) present decreasing sensibility to stabilization processes from high (ENRO, FLERO, GATI) to low (SARA, SPAR), including PhCs contents with no difference in the matrices from the same processes (LOME, MOXI, PIPE) (Jia et al., 2012).

Tetracyclines show significant concentrations in sludge reaching a few mg/kg. The highest observed concentrations for oxytetracycline (OTC), tetracycline (TC), doxycycline (DOXY) epitetracycline (EpiTC) and chlortetracycline (CTC) ranging from 7 to 4 mg/kg (dw), with significantly high medians of 450 $\mu\text{g}/\text{kg}$, 280 $\mu\text{g}/\text{kg}$, 180 $\mu\text{g}/\text{kg}$, 2000 $\mu\text{g}/\text{kg}$, 60 $\mu\text{g}/\text{kg}$ respectively. Minocycline (MINO) was quantified only once in sewage sludge but with a non-negligible average value of 1.9 mg/kg (dw) (Fig. 5 beige, Tab.SM1). The two newly tetracyclines demeclocycline (DMC) and methacycline (MC) were quantified at relatively lower contents as 131 $\mu\text{g}/\text{kg}$ and 21 $\mu\text{g}/\text{kg}$ (dw).

Regarding macrolides, only 3 of the 9 detected compounds show concentrations up to a few mg/kg. The most concentrated macrolides by decreasing concentrations are azithromycin (AZI), tylosin (TYLO), roxithromycin (ROXI), erythromycin (ERY), and clarithromycin (CLARI), which show maximum concentrations (dw) at respectively 6 mg/kg, 4 mg/kg, 1.3 mg/kg, 0.7 mg/kg, and 0.5 mg/kg. The median of AZI is significantly higher, around 400 $\mu\text{g}/\text{kg}$, than the other compounds reaching 30 $\mu\text{g}/\text{kg}$ in average. Tetracyclines as ERY, AZI, LINCO and ROXI show 2 times lower concentrations until undetectable values comparing digested sludge to raw sludge (Gonzalez-Gil et al., 2016; Gao et al., 2012; Mailler et al., 2017; Radjenović et al., 2009). Macrolides are detected in more than 50% of studied sludge with a tendency of decreasing concentrations along with sludge stabilization processes. Contrarily to other macrolides, TYLO was only detected in 4SS and never detected in stabilized sludge even if 11 matrices were studied (Fig. 5

blue, Tab.SM1).

Concentrations of sulfonamides are overall lower than that of the previous subcategories, and never exceed 1 mg/kg regardless. Their detection frequencies are quite variable ranging from 5% to 100% for sewage sludge and below 80% for stabilized sludge, generally closer to 25%. Sulfamethoxazole (SFMX) show the highest recorded concentration for this category, reaching 3347 $\mu\text{g}/\text{kg}$. Also, other concentrated sulfonamides (sulfamerazine SFMRZ, sulfamethazine SFMTZ, sulfadiazine SFDZ) were quantified lower than 668 $\mu\text{g}/\text{kg}$ and medians remains relatively low. Indeed, sulfonamides medians are mostly ranging from a few $\mu\text{g}/\text{kg}$ to 30 $\mu\text{g}/\text{kg}$ (Fig. 5 pink, Tab.SM1). SFMX concentrations seems to be consistently reduced by digestion until detection limits (Gonzalez-Gil et al., 2016; Martín et al., 2012b), while SFDZ presents no concentration variability through stabilization processes (Gao et al., 2012).

Other antibiotics such as trimethoprim (TMP) have been widely studied; however, it presents low concentrations below 845 $\mu\text{g}/\text{kg}$, with higher contents in sewage sludge compared to raw sludge (Gonzalez-Gil et al., 2016) and no differences after digestion processes (Radjenović et al., 2009). Chloramphenicol (CHLOR) also show a range of concentrations up to hundreds $\mu\text{g}/\text{kg}$ but is relatively less frequently detected and rarely in stabilized sludge (1%). It appears that no antibiotics of the penicillin-type were detected in sludge matrices excepted for ampicillin (AMPI), newly detected, and amoxicillin (AMOX) presenting maximum concentrations in sewage sludge at 231 $\mu\text{g}/\text{kg}$ and 79 $\mu\text{g}/\text{kg}$ (dw) respectively. Florfenicol (FLOR), recently detected, was quantified at levels close to ampicillin or macrolides, around 30 $\mu\text{g}/\text{kg}$ (dw). Similarly, cefradine (CEF) and cefoperazone (CFPRZ) as cephalosporin-type antibiotics were detected in sewage and stabilized sludge but at concentrations reaching 1.1 mg/kg or near the MQLs, respectively (Fig. 5 red, Tab.SM1).

The concentrations of the other PhCs widely vary from MDLs and MQLs of a few $\mu\text{g}/\text{kg}$ to a maximum of tens mg/kg, depending on compounds. However, the PhCs concentration ranges do not exceed 3 orders of magnitude except for the most concentrated PhCs, which can reach 4 orders of magnitude.

The antifungals, antidepressants, anti-inflammatories, analgesics, and antihistamines present the highest concentrated categories after antibiotics, with medians ranging mostly between ten to hundreds of $\mu\text{g}/\text{kg}$ (Fig. 6, Tab.SM1). Some compounds have been quantified at concentrations above 1 mg/kg (dw) (e.g., antifungals miconazole MICO, thiabendazole THIA, ketoconazole KETO, antidepressants sertraline

SER, venlafaxine VEN, escitalopram ESCI, citalopram CTLP, anti-inflammatories acetyl-salicylic acid SAL-CH₃CO, ibuprofen IBU, ketoprofen KTP, diclofenac DCF, antihistamines cimetidine CIME, diphenhydramine DIPH, loratadine LORA, fexofenadine FEXO, and analgesics tramadol TRAM, acetaminophen ACE), but their medians are mostly between ten to hundreds of µg/kg as the other PhCs in the same categories.

3.3.2.2. Antifungals. Antifungal's interest increases in research, appearing, for some of them, at orders of magnitude higher than macrolides and antidepressants with maxima of several mg/kg. Miconazole (MICO), thiabendazole (THIA), ketoconazole (KETO), clotrimazole (CLOTRI), and econazole (ECO) represent concentrations (dw) from 1 up to 10 mg/kg with medians varying between a few µg/kg to 250 µg/kg (250 µg/kg, 7 µg/kg, 250 µg/kg, 240 µg/kg, 70 µg/kg respectively). Metronidazole (MTNDZ) and tebuconazole (TEBU), two recently identified antifungals, were quantified at levels up to tens µg/kg (dw). The antifungal's detection frequency is usually over 50% and 60% in sewage sludge and stabilized sludge, respectively (Fig. 6 blue, Tab.SM1).

3.3.2.3. Antidepressants. Antidepressants are highly detected in sludge matrices, showing concentrations from MQLs up to 11.4 mg/kg, which is achieved by venlafaxine (VEN), with a median around 40 µg/kg. The mostly studied compounds exceed 1 mg/kg (dw): sertraline (STL), escitalopram (ESCI), citalopram (CTLP), fluoxetine (FLX), and amitriptyline (AMI) showing variable median of tens to hundreds of µg/kg (e.g., 220 µg/kg, 440 µg/kg, 110 µg/kg, 70 µg/kg, and 250 µg/kg respectively). Regardless of the treatment processes applied, detection frequencies are mostly of 100%, except for the lowest concentrated compounds such as paroxetine (PARO), bupropion (BPP), fluvoxamine (FLUV), mianserin (MIAN), which shows detection frequencies lower than 25% (Ivanová et al., 2018a; Subedi et al., 2017; Ait-Aissa et al., 2014). These compounds show relatively low concentrations below 91 µg/kg (dw) (Fig. 6 skyblue, Tab.SM1).

3.3.2.4. Anti-inflammatories. Anti-inflammatory compounds are among the most studied categories according to the number of reviewed papers that include this category (Fig. 4, Table 2, Tab.SM1). It also appears that they are more studied in stabilized sludge with detection frequencies highly variable from 51% to 100%. Their maximum concentrations can reach several mg/kg (dw) (e.g., ibuprofen IBP, diclofenac DCF, ketoprofen KTP, acetylsalicylic acid SAL-CH₃CO). This most concentrated anti-inflammatories are researched in more than 20 matrices. SAL-CH₃CO was researched in just 6 sludge matrices but showed highest concentrations than IBP, which have a median around 180 µg/kg (dw). Metabolites show concentrations highly negligible compared to their parent compounds around MQLs up to 15 µg/kg (dw). KTP and DCF are quantified at maximums in the same orders around 5 mg/kg, but their medians differ with 70 µg/kg and 20 µg/kg. Salicylic acid (SAL) and naproxen (NPX) present maximums concentrations 4 times lower reaching 1 mg/kg (dw), but medians in the same order of magnitude going from 25 µg/kg to 50 µg/kg (dw). Anti-inflammatories with maximum concentrations below 1 mg/kg (dw) are relatively less studied (N < 10). This review, showing high observed concentrations, leads to quite high medians for recently observed anti-inflammatories, fenoprofen (FNPF), flufenamic acid (FLU-COOH), and flunixin (FNX) ranging from 250 µg/kg to 370 µg/kg compared to mefenamic acid (MEF-COOH), niflumic acid (NIF-COOH), azathioprine (ATP), also recently identified, and indomethacin (INDO) with medians below 50 µg/kg (Fig. 6 darkblue, Tab.SM1).

3.3.2.5. Antihistamines. Antihistamines show high concentrations reaching a few mg/kg (dw). Cimetidine (CIME), diphenhydramine (DIPH), and loratadine (LORA) are the most concentrated compounds with maximums concentrations (dw) up to 8,7 and 1 mg/kg and

medians of 50 µg/kg, 180 µg/kg, and 40 µg/kg, respectively. Other antihistamines show concentrations close to the detection and quantification method limits (Fig. 6 petroleum, Tab.SM1). Fluoxetine (FLUO) mean to have sensibility to stabilization processes or composting because of it significantly reduced contents between processes until 6 times reduced contents (84 Ferhi, 86 Gonzalez, 85 Bourdat, 84 Ferhi).

3.3.2.6. Analgesics. Analgesics were quantified in most of the studies that investigated them occasionally reaching concentrations up to 1.7 mg/kg, even if a wide variable detection frequency is noted (3–100%). Tramadol (TRAM) and acetaminophen (ACE) are quantified in more than 10 matrices, with medians around 30 µg/kg and 100 µg/kg, respectively (Fig. 6 wine, Tab.SM1).

Fig. 7 shows that concentrations of antihypertensives, hormones, stimulants, lipid regulators and anticonvulsants do not exceed 1 mg/kg, with some of exceptions (e.g., verapamil VERA, hydrochlorothiazide HYDRO, telmisartan TEL, propranolol PROP, paraxanthine PARA, caffeine CAFE, gemfibrozil GEM, and carbamazepine CBZ) (Fig. 7, Tab. SM1).

3.3.2.7. Antihypertensives. Eleven antihypertensives are studied, but only 3 compounds (verapamil VERA, hydrochlorothiazide HYDRO, and telmisartan TEL) exceed 1 mg/kg reaching no more than 2 mg/kg. TEL and VERA are quantified with higher medians than HYDRO respectively 530 µg/kg, 220 µg/kg and 40 µg/kg. These compounds show relatively high detection frequencies ranging from 57% to 100%, regardless of the type of sludge. Similar variable detection frequencies from studies are observed among the beta-blockers, which are mostly quantified close to the MQLs. Medians range from a few µg/kg to 20 µg/kg (dw) even if beta-blockers are mostly researched in more than 20 studies (e.g., propranolol PROP, metoprolol METO, atenolol ATEN) (Fig. 7 pink, Tab. SM1). No differences are distinguished during stabilization processes on antihypertensives beta-blockers as ATEN, METO, PROP, SOTA or also bisoprolol BISO and celiprolol CELL, for concentrations lower than 100 µg/kg (dw) (Scheurer et al., 2010; Martín et al., 2015).

3.3.2.8. Hormones. Hormones are among the most studied and quantified category with 22 quantified compounds out of 27 investigated in almost all the sludge matrices with 10 recently identified compounds (e.g., estrone E1, 17-beta-estradiol E2, 17-alpha-ethinylestradiol EE2, estrone E3) (Fig. 7 orange, Tab.SM1). This category present concentrations extremely variables, but lower than previous described remaining to a few tens to hundred µg/kg (dw).

3.3.2.9. Stimulants. Caffeine presents the most referenced stimulant, constantly detected and reaching up to 2.3 mg/kg (dw). Paraxanthine (PARA) presents concentrations higher than CAFE reaching 6.2 mg/kg. However, it appears in only 4 studies at detection frequencies around 5%. Excepting these two stimulants, the category presents relatively low concentrations not exceeding hundreds of µg/kg (dw) (Fig. 7 blue, Tab. SM1).

3.3.2.10. Lipid regulators. Lipid regulators present concentrations in the order of a few mg/kg (dw), orders similar to the previous mentioned categories. Gemfibrozil (GEM) is the most concentrated and studied lipid regulator presenting maximum concentrations of 2 mg/kg and a median of 80 µg/kg. The other lipid regulators were quantified around hundreds of µg/kg (dw) (e.g., fenbufen FNBF, bezafibrate BEZA, clofibric acid CFB-COOH, and atorvastatin ATOR) except for rosuvastatin with a very low quantification at 6 µg/kg. Their medians are relatively low compared to GEM reaching up to 60 µg/kg. Clofibrate (CFBT), a recently identified compound, was also quantified in similar levels of 70 µg/kg (dw). Lipid regulators present variable detection frequencies ranging from 25% to 100% in sewage sludge and 42–100% in stabilized sludge. This observation is also approved for stimulants (Fig. 7 magenta,

Tab.SM1).

3.3.2.11. Anticonvulsants. Among the 17 investigated anticonvulsants, this category figures as the most studied category (Fig. 4), including 12 quantified compounds among carbamazepine (CBZ), which is considered as a tracer in WWTP studies because of its persistence through treatment processes (Table 2, Tab.SM1) (Martín et al., 2010, 2015). It reaches concentrations around 11 mg/kg and a median of 30 µg/kg in sludge matrices with detection frequencies above 40%. Its metabolites (e.g., epoxy-carbamazepine ECBZ, oxcarbamazepine OCBZ, licarbamazepine LCBZ) present a lower occurrence in sludge, with detection frequencies around 20% and 60% in sewage and stabilized sludge, respectively. The maximum concentrations of metabolites present 3–4 orders of magnitude lower with quantification limits at 20 µg/kg. The other anticonvulsants, valproic acid (VPC-COOH), lamotrigine (LAMO), primidone (PRIM), a recently identified compound, are relatively less concentrated than CBZ, with concentrations varying from the quantification method limits to a few hundreds of µg/kg (dw) (Fig. 7 brown, Tab. SM1).

The relatively less studied categories, represented by a grey color in Fig. 4, are quantified at levels as the most studied PhCs of a few mg/kg (dw) (Fig. 8). Their concentration variabilities do not exceed 2 orders of magnitude. In contrast, hormones and illicit drugs are quantified at concentrations lower than 1 mg/kg (dw), generally close to tens of µg/kg. Some categories could lead to further attention due to high PhCs concentrations (e.g., the antidiabetic glibenclamide GLI, the antiemetic domperidone DOM).

3.3.2.12. Illicit drugs. Illicit drugs, and their metabolites are also significantly detected in sludge as hormones, with 34 quantified compounds on 39 also take an important part of the research even if the median concentrations are much lower than most of categories ranging under tens µg/kg (Fig. 8 kaki, Tab.SM1). Quite a number of new compounds, 14, were searched and quantified showing the interest in that matter.

3.3.2.13. Other PhCs categories including the least investigated PhCs. The other categories, which referred to the relatively less studied categories, seems to be also significantly less quantified than the most referenced categories, potentially explained by the low number of associated studies ($N < 5$). By their concentration ranges, these categories could represent similar interest to the previously mentioned. It is important to note that compounds which are referenced by a unique study need to be deepening to better understand their affinity with the solid phase of sludge matrices and allow comparison with the most referenced PhCs (Fig. 8, Tab.SM1). Seventeen newly quantified compounds were referenced in that category.

Antivirals appear as an emerging category with concentration ranges reaching up to 5.8 mg/kg (dw) and medians from a hundred of µg/kg to several mg/kg (lamivudine LAMV, nevirapine NEV, zidovudine ZIDO). Antiarrhythmics such as amiodarone (AMIO) and its metabolite desmethylamiodarone (NorAMIO) were quantified up to 360 µg/kg, while lidocaine was measured above 160 µg/kg. Anthelmintics, even if they were not mostly investigated, present levels quite like antianxieties as for mebendazole (MBDZ) and albendazole (ABDZ), with medians around 65 µg/kg and 15 µg/kg, respectively. Half of the investigated antianxieties were quantified in sludge such as oxazepam (OXZP), aripiprazole (APZL), lorazepam (LZP) and some metabolites. Diazepam (DZP) is the most concentrated antianxiety quantified up to 131 µg/kg. Other compounds show lower concentrations up to 50 µg/kg (dw). Antineoplastics and antipsychotics were currently investigated, but only 5 and 3 compounds were quantified at levels up to hundreds µg/kg among 11 and 14 investigated compounds, respectively. High concentrations were also observed for the antidiabetic glibenclamide (GLI), the antiemetic domperidone (DOM), and the antiprotozoal pyrimethamine

(PRMTM) up to 7 mg/kg, 4 mg/kg, and 2 mg/kg, respectively. Except the tiamulin (TML), the 7 envisaged antibacterials showed concentrations lower than the MQLs.

It is interesting to note that the presence of PhCs metabolites in sludge matrices, always in lower concentrations than the parent molecules, highlights degradation mechanisms during stabilization processes under microbial activity, principally if they are not identified in wastewater inputs (Figs. 5–8, Tab.SM1).

3.3.3. Evaluation of PhCs properties on their sludge occurrence

The current models, that simulate the fate of PhCs in the WWTP, predict concentrations in sludge through model partitioning restricted to sorption processes. Many studies estimate the degree of a PhC sorption onto the sludge based on experimental distribution coefficients K_d (L/kg solid dw). This coefficient is derived from the linear regression of an equilibrium partition between the liquid and the solid phase (Ternes et al., 2005). The resulting K_d value is empirical and may vary by several orders of magnitudes depending on sludge properties and the operating conditions (e.g. intrinsic physical-chemical properties of the type of sludge tested as pH, temperature, oxygen level, residence time, organic carbon content), the surveyed compounds, and their single or combination concentrations at the beginning of the experiment (Yan et al., 2014; Hörsing et al., 2011; Hyland et al., 2012; Jelic et al., 2012; Liu et al., 2019; Lajeunesse et al., 2012; Ternes et al., 2005; Stevens-garmon et al., 2011).

Hence due to the many parameters involved, simulations based on literature K_d values can create significant disparities between the quantified and simulated concentrations (Yan et al., 2014; Khan and Ongerth, 2002). Indeed, the studies observed that predicting concentrations based on estimated K_d from other studies would often lead to overestimation for hydrophobic compounds and underestimation for ionic and polar compounds (Yan et al., 2014; Stevens-garmon et al., 2011; Citulski and Farahbakhsh, 2010). These differences could be explained by the modifying operating parameters leading to greater sorption of ionized than neutral PhCs. The presence of hydrophilic compounds would be induced by both adsorption and absorption mechanisms; the latter involve competitive effects by electrostatic interactions depending on the operating conditions, modifications of the functional groups of the sludge surface and ionization states of the target species. These observations result from the complexity of sorption mechanisms due to the nature of the target compounds and all conditions involved during the sludge treatment.

Tendencies are emerging to estimate the sorption behavior of target PhCs on sludge based on their physical-chemical properties, especially their availability to ionization in the considered matrix. The interactions of charged PhCs with particles is thus estimated using a fitted partition coefficient $\log D_{ow}$ (measure of the pH-adjusted hydrophobicity of an ionizable compound in a particular environment) using the $\log K_{ow}$ of the target compound and their acidic constants (pK_a , pK_b) (Stevens-garmon et al., 2011; Carballa et al., 2008). In general terms, the partition coefficient of the neutral species is typically more than two orders of magnitude larger than the distribution ratio of the ionic species. Thus, at $pH < pK_a + 2$ (acid PhCs) and $pH > pK_a - 2$ (basic PhCs), the neutral species are the dominant species determining D_{ow} . The affinity to sludge was correlated with basic compounds suggesting that hydrophobic sorption interactions are still important for these positively charged compounds, although electrostatic interactions are involved and, in some cases, maybe dominant (Stevens-garmon et al., 2011). For neutral and negative charged compounds, the increase in $\log D_{ow}$ indicates an increase of sorption potential. Thus, PhCs with a $\log D_{ow} > 1.5$ would generally exhibit sorption greater than 50% in sludge, averaging 67% in the solid phase (Phan et al., 2018). Thus, it was noted that compounds with $\log D_{ow} > 3$ exhibit high sorption instead of $\log D_{ow} < 1$ (Verlicchi and Zambello, 2015).

By the existing gaps on the physical-chemical properties of sludge (Section 2.1.) and knowing that pH modifications conduct to variable

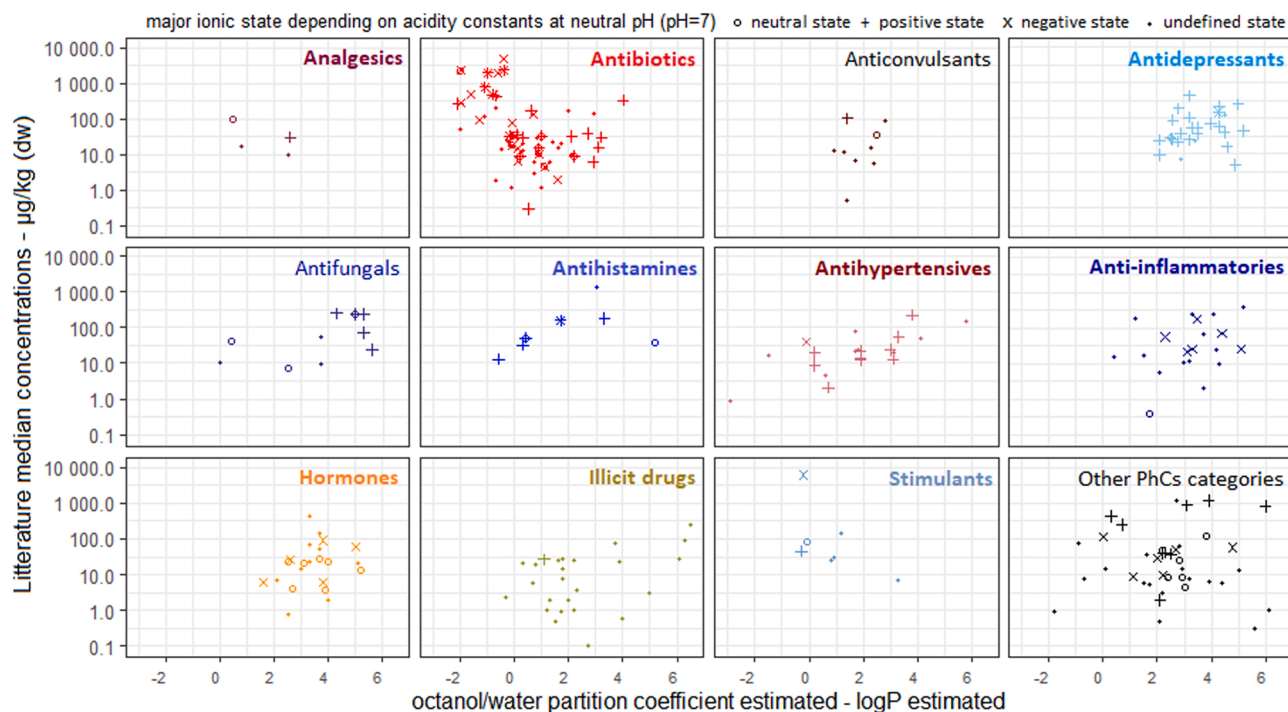


Fig. 9. Representation of median concentrations according to the pharmaceutical properties. Figure is classified through investigated therapeutical categories, as presented in Fig. 4, presenting the median from reviewed studies according to hydrophobicity characteristics (log) and specification of the major ionic state at sludge pH as negative, positive, or neutral species. The undefined states are also noted by a point.

log D_{ow} by changing the ratio of neutral and charged species, the relationship between the median concentrations of PhCs and their corresponding log K_{ow} value was investigated (Fig. 5). The ionic state of some compounds is considered at neutral pH, according to the variability of the sludge pH range from literature (Section 2.1.). Fig. 9 globally, supports that PhCs sludge concentration is related to hydrophobic properties among trends as:

- Tendency at increasing concentrations with the increase of the hydrophobicity (e.g., antihistamines, antifungals).
- Whatever the species, positive or negative PhCs (antihypertensives, antidepressants or anti-inflammatories, respectively) show median concentration around hundreds of $\mu\text{g}/\text{kg}$ with a hydrophobic property ($\log K_{ow} > 2$, Fig. 9, Tab.SM1).
- Antifungals, hormones, or other PhCs categories demonstrate differences in the electrostatic interactions between sludge and several ionic species. Indeed, positively charged compounds show higher medians than neutral compounds. Although specific charged species represent some categories, global tendency highlights those positive compounds are more concentrated than negative. The positive antidepressant species tend to be clustered at high median concentrations ($\sim 43 \mu\text{g}/\text{kg}$ - Fig. 4, Tab.SM1) compared to negative anti-inflammatory species, which are more dispersed and less concentrated ($\sim 24 \mu\text{g}/\text{kg}$ - Fig. 4, Tab.SM1).
- Compounds presenting several charged functional groups support the domination of electrostatic interactions against hydrophobic mechanisms, by their highest concentrations. In fact, quinolone's antibiotics-type with positive and negative charge species are quantified at highest medians ($\sim 170 \mu\text{g}/\text{kg}$, $\log K_{ow} < 1$ - Fig. 4, Fig. 9, Tab.SM1) compared to sulfonamides ($\sim 8 \mu\text{g}/\text{kg}$ with $\log K_{ow} \sim 0.5$) or macrolides ($\sim 30 \mu\text{g}/\text{kg}$ with $1 < \log K_{ow} < 4$, respectively).

This review notes strong disparities of PhCs contents for similar physical-chemical properties. These differences support that partition on solid phase and resulting concentrations in sludge depend on wastewater and sludge characteristics (pH, organic matter, surface

functional groups) as target compounds properties. Indeed, their affinity to the lipidic phase ($\log K_{ow}$) and their ionization state (pK_a) in the studied matrices tend to lead them having variable partition though the influent properties and the operating conditions. Hence, estimations based on the physical-chemical properties of PhCs are complex and may not precisely evaluate their partitioning but provide good indications and trend on sorption processes. The predicting models of the PhCs contents could also integrate the susceptibility of compounds to biological degradation, but it implies to know their tendency to be degraded by the associated biomass.

3.3.4. Evaluation of the qualitative distribution

To our knowledge, this review is the first study showing a global evaluation of the current relative proportions of the 305 pharmaceuticals identified among the therapeutical categories searched in sludge matrices. Regarding the PhCs occurrence in sludge, their cumulative contents can reach several hundreds of mg/kg . These contents are, moreover, noted by the studies restricted by the number of investigated PhCs (e.g., 22PhCs $383.3 \text{ mg}/\text{kg}$ (Mailler et al., 2017), 5PhCs $45.2 \text{ mg}/\text{kg}$ (Tang et al., 2012), 19PhCs $32.9 \text{ mg}/\text{kg}$ (Jia et al., 2012), 22PhCs $31.5 \text{ mg}/\text{kg}$ (Gao et al., 2012), 40PhCs $28.4 \text{ mg}/\text{kg}$ (Ben et al., 2018), 19PhCs $24.9 \text{ mg}/\text{kg}$ (Kinney et al., 2006), 25PhCs $23.7 \text{ mg}/\text{kg}$ (Yuan et al., 2014), 40PhCs $21.9 \text{ mg}/\text{kg}$ (Ashfaq et al., 2017), 68PhCs $21.4 \text{ mg}/\text{kg}$ (McClellan and Halden, 2010), 127PhCs $20.3 \text{ mg}/\text{kg}$ (Peysson and Vulliet, 2013), 8PhCs $16.9 \text{ mg}/\text{kg}$ (Huang et al., 2014), 6PhCs $15.4 \text{ mg}/\text{kg}$ (Dong et al., 2016), 5PhCs $13.8 \text{ mg}/\text{kg}$ (Salvia et al., 2015), 44PhCs $12.3 \text{ mg}/\text{kg}$ (Narumiya et al., 2013), 11PhCs $12.1 \text{ mg}/\text{kg}$ (Lindberg et al., 2005), 13PhCs $10.8 \text{ mg}/\text{kg}$ (Ferhi et al., 2016)). This observation supports the limitations of selecting lists of target compounds in assessing the contamination of study matrices.

This study provides a valuable contribution to assess the contamination of sludge on all the detected compounds identified, knowing that their analysis depends on their investigation. Also, the overall medians of the quantified compounds were determined for all the studied sludges reported by the literature to comprehensively evaluate the relative PhCs concentrations. A ratio of the sum of PhCs medians from therapeutical

variable properties and low number of investigations on studies, relatively less studied categories need further research. Antivirals, vasodilators, antiarrhythmics deserve more attention due to their high medians around 100 µg/kg, as for antiprotozoals, antiemetics, antineoplastics, or antipsychotics due to their relative high proportions in sludge.

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. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhazmat.2021.128104.

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