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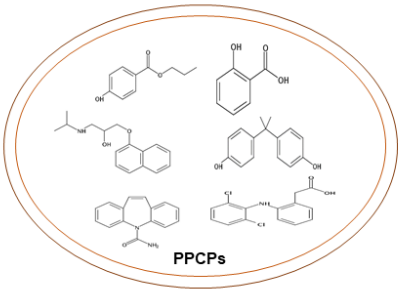

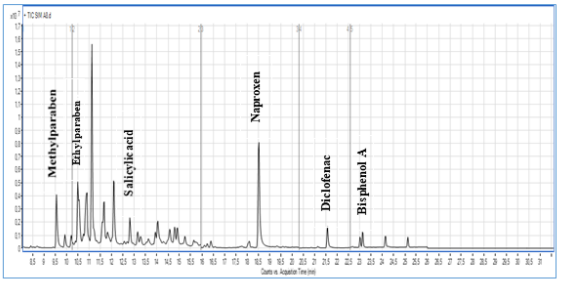

Sewage sludge

Instrumental analysis

Sample Pretreatment

Analytical methodologies for the determination of pharmaceuticals and personal care products (PPCPs) in sewage sludge: a critical review

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ABSTRACT

Several analytical approaches have been developed for the determination of emerging pollutants (EPs), including pharmaceuticals and personal care products (PPCPs) in environmental matrices. This paper reviews the sample preparation and instrumental methods proposed in the last few years (2012-2018) to assess PPCPs in sewage sludge. Three main steps are examined: extraction, clean-up and analysis. Sample preparation is critical as target compounds are normally found at low concentrations in complex matrices. Most procedures include sewage sludge pretreatment mostly through ultrasound-assisted extraction (UAE) although other novel techniques such as QuEChERS (Quick, Easy, Cheap, Effective, Rugged and Safe) or MSPD (matrix solid-phase dispersion) have been also employed. In one report, no differences in extraction efficiency were detected among the most commonly used extraction techniques such as ultrasound, microwave and pressurized liquid. Clean-up usually involves a conventional method such as solid phase extraction (SPE). This step is needed to appreciably reduce matrix suppression, and is followed by an instrumental analysis using techniques of preference such as gas chromatography (GC) or liquid chromatography (LC), mostly coupled to mass spectrometry (MS). A fully automated on-line system that includes extraction, chromatographic separation, and mass spectrometry in one-stage is here presented as a novel way of determining PPCPs in sewage sludge. This review also discusses the advantages and limitations of the different techniques used. Miniaturizing analytical

techniques and the use of novel solid and liquid phase materials are emerging as efficient options that fulfill the principles of so-called "green chemistry".

1. Introduction

Emerging pollutants (EPs) are a great concern because of their detrimental effects on the health of human beings as well as aquatic and terrestrial life [1]. EPs include pharmaceuticals and personal care products (PPCPs) whose presence in the environment has not been yet regulated as stated in Directive 2013/39/EU on priority substances in the field of water policy [2].

PPCPs represent a large number of chemicals used in daily life including medicines, cosmetic and personal hygiene products. The active ingredients of PPCPs are products such as non-steroidal drugs like analgesics, antibiotics, antiepileptics, β-blockers, blood-lipid regulators, antiretroviral drugs and steroid drugs (hormones). As an example, non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed pain medications. NSAIDs are used for the treatment of osteoarthritis, rheumatoid arthritis, inflammation, fever and sever and chronic pain and therefore improve quality of daily life [3]. Personal care products include cosmetic and personal hygiene products such as antimicrobials, fragrances, UV filters, and surfactants, among others. For instance, endocrine disrupting compounds such as parabens, are widely used as preservatives in PPCPs because their toxicity levels are theoretically low [4]. These drugs (active ingredients and preservatives), excreted in the environment via urine, feces, wastewater, sewage sludge and manure [5–6], are known to be persistent, bio-active and bio-accumulative as they are cleared at a faster rate than that of their natural degradation. These agents can pose a threat to drinking water supplies [7] and may be a health risk due to their estrogen activity and effects on the endocrine system [1,4,8,9]. PPCPs have been detected in water bodies throughout the world, even in Antarctic waters [10]. Moreover, in Europe, the rate of increase in the consumption and production of PPCPs has grown markedly in the last 20 years. Several studies examining the impacts of a wastewater treatment plant (WWTP) in Spain have shown that PPCPs contribute to water toxicity in a greater measure than traditional priority pollutants [11]. Conventional WWTPs are not designed to remove organic micropollutants. In fact, effluents from such plants are now considered to be a major point source of endocrine disrupting compounds and PPCPs in

the receiving environment. For this same reason, PPCPs are commonly found in sewage sludge, as the residue left behind after the treatment of wastewater from various sources, including homes, industrial plants, and medical facilities [12]. The sewage sludge generated is often employed in agricultural and forestry activities, mainly due to its capacity to fertilize soils and the low economic impact of this practice [13], which leads to their spread in the environment.

In the past few years, numerous procedures for the determination of these emerging contaminants have been developed for use on the sewage sludge solid matrix. From an analytical perspective, sewage sludge (i.e., primary, secondary, digested sludge, compost) is challenging because of the complex nature of its matrix. In addition, its characteristics vary depending on the inputs to the WWTP.

In this study, the latest trends in methodology for the determination of PPCPs in sewage sludge are reviewed in detail. Focusing on the past six years after the last review published in 2012 (used as a reference for the present review) [14], 273 papers were identified, 67 of which deal explicitly with the determination of PPCPs in sewage sludge samples. A couple of recent general reviews have considered emerging contaminants in sludge samples [15] and aquatic ecosystems [16]. Martín-Pozo et al. recently provided a general overview of methodologies used to determine emerging contaminants in sewage sludge [15]. Here we present a holistic collection and critical review of all methodologies described to date that have been used for the determination of PPCPs throughout in sewage sludge. In effect, 85% of the literature gathered in this compilation has never been analyzed or discussed before.

The present article focuses on both current sample preparation procedures and instrumental analysis techniques including an assessment of the impact and efficiency of each stage and technique on several validation parameters. In addition, we discuss possible analytical perspectives for the future and provide novel information on the use of miniaturized and automated techniques as well as green chemistry approaches.

2. Analysis of sewage sludge samples

Studies worldwide have observed the presence of PPCPs in several environmental matrices. Concentrations of some PPCPs such as diclofenac (NSAID), propranolol (antihypertension

agent), triclosan (broad-spectrum antibacterial agent), triclocarban (antibacterial agent), and miconazole (azole antifungal agent) are commonly observed in the sewage sludge of most WWTPs. For instance, in Brazil, diclofenac has been found at concentrations of 25 to 60 ng/g, propranolol at 61.2 to 94.3 ng/g, triclosan at 2086 to 5466 ng/g and miconazole at 313 to 515 ng/g [93]. In India, propranolol has been detected in samples at concentrations of 46 to 54 ng/g, triclocarban at a mean concentration of 11.125 ng/g and miconazole averaged a concentration of 250 ng/g [59]. In France, diclofenac, triclosan and miconazole have been found at concentrations around 24 ng/g, 824 and 63 ng/g, respectively, and propranolol was observed at levels between 82 and 849 ng/g [100].

Sewage sludge is a complex matrix. It is not uniform in composition and concentrations of organic contaminants depend on the nature of inputs to the WWTP. Further, sludge contains substances that could interfere when trying to determine analytes of interest. Such interference may impact the whole analytical process, from sample preparation to instrumental detection. Thus, it is necessary to first remove these from samples using clean-up procedures.

Table 1 and 2 present a summary of the references reviewed here. All types of sludge (i.e., primary, secondary, digested, and compost) were subjected to similar analytical approaches which roughly consisted of a sample pretreatment followed by an instrumental analysis. The different methods used are described in the following sections.

Despite similar analytical protocols (extraction, clean-up and analysis), differences did exist in terms of the quantity of sample treated or the amount of solvent in each matrix. Some of the studies reviewed used different amounts of sample and extraction solvent for different types of sludge with ultrasound as the extraction technique: Kopperi et al. [37] used 0.05 g of sample and 6 mL of solvent (acetonitrile) in composted sludge samples; Abril et al. [58] used 1 g of sample and 3 mL of solvent (methanol: acetic acid (1:1)) in digested sludge samples; Shafrir [49] used 2 g of sample and 10 mL of solvent (methanol: water (1:1) in secondary sludge samples; Lonappan et al. [31] used 0.5 g of sample and 20 mL of solvent (methanol) in primary sludge samples; and Yan et al. [40] used 2 g of sample and 10 mL of solvent (methanol/citric acid/Na_2EDTA (2:1:1)) in dewatered sludge samples.

Further, sample quantities and solvents also varied for different extraction techniques on the same type of sludge. Examples for digested sludge are 0.1 g [43], 1.5 g [76] or 3g [64] and 6 mL of methanol:water (1:1) [43], 22 mL of hexane: dichloromethane (1:1) [76] or 20 mL of

methanol:water (1:1)) [64] used in ultrasound [43], pressurized liquid [76], or microwave [64] extraction procedures, respectively.

The matrices associated with each type of sludge differ because their characteristics vary as the sludge goes through several treatment stages. For instance, major changes are produced by thickening, dewatering and digestion. In thickening and dewatering treatments, total solid (dry solids) concentrations increase and the volume of sludge is reduced. Following digestion treatment, the load of total solids is reduced (via the reduction of volatile suspended solids). Several sludge matrices should be, therefore, treated separately and their analysis should be viewed as a challenge to be addressed in future work.

2.1. Sample pretreatment

The sampling of different types of sludge is particularly important to assess the distribution of PPCPs along the sludge line. According to Tables 1 and 2, sampling sludge locations within WWTPs depends on the type of sewage sludge sample required for the subsequent analysis. In the literature reviewed, a large number of studies preferred sampling sewage sludge [92,100] (suspension with a dry solids content of 3 to 4 % weight arising from the purification of wastewaters). Some authors sample the sludge after the final dewatering step to obtain a representative bulk product [22,78]. Other researchers carry out their sampling after the anaerobic digestion step in which some of the organic matter is removed [43,64]. However, few publications considered sampling in primary and secondary tanks [42,77].

Representative sludge samples can be collected from the WWTP sludge line. Sample volumes in the studies reviewed differed, e.g.: 1 L samples were collected weekly over a period of four weeks by Schoeman et al. [53]; random grab samples were pooled to provide a sample weighing about 500 g by Gago-Ferrero et al. [34]; and five grab samples collected daily were pooled to give a single sample (approximately 2 L) of sludge per day over three consecutive days by Jelic et at. [74].

The materials used for sample collection also differed. Thus, one report describes the collection of solid pasty sludge using a metal bucket and the collection of liquid sludge using a sample probe. Thereafter, the samples were packed in glass bottles with a wide-mouth PTFE stopper [100]. Other materials such as 1L clear Schott bottles [53] or antimicrobial

plastic bags after sewage sludge dewatering [34] were also utilized for sample collection. These samples were then transported to the laboratory where they were frozen and lyophilized [53, 59, 88] or dried in air to room temperature [50], and passed through a 2 mm Ø sieve and homogenized [50] or were macerated in a glass mortar for some minutes [93]. Finally, the lyophilized samples were stored at −20 °C [65] until their analysis.

Sample preparation takes up most of the analysis time. It usually includes a process of extraction followed by a clean-up step. A variety of techniques have been used to extract PPCPs from sewage sludge samples in the last 6 years. Besides traditional approaches such as Soxhlet [20,21] and ultrasound [28,34], other methods based on microwave [62,65] or pressurized liquid [72,74] are gaining popularity. Most extraction techniques are not sufficiently selective and clean-up procedures are also needed after extraction.

Figures 1 and **2** show each of the extraction and clean-up techniques used, respectively, over the last 6 years (reviewed here) compared with the previous five-year period.

2.1.1. Extraction

Solvent extraction of solid samples, commonly known as solid–liquid extraction, is one of the oldest techniques of solid sample preparation. This technique serves to remove and separate compounds of interest from insoluble high-molecular-weight fractions and other compounds that could interfere with subsequent steps of the analytical process [17]. Soxhlet is a reference extraction technique that belongs to that group. Some authors prefer this extraction procedure because of some advantages. For example, samples are repeatedly brought into contact with fresh portions of extractant, which facilitates displacement of the transfer equilibrium. In addition, filtration is not necessary after leaching, which increases sample yield. Further, several simultaneous extractions can be performed in parallel because of the low cost of basic equipment [18]. However, Soxhlet also has some shortcomings: it is time consuming, labor intensive and requires the use of large volumes of organic solvents (300-500 mL) and large samples (10-30 g). These features go against some of the main objectives of so-called “green chemistry” such as sustainable development and being environmentally friendly. Recent modifications have tried to bring the Soxhlet technique closer to these objectives. Hence, a technical version designated automated Soxhlet extraction was developed as a more

competitive extraction technique. This was initially implemented with the commercial equipment Soxtec® System HT, which provided fundamental savings in time and extractant volume [19]. Automated Soxhlet extraction (Soxtec) uses a combination of reflux boiling and Soxhlet extraction in two extraction steps boiling and rinsing, followed by solvent recovery. Despite such developments, Soxtec does not improve on the scarce versatility of the conventional Soxhlet device. Only 7% of the reports reviewed here have employed the Soxhlet technique [20,21,22,23,24] (Table 1) as also observed in the previous review published in 2012 [14]. Despite the development of Soxtec, the publications mentioned above used Soxhlet as the extraction technique. **Figure 1** summarizes all the information analyzed.

Ultrasound-assisted extraction (UAE) is an alternative to Soxhlet extraction for solid matrices and has been widely used in PPCP procedures. Some of the latest examples are described in three of the reports reviewed here [28,53,54]. The cavitation of UAE reduces the extraction time in comparison with Soxhlet but, in contrast, it is less reproducible. This cavitation process consists of bubble formation, growth and implosion occurring during the propagation of an ultrasound wave in a liquid medium [25]. The principle of ultrasound cavitation is described in a diagram included in the publication [142].

The solvent is chosen based on physical criteria such as viscosity, surface tension and vapor pressure. All these parameters will affect the acoustic cavitation phenomenon [26]. Sonication extraction is faster than Soxhlet extraction (30–60 min per sample) but filtration is required after extraction. UAE is an environment-friendly technique in that it is energy- and time saving. Compared to Soxhlet, less solvent is required and the extraction time is shorter. Hence, using ultrasound, extractions can be completed in minutes, simplifying manipulation and work-up, and employing just a fraction of the energy usually required for a traditional extraction method such as Soxhlet [27]. As mentioned earlier, many studies in the last six years have examined this extraction technique (**Figure 1**).

A more modern technique used to determine PPCPs in sewage sludge is microwave-assisted extraction (MAE). This approach uses microwave energy to directly heat the solvent to extract compounds of interest, thus accelerating the speed of extraction. The benefit of MAE is the use of small amounts of solvent compared to Soxhlet and sonication extraction (30 mL in MAE versus 300–500 mL for Soxhlet extraction) which enables the control of extraction parameters such as time, power or temperature [60]. In addition, this green technique offers protection for thermo-labile constituents. However, as UAE, MAE also has its shortcomings:

a filtration step is required after extraction, and organic solvents and a subsequent extract cleaning-up step are needed. Further, the equipment for MAE is relatively expensive. Thus, probably because of all these downfalls, only a small number of studies addressing MAE have been reported in the literature reviewed [55, 61-65] over the last 6 years (Table 2). However, the number of studies reviewed is still higher compared to the previous review [14], which only mentioned four references [66-69].

Another extraction method is pressurized liquid extraction (PLE), also known as accelerated solvent extraction (ASE). This is a fully automatic technology which uses low volumes of liquid extractants such as hexane, ethanol and acetone at high pressure (usually up to 200 bar) and temperature (usually up to 200 ºC) without reaching the critical point to recover those target analytes with short extraction times [70]. PLE has proven very effective for extracting target analytes. However, extracts usually contain a complex matrix as well. Thus, a clean-up procedure is often needed after extraction to remove interferences. Solid phase extraction (SPE) with a great variety of sorbents has been the most common clean-up technique when PPCPs are the target analytes [13,71-81]. However, gel permeation chromatography (GPC) has also been used to purify organic pollutants [35]. PLE has many advantages over traditional extraction techniques as efficient ways of increasing automation, shortening the extraction time and reducing the amount of organic solvents. PLE usually entails extraction times of around 15 minutes per sample and uses between 15-40 mL of solvent. In addition, the instrumentation allows for extraction in an unattended operation. It is regarded as reasonably easy and exhaustive, offering quantitative recoveries with little spare time spent on method development [70]. All these attractive features have meant that many of the works reviewed used PLE to extract PPCPs from sewage sludge. Some of the most relevant examples are [13,55,71,80,81]. The number of recent publications is comparable to those reported [82-84] (Table 2) in the previous review published in 2012 [14] (**Figure 1**).

An even more environmentally-friendly technique is pressurized hot water extraction (PHWE). This technique uses pressurized water as an extraction fluid at elevated temperature. Water has several positive features such as easy access, safety and can be recovery or disposed of with minimal environmental concerns [85]. Temperature is the most important parameter to optimize in this technique as it affects extraction efficiency and selectivity. Elevated temperatures provide certain advantages such as high diffusion, low viscosity and surface tension [85]. The best features of PHWE are the use of small amounts of organic

solvents [86] and its low cost. In the future, this green extraction technique is expected to help manipulate large sample sizes for industrial applications. Despite these commented advantages, only two references of the use of PHWE as the extraction technique was found in the last 6-years reviewed [87,144] along with one more [88] in the previous five-year period [14].

Recently some authors have replaced the more traditional extraction techniques such as UAE or Soxhlet and also MAE or PLE with novel methodologies including MSPD (matrix solid-phase dispersion) or QuEChERS (Quick, Easy, Cheap, Effective, Rugged and Safe). These approaches have as their main goal to improve the method's sensitivity and selectivity as isolation and purification are combined in a single step. The main sources of error of most analytical methodologies are avoided. Main benefits are the short time required for sample preparation and their efficiency in cleaning-up the extract [93, 101].

MSPD for the extraction of PPCPs in sewage sludge was introduced in 1989 and applied to the extraction of solid, semisolid or viscous samples. It consists of homogenizing the sample with a dispersing agent (abrasive solid) onto a solid support, allowing the disruption of the sample and the extraction of target analytes by means of a suitable elution solvent [89]. The great interest in MSPD may be attributed to the advantages it offers and its simplicity and flexibility which have contributed to its choice over more classical sample preparation methods [90]. MSPDE is rapid, scarcely manual-intensive and eco-compatible. After extraction, depending on the nature of target analytes and the instrumentation used for their detection, a clean-up procedure may or not be needed. This technique and PLE have sometimes been employed together as the solvents used at high pressures and temperatures increase analyte recoveries when interactions of the analytes with the solid matrix are really strong. The method's selectivity is related to the elution solvent utilized and the nature of the sorbent materials. Lipophilic sorbent materials such as C_{18}-bonded silica or C_8-bonded silica are employed in numerous applications, although the latter is used less frequently [90]. The solvents chosen for elution depend on the nature of the solid material. Organic solvent mixtures are mainly used, however, hot water offers excellent results in certain applications (mostly in PLE procedures). MSPD extraction has several benefits such as reduced amounts of solvents and sample, short extraction times, low cost and good performance at room temperature and atmospheric pressure with acceptable yields and selectivity. The technique is suitable for a great variety of analytes and environmental matrices due to its flexibility and

versatility. Some reports exist in the literature [91-95] (Table 2) for the last 6 years. In contrast, only one study was found in the previous period from 2008 to 2012 [94]. This indicates a large increase in the use of this technique.

Finally, one of the most novel techniques employed to determine PPCPs in environmental matrices is QuEChERS. This procedure offers benefits such as the use of a small content of organic solvents, scarcely time consuming, good recoveries and high selectivity. It mainly consists of two steps, salting-out liquid-liquid extraction (SALLE) and dispersive solid-phase extraction (DSPE) for extract clean-up [97].

QuEChERS encompasses both extraction and clean-up steps for complex environmental matrices. This reduces sample preparation to approximately 20 minutes. The technique uses less solvent than ASE (usually up to 10 mL), and entails minimal times and costs. Some reports of QuEChERS applications exist in the literature reviewed here [98-102] (Table 2) but no studies addressed this issue in the five-year period before 2012 [14].

Overall, as depicted in **Figure 1**, UAE emerges as the most popular extraction technique (49%), followed by PLE (19%) and MAE (9%). Thus, the trend observed until 2012 reviewed by [14] has been maintained in the last six years. Nonetheless, UAE seems to have lately experienced a boost, most probably because of its simplicity and high performance as well as affordability and availability at most of laboratories around the world.

2.1.2. Clean-up

Most extraction techniques for PPCPs in sewage sludge are not sufficiently selective and a clean-up step is usually subsequently necessary. Some of the most common interfering constituents of sludge are compounds such as lipids and substances added to sewage sludge during processing such as surfactants and polymer colloids, among others. Although interference can occur at any stage of the analytical process, instrumental analysis based on liquid chromatography interphase to mass spectrometry by electrospray ionization is especially sensitive to matrix effects [55].

C_{18} is a clean-up agent commonly used to remove interfering lipids and lipophilic compounds in extracts contained in organic solvents. PSA (primary and secondary amine) has also proved

effective for the removal of acidic interferences such as humic and fulvic acids (main components of compost) among others [55]. C_{18} and PSA (primary and secondary amine) are examples of some clean-up agents commonly used in dispersive solid-phase extraction (d-SPE) [102]. Thus, the choice of sorbent must be adequate to retain interferences present in each particulate sludge matrix. Deficiencies in the extraction process have been also attributed to the presence of co-extracted matrix components [34].

Solid-phase extraction (SPE) is the most popular technique for the clean-up of PPCPs after extraction from sewage sludge, and from environmental samples in general [28,30,54,78]. This procedure is quick and simple to operate and can be easily automated and coupled to instrumental techniques such as liquid chromatography (LC) [103].

There are three general extraction mechanisms used in SPE: polar, non-polar and ion exchange. More than half of the works found in the literature during the last 6 years have employed reverse-phase SPE (63%). The retention mechanism is the interaction of non-polar groups of the analytes of interest and the non-polar functional groups on the sorbent (Van der Waals forces) [104]. In many cases, extraction was performed in a polar solvent [13,24,39-43,45-48,50,52,56,59,62,64,74,75,77,80,81]. Mixed-mode SPE is an extraction approach involving sorbents which are designed to exhibit two or more primary interactions for analyte retention. Most mixed-mode sorbents include hydrophobic functional groups in combination with ion-exchange functional groups. In some cases, Oasis MCX (Mixed-Mode Cation-eXchange) has been used for the clean-up of extracts containing acidic pharmaceuticals [39,62,64]. Oasis MAX (Mixed-Mode Anion-eXchange) has been also used in other cases [62,64]. However, the reverse phase sorbent patented in Oasis HLB (Hydrophilic-Lipophilic Balanced) has been the preferred option over the last six years [13,24,29,30,32,39,40,42,48-50,56,59,64,74,75,77,80,81]. It is a universal polymer reversed-phase sorbent that was developed for the extraction of a wide range of acidic, basic and neutral compounds from various matrices. Another type of adsorbent is based on C_{18}-silica and used to adsorb analytes of even weak hydrophobicity from aqueous solutions [43,52]. In the 1990s, a miniaturized variation of SPE emerged as a solid-phase microextraction technique (SPME). This method involves an alternative preconcentration technique to LLE or SPE. It consists of a silica fiber coated with a thin layer of an extractant polymer, which can be placed in the head space (HS-SPME) or subjected to direct immersion (DI-SPME) in solid, liquid or gaseous samples. As the fiber is desorbed in the injection port of a gas chromatography system, the use of solvents

is eliminated and possible losses of analytes and contamination of the samples are reduced. [28,57] are examples found in the literature reviewed here.

Gel permeation chromatography (GPC), also known as size-exclusion chromatography (SEC), is a method in which component separation is based on differences in molecular weight or size. It requires short analysis times and small volumes of mobile phases. It has been widely employed to isolate and analyze biomacromolecular substances such as sugar, peptides, proteins, rubbers, and others, on the basis of their size. GPS has been also applied to PPCPs, usually in combination with other clean-up techniques. In particular, [35] made use of GPC along with a silica gel column to clean up 153 pharmaceuticals, herbicides, antioxidants, intermediates, organic solvents and chemical raw materials. Three studies reviewed by [14] for the period 2008 to 2012 included GPC and normal-phase SPE used together as the clean-up procedure [106-108].

Liquid–liquid extraction (LLE) is an effective separation method for compounds having different solubility in two immiscible liquids. These two liquids are generally water, with or without additives, and a nonpolar organic solvent. Polar compounds prefer the aqueous layer while nonpolar compounds are extracted into the organic layer. In salting-out systems, water-miscible solvents have been investigated for the extraction or concentration of analytes that cannot be extracted by conventional LLE methods. This salting-out often occurs at high salt concentrations [109]. However, LLE extracts are not particularly clean in comparison with other more intensive sample preparation procedures. The first applications of this technique to PPCPs in sludge were reported by [54,63].

Overall, the vast majority of publications, 60% of the reports reviewed here, chose SPE as the clean-up approach, as shown in **Figure 2**. Only isolated examples of other techniques have been found such as florisil [51], silica [90] or $MgSO_4$ [98].

2.2. Instrumental analysis

Instrumental analysis for PPCPs in sewage sludge is basically based on chromatographic separation coupled to mass spectrometry. PPCPs are mostly polar compounds with limitations of volatility and/or thermal stability for their analysis by gas chromatography (GC) [28]. Nonetheless, these limitations have been overcome by derivatization processes such as

acylation (acetylation), alkylation [33] and silylation [28,37,50,65]. GC is a relatively inexpensive instrumental technology which enables this kind of analysis to be carried out by a wide range of laboratories around the world, including those in developing countries [20,53]. Overall, 25% of the reports reviewed chose GC-based on instrumental techniques. In comparison to the period reviewed by [14], there seems to have been a decline in the popularity of GC **(Figure 3)**. Most GC approaches are coupled to mass spectrometry (MS) detection in both a single and tandem (MS/MS) modality. Other detection approaches were found coupled to GC such as electron capture detector (ECD) [22]. Triple quadrupole (QqQ) is the most common analyzer mainly used in selected reaction monitoring (SRM) mode for quantitative analysis [51,76]. However, some examples of target analysis in high resolution by quadrupole to time-of flight (Q-TOF) couplings have been also found in the literature [37,53,79]. As pointed out in the previous section, SPME is a pretreatment technique which allows automation when coupled to GC and was employed by [28] and [129] for the analysis of 12 PPCPs and 8 macrocyclic musk fragrances in sewage sludge respectively. This constitutes the only examples of pretreatment coupling to instrumental analysis in our realm.

However, despite the above, LC-based on instrumental analysis has become the most popular technique **(Figure 3)** in the determination of PPCPs in environmental matrices including sewage sludge. This is probably because of its higher versatility as a larger spectrum of compounds can be readily analyzed with no prior derivatization or alike. Again, mass spectrometry is the preferred detection option, but some examples (2) of coupling to fluorescence detection have been also found [61,99]. This repeats the scenario as in the period reviewed by [14] where a single example of this coupling was cited [110]. In contrast, ultraviolet (UV) detection cited years ago [111] is no longer an interesting option. Within MS modalities, MS/MS was found to have the greatest applicability, in particular using QqQ in SRM mode for target analysis. Hence, 63% of the LC works reviewed fit this classification. Nevertheless, interest in the use of other tandem combinations such as Q-TOF has been recently sparked due to improvements in the dynamic range and sensitivity of TOF. In addition, TOF analyzers offer a high resolution capacity. This ensures high selectivity and reduces the probability of false positive results. In addition, they open the possibility of qualitative analysis of un-known compounds, which is not readily available in QqQ. Electrospray ionization (ESI) is the most commonly used ionization approach as it allows mild ionization of the target analyte and molecular ions usually remain un-fragmented [47,75,100]. Nonetheless, apolar compounds might undergo poor ionization by ESI, and

atmospheric pressure chemical ionization (APCI) is then recommended as in [31,49]. Weak acids and bases such as formic acid and ammonium acetate are usually used as mobile phase modifiers when working at +ESI and –ESI respectively. Moderate acidic (~3) and basic pHs (~8) are provided by formic acid and ammonium acetate respectively. In this regard, a larger number of PPCPs contain basic functional groups (such as amines) with pKa values above pH 3 rather than acidic functional groups (such as alcohols) with pKa values below pH 8. Therefore, PPCPs are more prone to be positively ionized and are more efficiently analyzed by +ESI rather than -ESI.

Within LC, fast chromatography has emerged as an improved modality over high performance liquid chromatography (HPLC). The ultra-high version (UHPLC) was introduced under the trade mark UPLC^{TM} in 2004 and triggered many advances in instrumentation and column technology, which have led to a significant increase in resolution, speed and sensitivity. Column efficiency increases with reduction of stationary phase particle size (usually <1.7µm) and mobile phase delivery is done at <15,000 psi (about 1000 bar) [112]. Separations are mostly completed in less than 10 min and some even in under 2 min [32,62,72]. UHPLC often provides narrow peaks (in few seconds or even less) offering a high-speed detection response (> 100Hz) [112].

Over these past 6 years, out of 47 of the applications using LC, 14 were fast chromatography. This in comparison to the previous 5-year period reviewed by [14], in which only 8% of studies examined this kind of liquid chromatography, reveals a clear upward trend in the use of UHPLC likely attributable to its many benefits mentioned. Overall, as depicted in **Figure 3**, LC has been the most popular instrumental technique (73%) for the determination of PPCPs in environmental matrices including sewage sludge. Hence, the trend observed up until 2012 and reviewed by [14] has been maintained over the last six years.

2.3. Current trends and future perspectives in the determination of PPCPs in sewage sludge

The concept of "green chemistry", otherwise known as sustainable chemistry, was introduced 20 years ago and refers to the design of chemicals and processes that reduce and eliminate the use or generation of hazardous substances. When applying and proposing new methods and processes of analysis, sustainability should be considered a necessary characteristic. By

automatizing a technique, the use of resources, including time, usually becomes more efficient. In addition, human error and analyst exposure to hazards are minimized [113]. Besides automation, miniaturization in analytical chemistry has also become a dominant trend recently replacing traditional sample preparation. The goal is to provide high extraction efficiencies in short times and minimize the amount of sample and so reduce the consumption of reagents and solvents. In addition, after automation and miniaturization, many sample preparation methodologies are susceptible to being incorporated into instrumental analysis systems such as GC or LC [113]. Hence, in the early 2000s, a research group developed simple procedures based on SPME or USAEME (ultrasound-assisted emulsification-microextraction) for the analysis of allergenic fragrances, synthetic musks, phthalates and preservatives in water samples [114-116]. While the use of miniaturized and automatized methodologies for the determination of PPCPs in water matrices is a reality [117,118], the reports reviewed here barely show the use of miniaturization techniques for the determination of the contaminants of interest in sewage sludge. Only two studies found in the literature offer an analytical method for the determination PPCPs and PCPs in sewage sludge by DI-SPME-On-fiber derivatization-GC-MS [28] and HS-SPME-GC-MS [129] respectively. Interest in microextraction processes has been renewed due to the incorporation of new materials, either as suitable substitutes for conventional halogenated organic solvents or other types of toxic reagents [113]. At present sufficient technology already exists for research groups to develop miniaturized and automatized analytical methods for the determination of PPCPs in sewage sludge.

Additionally, there are concerns in the scientific community over the presence of transformation products (TPs). Many of these TPs have shown to be as pernicious as the parent PPCPs they come from. Clear efforts are currently focusing on the identification in environmental water samples of metabolites and other TPs generated over the PPCP life cycle, such as during treatment processes in WWTPs [28,36]. However, there is no evidence in the literature yet of this trend in relation to sewage sludge.

Many PPCPs consist of chiral molecules and each enantiomer usually exerts different toxicity according to its biological properties [119]. Hence, reports exist of the determination of chiral pharmaceuticals by chiral LC-MS/MS [64,120] in sewage sludge samples. Nonetheless, much more work is still needed in this area.

Future perspectives related to the development of new sample preparation methods differ depending on the type of the pollutant. There is increasing interest in nanotechnology in important sectors of science and technology such as engineering, medicine or agriculture, among others. Nanotechnology is making progress in technologies for protecting the environment too. However, nanotechnology's unique characteristics can lead to unforeseen environmental problems [121]. In parallel, the use of novel solid and liquid phase materials has increased in the last years including nanomaterials (NMs), ionic liquids (ILs) or supramolecular solvents (SUPRAS) used in the analysis of environmental samples. Engineered nanomaterials (ENMs) are materials or chemical substances with particle sizes between 1 to 100 nanometers in at least one dimension [122]. There is great interest in innovations produced in the industrial, commercial and medical sectors due to the physical and chemical properties of these materials. However, some of their properties (chemical reactivity, surface area and particle size) pose a risk to health and the environment [123]. Some works have described applications of nanoadsorbents in environmental water samples [124,125]. In the near future, NMs could be applied to sewage sludge samples. SUPRAS are nanostructured liquids generated from compounds with both hydrophilic and lipophilic properties (amphiphiles) [126]. SUPRAS have been employed for the extraction and preconcentration of emerging pollutants in environmental water samples [127]. However, there are still no reports of applications of SUPRAS to sewage sludge. ILs are salts whose ions are poorly coordinated, which makes these solvents liquid at temperatures below 100°C, or even at room temperature (room temperature ionic liquids) [128]. One publication reports on the determination of musk fragrances in sewage sludge based on IL-HS-SPME followed by GC-MS/MS [129].

3. Data processing

Environmental sample matrices are complex and their analysis and subsequent data processing are extremely difficult. For many years, a traditional approach offering reliable rapid identification and quantification of target compounds has been used [130]. In total, 98% of the reports reviewed employed target analysis to determine PPCPs in sewage sludge samples. However, target analysis has the drawback that only a limited number of compounds can be determined and many pollutants present are ignored [131].

A comprehensive picture can be obtained by non-target analysis which does not require "a priori" selection of contaminants. This approach is able to detect any analyte present above the MDL. In addition, retrospective analysis is possible [131]. Anthropogenic compounds such as pharmaceuticals and personal care products, flame retardants, plasticizers, polymer additives and other well-known persistent organic pollutants can be identified using this approach. Suspect screening is a non-target analysis. Both suspect and non-target analysis are based on the power and development of high-resolution mass spectrometric instruments. These techniques serve to acquire full scan spectra and allow a retrospective analysis of emerging contaminants after the data has been acquired, while providing two essential factors for non-target analysis: accurate-mass and high-resolution [131]. The most common MS analyzers used for this purpose, such as Orbitrap or the Fourier transform ion cyclotron resonance (FT-ICR) device, can be linked to different ionization sources (ESI, APPI and APCI) and different separation techniques (GC, LC and GCxGC) depending on the class of compounds to be examined [128]. However, in the past 6 years, only one study has used this method to determine emerging contaminants in sewage sludge. This study [37] described a non-targeted approach based on GCxGC-TOFMS. In contrast, numerous reports exist of a non-target approach for the determination of these contaminants in wastewater; some examples being [132,133].

Target methods are usually quantitatively more powerful as they show a greater sensitivity and dynamic range than untargeted methods. Regardless, analyte quantification is usually performed through the use of authentic chemical standards and the construction of calibration curves. Calibration curves are used to understand the instrumental response to an analyte and to predict its concentration in a sample. Over the past six years, the calibration methods reported in the literature to determine PPCPs have been based on approaches including an internal standard, standard additions, matrix matched or external standard. The choice of a specific calibration method depends on a number of factors such as affordability, matrix complexity, and number of samples, among others. External standard calibration has been one of the most commonly used calibration approaches among the reports reviewed here. This approach is inexpensive as well as quick and easy to set up. On the downside, it is greatly affected by the stability of the chromatographic detector system and the presence of chromatographic interferences in the sample. Some of the publications reviewed make use of this quantification approach [53,75,77,95] (Table 1 and 2). When matrix problems are suspected, a more reliable calibration may be obtained via matrix-matched calibration. This

may make up for matrix effects although it does not eliminate the underlying cause because the effect intensity may differ from one matrix or sample to another, and can be also affected by the matrix concentration. In fact, matrix-matched calibration is a particular type of external calibration in which the calibration standards are prepared using a simulated sample that initially does not contain the analyte. Of the reports reviewed, 22% chose matrix-matched as calibration method (Tables 1 and 2), which represents an increase in comparison with the period reviewed by [14], in which only 6% of the publications selected the matrix-matched method [134-136]. Another calibration alternative is based on standard addition. This method is more accurate and precise and overcomes more matrix effects than external and matrix-matched calibration approaches, as it uses the sample itself to build the calibration curve. However, it entails the preparation of a different calibration curve per sample. It is therefore labor intensive, time-consuming, and requires large sample amounts, which is usually in disagreement with green chemistry principles. Overall, 14% of the publications reviewed here used this calibration method (Tables 1 and 2). In contrast, previous publications reviewed by [14] reported this calibration approach less frequently (9%). Finally, an internal standard (IS) is a reference species with similar physicochemical properties and similar analytical behavior to the compounds of interest not expected to be found in the samples. This calibration method is not as useful for GC and HPLC methods involving non-MS detectors unless the internal standards can be separated from target compounds chromatographically. The advantage of this calibration method is that fluctuations are monitored in every sample. It assumes that the behavior of the IS is identical to that of the analyte. Thus, the selection of a suitable IS is mandatory. The use of internal standard calibration approaches has experienced a boom in the last few years. In effect, 47% of the reports reviewed selected this procedure (Tables 1 and 2) versus 4% reported in the prior review [14]. In particular, the use of stable-isotope-labeled analogues of the analytes has become popular because of its efficiency and reliability to compensate for any alteration in the signal due to casualties across the whole analytical process. However, for highly multi-component applications, it requires a significant economic investment, unaffordable for many laboratories.

Figure 4 depicts the frequency of each calibration method used in the reports reviewed. The use of isotopically labeled analogues in internal standard calibrations has been the most popular choice.

4. Validation

The purpose of validation of an analytical procedure is to confirm that the analytical method used for experimental tests is suitable for that purpose. Method validation was established in analytical laboratories in the late 1970s, recognizing its importance in obtaining standard methods. The United States Food and Drug Administration (FDA) [137] and Eurachem [138] have published guidelines for methods validation.

To a large extent, the reliability and capacity of analytical methods have improved to a large extent as a result of recent technical advances [139]. The main validation parameters provided in the publications are (Tables 1 and 2):

a. Accuracy is the closeness of agreement between test results across the specified range and an accepted reference value. In our particular case, it is expressed as the percentage recovery of each analyte after the whole analytical protocol (absolute recovery). Some authors also provide improved recovery rates after adjusting for method deficiencies when applying an internal standard calibration approach (relative recovery). The reports reviewed showed considerably high analyte relative recoveries. Thus, 35 out of 67 publications showed percentages higher than 70% and 22 out of 67 publications obtained values below 70%. In contrast, 17 out of 47 publications were found for the five years before 2012 with percentages higher than 70% and 13 studies with values below 70%.
b. Precision is the closeness in agreement between individual results obtained for a repeatedly applied procedure on a homogeneous sample, comprising repeatability and intermediate precision. In our particular case, method repeatability is usually expressed as the standard deviation, relative standard deviation or coefficient of variation. Overall, 72% of the reports reviewed cited values below 20%. In comparison, for the period reviewed by [14], 23 out of 47 publications reported values below 20%.
c. Sensitivity expressed as both limits of detection (LOD) and limits of quantification (LOQ) can be directly obtained from the linearity test in the validation protocol. Hence, the lowest amount of analyte that can be detected under the stated experimental conditions is the LOD, while LOQ is the lowest amount of analyte that can be quantitatively determined with precision and accuracy under the stated experimental conditions. Among the publications included in the present review, 35%

obtained LOQs below 100 ng/g. Additionally, 16 and 22 out of 67 publications obtained LOQs below 50 and 10 ng/g, respectively. These figures reflect the improvement in sensitivity of current analytical methodologies produced over the last few years. Effectively, LOQs levels were commonly reported as LODs in studies conducted before 2012.

d. The matrix effect is attributable to components of the sample matrix that co-elute with the compound(s) of interest and interfere with the ionization process in the mass spectrometer. This may cause ionization suppression or enhancement and negatively affect method accuracy. It is usually expressed as the percentage of signal suppression, and consequently negative values are interpreted as signal enhancement. In most cases, signal suppressions were measured. Some reports cite moderate signal suppression values such as means of 44% [47] or 46% [98]. In contrast to that observed in the review of 2012 [14], strong effects of signal suppression were described including values from 14 to 100% [140] or higher than 30% [141].

   In one study [34], 148 pharmaceuticals and illicit drugs were analyzed in sewage sludge and the matrix effect assessed. For 12 out of the 148 target compounds, a signal enhancement in the range 11-90% was reported, and for 136 target compounds, signal suppression was reported in the range −92 to −3%.

e. The dynamic range is closely related to the response of the instrumental detector, and describes the concentration span, in orders of magnitude, over which the method provides a response proportional to the concentration of a given compound. Accordingly, linearity ranges of 3 orders of magnitude are usually reported for single quadrupole [28] and TOF [100] MS detectors, and of 5 orders of magnitude for triple quadrupole [102] MS detectors.

Tables 1 and 2 summarize the validation values cited in the 67 reports reviewed for the determination of PPCPs in sewage sludge samples from 2012 to the present.

5. Impacts of sewage sludge analytical procedures on validation parameters

Each stage in the analytical procedure (extraction, clean-up, instrumental analysis, etc.) may to some extent have an effect on the validation parameters examined.

Extraction and clean-up steps are thought to be the main contributors to absolute recovery [55]. In the literature reviewed, various studies have addressed the determination of PPCPs both in sewage sludge and sewage. In many of those cases, methodology was common for both matrices but an extraction step was added at the beginning of the protocol for the sludge samples. For instance, Křesinová et al. [72] used PLE followed by SPE with ENVI C18-DSK SPE disk and LC-ToFMS for the determination of PPCPs in sludge. The same methodology was employed when these PPCPs were determined in water samples, but a PLE extraction step did not precede the protocol. This extra step for the solid samples led to lower absolute recoveries for most of the compounds, indicating how extraction influences method accuracy. Accordingly, amitriptyline, 2-chloroprothioxanthen-9-one and melitracene carbinol rendered recoveries of 97.6%, 96.7%, 88.1%, respectively. These percentages decreased to 92.8%, 89.5 % and 86.8%, for the same compounds in solid samples [72]. Additionally, López-Serna et al. [28] showed how dramatic the impact of the extraction step can be on the accuracy. These authors employed a fully automated method based on online extraction by DI-SPME followed by on-fiber derivatization coupled to GC-MS for sewage samples. In sewage sludge samples, UAE preceded the sewage methodology. The absolute recoveries reported in this paper for compounds such as ibuprofen, salicylic acid and diclofenac were 77.77%, 21.43%, and 83.07%, respectively, in sewage samples. However, in sludge, these recoveries dropped to 18.18% for ibuprofen, 17.92% for salicylic acid, and 65.89% for diclofenac. Among the different extraction techniques discussed in the present paper, UAE, MAE and PLE seem the most popular. PLE is considered to be much more effective at extracting analytes from solid samples than UAE or MAE, leading to higher real recoveries. However, PLE is also described to extract more components of the matrix along with the analytes of interest. This means the associated matrix effect diminishes the given absolute recovery rate [70]. Nonetheless, PLE and MAE are usually shown to be slightly more efficient than UAE for extracting PPCPs from sludge as observed by Dorival-García et al. [55]. For instance, Gao et al. [77] tested a method based on PLE-SPE-LC-MS/MS and the absolute recoveries reported for compounds such as sulfamethoxazole, tetracycline and oxytetracycline in sludge samples were 78%, 54%, and 52%, respectively. Similarly, Shafrir et al. [49] used a method based on UAE-SPE-LC-MS/MS and reported absolute recoveries such as 17%, 22%, and 17% for sulfamethoxazole, tetracycline and oxytetracycline, respectively. Gago-Ferrero et al. [34] developed a method that combined UAE and LC-MS/MS, and absolute recoveries reported in this paper for compounds such as propranolol, diclofenac and sulfamethoxazole in sewage sludge samples

were 53%, 27%, and 63%, respectively. In contrast, Eyser et al. [73] made use of a method based on PLE followed by LC-MS/MS and reported recoveries of up to 96% for propranolol, 85% for diclofenac, and 33% for sulfamethoxazole in sewage sludge samples.

The presence of the analytes of interest along with matrix components in the sample influences every step of the analysis. GC combined with EI ionization MS operating in SIM mode did not cause any apparent matrix effect during the determination of PPCPs in sewage sludge [50]. In LC, the matrix effect differs when it is interphased with MS by ESI or APCI. Lonappan et al. [31] compared the use of LC-ESI-MS/MS and LDTD-APCI-MS/MS to quantify diclofenac in wastewater sludge samples. These authors reported that matrix effects due to interactions between diclofenac and co-extracted compounds could cause signal suppression in the ESI source. In fact, competition for ionization could exert signal enhancement or suppression phenomena [50] [73]. However, they reported that matrix interferences in LDTD-APCI-MS/MS did not significantly affect the signal [31]. Additionally, Luque-Muñoz et al. [54] used UHPLC-MS/MS in their instrumental analysis and reported matrix effect values such as -25% for propylparaben or -37% for benzophenone-6. However, Abril et al. [58] reported matrix effects of -79% for propylparaben and -81% for benzophenone-6 for HPLC-MS/MS. This lesser matrix effect might be attributed to the better resolution capacity of UHPLC. While in conventional HPLC, analytes could co-elute with the matrix compounds, in UHPLC they may reach the detector at different retention times. Sample preparation usually includes a clean-up step that partially removes interferences from the matrix [73]. SPE has been the preferred method among those examined here due to its simplicity and the use of small volume of organic solvents. However, these clean-up procedures might have marked performance deficiencies in multi-residue-methods [73]. Oasis HLB SPE cartridges are based on a co-polymer which is very efficient at recovering a wide range of compounds in environmental matrices. Nonetheless, it is not highly selective and matrix interferences may not be successfully reduced [62]. Petrie et al. [62] observed that Oasis MCX and MAX reduced matrix suppression more satisfactorily. These authors reported matrix suppression values of 59.2% for diclofenac, 88.6% for naproxen and 80.0% for ibuprofen using MCX SPE [62]. Other authors such as Gago- Ferrero et al. [33] reported matrix enhancement values for the same pollutants: -18% for diclofenac, -36% for naproxen and -43% for ibuprofen without the use of any clean-up step. After comparing examples from the literature for sewage samples, we found that Klančar et al. [143] employed Strata X cartridges for SPE combined with LC-MS/MS and reported matrix effect values of 83% for

naproxen, 79% for propranolol and 96% for tramadol. These matrix effect rates are substantially higher than those observed by Petrie at al. [62] who used Oasis HLB-based SPE followed by LC-MS/MS and reported percentages of around 30%, 57% and 62% respectively for the same compounds.

Precision (expressed as repeatability) is usually affected by the number of stages included in the analytical procedure. A strategy to achieve good precision has been to automatize some of the method stages (e.g., PLE, SMPE) to minimize the human error impact. In the literature, two fully automated methods DI-SPME – on fiber derivatization-GC-MS [28] and HS-SPME-GC-MS [129] have been used to determine PPCPs and PCPs in sewage sludge, respectively. López-Serna et al. [28] reported satisfactory intra-day repeatability (expressed as %RSD) values such as 0.87% for propylparaben, 1.59% for naproxen and 2.99% for triclosan, among others. Vallecillos et al. [129] also reported good intra-day repeatability results such as 1% for exaltone, 8% for muscone, and 9% for exaltolide, among others. However, SPME fibers used for a large number of samples might lead to significant carry over effects. López-Serna et al. [28] reported carry over rates of up to 10% and 13% for diclofenac and triclosan, respectively.

Sensitivity is mainly affected by the instrumental analysis technique employed [28]. In the revised literature, different groups have examined the use of similar methods with different detectors such as FL [61], Q-MS [13], QqQ-MS [62], or QToF-MS [72] for the determination of PPCPs in sludge samples. For instance, Morales-Toledo et al. [61] developed a method based on MAE and SPE combined with UHPLC-FLD for the determination of pharmaceuticals in sludge samples, and reported method LODs for naproxen and ibuprofen below 86.5 ng/g. Much lower LODs were observed by Petrie et al. [62] for a similar method based on MAE and SPE followed by UHPLC-MS/MS. In particular, they reported method LODs of 0.07 ng/g for ibuprofen and 0.60 ng/g for naproxen. Among the analyzers used in mass spectrometry, QqQ has usually provided lower LODs than QToF. Hence, Peysson et al. [100] made use of a method based on QuEChERs followed by UPLC-QToF and reported LODs as low as 17 ng/g for sulfamethoxazole and 3 ng/g for propranolol, among others. Even lower limits of 0.6 ng/g and 0.3 ng/g respectively for the same compounds were reported by Cerqueira et al. [101] for a similar pretreatment method followed by UHPLC-QqQ-MS. The use of GC usually leads to higher LODs in comparison to LC, even when the detection method is MS. This is usually attributed to incomplete derivatization of the non-volatile PPCPs and/or a poorer ionization rate of the resulting substance. UHPLC provides narrower

chromatographic peaks than conventional HPLC. Accordingly, the same area will offer a greater height, which entails an increase in signal intensity, and so sensitivity. For instance, Gago-Ferrero et al. [34] achieved LOQs of 4.1 ng/g for diclofenac and 9.8 ng/g for salicylic acid by applying a method based on UAE and UHPLC-MS/MS. In contrast, Boix et al. [38] reported lower limits (eg., 63 ng/g for diclofenac and 35 ng/g for salicylic acid) using a similar method but with HPLC as the chromatographic stage.

Selectivity and throughput (multiresiduality) are usually improved following the same pattern as sensitivity. Thus, the probability of providing false negatives or positives is decreased when a MS detector is used, especially if in a tandem configuration (QqQ or QToF). Gago-Ferrero et al. [34] used LC-MS/MS as the instrumental analysis technique for the simultaneous determination of 148 pharmaceuticals and illicit drugs in sewage sludge. Similarly, Peysson et al. [100] used LC-ToF/MS to determine 136 pharmaceuticals and hormones in sewage sludge. In contrast, Morales-Toledo et al. [61] only determined four substances (acetylsalicylic acid, ibuprofen, naproxen and gemfibrozil) in sludge samples by LC-FLD.

Differences in linearity range have been reported depending on the instrumental detector. Hence, for instance methods including QqQ usually attain 5 orders of magnitude [102]. However, up to 3 orders are reported for QToF-based methods [100].

Regardless of these factors, through the use of quantification approaches such as internal standard with isotope dilution, standard addition or matrix-matched techniques most technical deficiencies during extraction, clean-up, instrumental analysis, etc. may be circumvented, compensated and corrected. This means that a partial, non-optimal method developed for the pretreatment and instrumental stages might still be sufficient to achieve a methodology capable of fulfilling analytical requirements, provided sensitivity is appropriate and the quantification approach is powerful.

6. Conclusions

The studies reviewed here examining the determination of PPCPs in sewage sludge consider a wide variety of emerging pollutants in environmental matrices. The most frequently investigated PPCPs belong to the class of pharmaceutical products. In effect, 49 out of the 67

reports reviewed focused on the detection and quantification of pharmaceuticals in sewage sludge.

In some studies, traditional sample pretreatment techniques such as Soxhlet were replaced with more modern techniques such as MAE or PLE, or alternative techniques like QuEChERS or MSPD. However, UAE emerged as the most popular extraction technique for determining PPCPs in sewage sludge reported in almost half of the publications. This method provides safe, fast and easy sample preparation. It also makes use of small sample sizes and amounts of solvents. Usually after the extraction step, a clean-up protocol is needed as extraction is never completely selective. For this purpose, SPE was the technique most frequently used on pollutants after their extraction from environmental samples. For the determination of PPCPs in sewage sludge, LC and GC coupled to MS were the techniques of choice. Among the LC procedures, several studies chose UHPLC over HPLC because of its better resolution and shorter run times as well as its lesser demands in terms of solvent and sample quantities.

In recent years, novel solid and liquid phase materials and miniaturization and automation of the analytical techniques are becoming a dominant trend as they eliminate the limitations of current analysis technologies. Minimizing sample size decreases the consumption of expensive and toxic reagents and solvents, thus fulfilling the principles of green chemistry.

Most reported studies employed a target analysis to determine PPCPs in sewage sludge samples. Only one of the studies reviewed applied a non-target quantification method. Thus, a challenge to be addressed in the near future might be the individual treatment of each sludge-associated matrix. A boost in non-targeted approaches is expected for the determination of PPCPs in sewage sludge, as occurred for their analysis in aqueous matrices.

Finally, this review reports improved validation parameters in comparison with previously reviewed periods, especially regarding precision and sensitivity. This is mostly attributed to developments in analytical instrumentation.

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References

[1] F.A. Caliman, M. Gavrilescu, Pharmaceuticals, personal care products and endocrine disrupting agents in the environment - A review, Clean - Soil, Air, Water. 37 (2009) 277–303. doi:10.1002/clen.200900038.

[2] European Commission, Directive 2013/39/EU of the European parliament and of the council of 12 August 2013, Off. J. Eur. Union. 24.8.2013 (2013) L 226/1-L 226/17.

[3] I. Brabcová, D. Šatínský, P. Solich, A fast on-line micro-column sample pretreatment with a HPLC column switching technique and large volume sample injection for determination of non-steroidal anti-inflammatory drugs in human serum, Anal. Methods. 5 (2013) 6153–6159. doi:10.1039/c3ay40505b.

[4] I. Márquez-Sillero, E. Aguilera-Herrador, S. Cárdenas, M. Valcárcel, Determination of parabens in cosmetic products using multi-walled carbon nanotubes as solid phase extraction sorbent and corona-charged aerosol detection system, J. Chromatogr. A. 1217 (2010) 1–6. doi:10.1016/j.chroma.2009.11.005.

[5] P. Paíga, L.H.M.L.M. Santos, C.G. Amorim, A.N. Araújo, M.C.B.S.M. Montenegro, A. Pena, C. Delerue-Matos, Pilot monitoring study of ibuprofen in surface waters of north of Portugal, Environ. Sci. Pollut. Res. 20 (20castro13) 2410–2420. doi:10.1007/s11356-012-1128-1.

[6] M.A. Mottaleb, C. Stowe, D.R. Johnson, M.J. Meziani, M.A. Mottaleb, Pharmaceuticals in grocery market fish fillets by gas chromatography-mass spectrometry, Food Chem. 190 (2016) 529–536. doi:10.1016/j.foodchem.2015.06.003.

[7] V.L. Cunningham, S.P. Binks, M.J. Olson, Human health risk assessment from the presence of human pharmaceuticals in the aquatic environment, Regul. Toxicol. Pharmacol. 53 (2009) 39–45. doi:10.1016/j.yrtph.2008.10.006.

[8] J.C. Benítez-Villalba, A. Zafra-Gómez, N. Dorival-García, F. Javier Camino-Sánchez, S. Cantarero, J.L. Vílchez, Ultra-performance liquid chromatography MS/MS method for the determination of parabens in compost from sewage sludge: Comparison of the efficiency of two extraction techniques, J. Sep. Sci. 36 (2013) 2635–2645. doi:10.1002/jssc.201300318.

[9] F. Vela-Soria, I. Jiménez-Díaz, R. Rodríguez-Gómez, A. Zafra-Gómez, O. Ballesteros, M.F. Fernández, N. Olea, A. Navalón, A multiclass method for endocrine disrupting chemical residue analysis in human placental tissue samples by UHPLC-MS/MS, Anal. Methods. 3 (2011) 2073–2081. doi:10.1039/c1ay05162h.

[10] P. Emnet, S. Gaw, G. Northcott, B. Storey, L. Graham, Personal care products and steroid hormones in the Antarctic coastal environment associated with two Antarctic research stations, McMurdo Station and Scott Base, Environ. Res. 136 (2015) 331–342. doi:10.1016/j.envres.2014.10.019.

[11] I. Muñoz, M. José Gómez, A. Molina-Díaz, M.A.J. Huijbregts, A.R. Fernández-Alba, E. García-Calvo, Ranking potential impacts of priority and emerging pollutants in urban wastewater through life cycle impact assessment, Chemosphere. 74 (2008) 37–44. doi:10.1016/j.chemosphere.2008.09.029.

[12] E.Z. Harrison, S.R. Oakes, M. Hysell, A. Hay, Organic chemicals in sewage sludges, Sci. Total Environ. 367 (2006) 481–497. doi:10.1016/j.scitotenv.2006.04.002.

[13] G. Llorens-Blanch, M. Badia-Fabregat, D. Lucas, S. Rodriguez-Mozaz, D. Barceló, T. Pennanen, G. Caminal, P. Blánquez, Degradation of pharmaceuticals from membrane biological reactor sludge with Trametes versicolor, Environ. Sci. Process. Impacts. 17 (2015) 429–440. doi:10.1039/c4em00579a.

[14] O. Zuloaga, P. Navarro, E. Bizkarguenaga, A. Iparraguirre, A. Vallejo, M. Olivares, A. Prieto, Overview of extraction, clean-up and detection techniques for the determination of organic pollutants in sewage sludge: A review, Anal. Chim. Acta. 736 (2012) 7–29. doi:10.1016/j.aca.2012.05.016.

[15] L. Martín-Pozo, B. de Alarcón-Gómez, R. Rodríguez-Gómez, M.T. García-Córcoles, M. Çipa, A. Zafra-Gómez, Analytical methods for the determination of emerging contaminants in sewage sludge samples. A review, Talanta. 192 (2019) 508–533. doi:10.1016/j.talanta.2018.09.056.

[16] M. Lorenzo, J. Campo, Y. Picó, Analytical challenges to determine emerging persistent organic pollutants in aquatic ecosystems, TrAC - Trends Anal. Chem. 103 (2018) 137–155. doi:10.1016/j.trac.2018.04.003.

[17] W.B. Jensen, The Origin of the Soxhlet Extractor, J. Chem. Educ. 84 (2007) 1913. doi:10.1021/ed084p1913.

[18] M.D. Luque de Castro, F. Priego-Capote, Soxhlet extraction: Past and present panacea, J. Chromatogr. A. 1217 (2010) 2383–2389. doi:10.1016/j.chroma.2009.11.027.

[19] M. L. de Castro, L. Gracia-Ayuso, Soxhlet extraction of solid materials : an outdated technique with a promising innovative future, Anal. Chim. Acta. 369 (1998) 1–10.

[20] P.J. McNamara, C.A. Wilson, M.T. Wogen, S.N. Murthy, J.T. Novak, P.J. Novak, The effect of thermal hydrolysis pretreatment on the anaerobic degradation of nonylphenol and short-chain nonylphenol ethoxylates in digested biosolids, Water Res. 46 (2012) 2937–2946. doi:10.1016/j.watres.2012.03.015.

[21] A. Gupta, I.S. Thakur, Biodegradation of wastewater organic contaminants using Serratia sp. ISTVKR1 isolated from sewage sludge, Biochem. Eng. J. 102 (2014) 115–124. doi:10.1016/j.bej.2015.02.007.

[22] A.P. Daso, O.S. Fatoki, J.P. Odendaal, O.O. Olujimi, Occurrence of selected polybrominated diphenyl ethers and 2,2',4,4',5,5'-hexabromobiphenyl (BB-153) in sewage sludge and effluent samples of a wastewater-treatment plant in Cape Town, South Africa, Arch. Environ. Contam. Toxicol. 62 (2012) 391–402. doi:10.1007/s00244-011-9720-9.

[23] J.R. Nyholm, R. Grabic, H.P.H. Arp, T. Moskeland, P.L. Andersson, Environmental occurrence of emerging and legacy brominated flame retardants near suspected sources in Norway, Sci. Total Environ. 443 (2013) 307–314. doi:10.1016/j.scitotenv.2012.10.081.

[24] S. Montesdeoca-Esponda, T. Vega-Morales, Z. Sosa-Ferrera, J.J. Santana-Rodríguez, Extraction and determination methodologies for benzotriazole UV stabilizers in personal-care products in environmental and biological samples, TrAC - Trends Anal. Chem. 51 (2013) 23–32. doi:10.1016/j.trac.2013.05.012.

[25] S.K. and M. Ashokkumar, The Physical and Chemical Effects of Ultrasound, in: Rev. Mex. Fis., 2011: pp. 1–12. doi:10.1007/978-1-4419-7472-3.

[26] B. Sanderson, Applied sonochemistry– the uses of power ultrasound in chemistry and processing. By Timothy J Mason and John P Lorimer, Wiley-VCH Verlag, Weinheim, 2002, 303 pp, ISBN 3-527-30205-0, J. Chem. Technol. Biotechnol. 79 (2004) 207–208. doi:10.1002/jctb.957.

[27] F. Chemat, N. Rombaut, A.G. Sicaire, A. Meullemiestre, A.S. Fabiano-Tixier, M. Abert-Vian, Ultrasound assisted extraction of food and natural products. Mechanisms, techniques, combinations, protocols and applications. A review, Ultrason. Sonochem. 34 (2017) 540–560. doi:10.1016/j.ultsonch.2016.06.035.

[28] R. López-Serna, D. Marín-de-Jesús, R. Irusta-Mata, P.A. García-Encina, R. Lebrero, M. Fdez-Polanco, R. Muñoz, Multiresidue analytical method for pharmaceuticals and personal care products in sewage and sewage sludge by online direct immersion SPME on-fiber derivatization – GCMS, Talanta. 186 (2018) 506–512. doi:10.1016/j.talanta.2018.04.099.

[29] J.L. Chen, S. Ravindran, S. Swift, N. Singhal, Changes in estrogenicity and micropollutant concentrations across unit processes in a biological wastewater treatment system, Water Sci. Technol. 77 (2018) 1673–1682. doi:10.2166/wst.2018.047.

[30] M. Ashfaq, Y. Li, Y. Wang, W. Chen, H. Wang, X. Chen, W. Wu, Z. Huang, C.P. Yu, Q. Sun, Occurrence, fate, and mass balance of different classes of pharmaceuticals and personal care products in an anaerobic-anoxic-oxic wastewater treatment plant in Xiamen, China, Water Res. 123 (2017) 655–667. doi:10.1016/j.watres.2017.07.014.

[31] L. Lonappan, R. Pulicharla, T. Rouissi, S.K. Brar, M. Verma, R.Y. Surampalli, J.R. Valero, Diclofenac in municipal wastewater treatment plant: Quantification using laser diode thermal desorption-atmospheric pressure chemical ionization-tandem mass spectrometry approach in comparison with an established liquid chromatography-electrospray ionizat, J. Chromatogr. A. 1433 (2016) 106–113. doi:10.1016/j.chroma.2016.01.030.

[32] J. Hou, C. Wang, D. Mao, Y. Luo, The occurrence and fate of tetracyclines in two pharmaceutical wastewater treatment plants of Northern China, Environ. Sci. Pollut. Res. 23 (2016) 1722–1731. doi:10.1007/s11356-015-5431-5.

[33] L. Bo, L. Feng, J. Fu, X. Li, P. Li, Y. Zhang, The fate of typical pharmaceuticals in wastewater treatment plants of Xi'an city in China, J. Environ. Chem. Eng. 3 (2015) 2203–2211. doi:10.1016/j.jece.2015.08.001.

[34] P. Gago-Ferrero, V. Borova, M.E. Dasenaki, N.S. Thomaidis, Simultaneous determination of 148 pharmaceuticals and illicit drugs in sewage sludge based on ultrasound-assisted extraction and liquid chromatography-tandem mass spectrometry, Anal. Chim. Acta. 407 (2015) 4287-4297. doi:10.1007/s00216-015-8540-6.

[35] G. Wang, H. Ma, L. Wang, J. Chen, X. Hou, Non-target screening of organic pollutants in sediments and sludges using gas chromatography-mass spectrometry and automated mass spectral deconvolution, Chinese J. Chromatogr. (Se Pu). 33 (2015) 1294–1300. doi:10.3724/SP.J.1123.2015.08022.

[36] C. Boix, M. Ibáñez, D. Fabregat-Safont, E. Morales, L. Pastor, J. V. Sancho, J.E. Sánchez-Ramírez, F. Hernández, Behaviour of emerging contaminants in sewage sludge after anaerobic digestion, Chemosphere. 163 (2016) 296–304. doi:10.1016/j.chemosphere.2016.07.098.

[37] M. Kopperi, J. Parshintsev, J. Ruiz-Jiménez, M.L. Riekkola, Nontargeted evaluation of the fate of steroids during wastewater treatment by comprehensive two-dimensional gas chromatography–time-of-flight mass spectrometry, Environ. Sci. Pollut. Res. 23 (2016) 17008–17017. doi:10.1007/s11356-016-6800-4.

[38] C. Boix, M. Ibáñez, D. Fabregat-Safont, E. Morales, L. Pastor, J. V. Sancho, J.E. Sánchez-Ramírez, F. Hernández, Analytical methodologies based on LC-MS/MS for monitoring selected emerging compounds in liquid and solid phases of the sewage sludge, MethodsX. 3 (2016) 333–342. doi:10.1016/j.mex.2016.04.010.

[39] E. Topuz, S. Sari, G. Ozdemir, E. Aydin, E. Pehlivanoglu-Mantas, D. Okutman Tas, Optimization of diclofenac quantification from wastewater treatment plant sludge by

ultrasonication assisted extraction, J. Chromatogr. B Anal. Technol. Biomed. Life Sci. 958 (2014) 48–54. doi:10.1016/j.jchromb.2014.02.047.

[40] Q. Yan, X. Gao, L. Huang, X.M. Gan, Y.X. Zhang, Y.P. Chen, X.Y. Peng, J.S. Guo, Occurrence and fate of pharmaceutically active compounds in the largest municipal wastewater treatment plant in Southwest China: Mass balance analysis and consumption back-calculated model, Chemosphere. 99 (2014) 160–170. doi:10.1016/j.chemosphere.2013.10.062.

[41] P. Guerra, M. Kim, A. Shah, M. Alaee, S.A. Smyth, Occurrence and fate of antibiotic, analgesic/anti-inflammatory, and antifungal compounds in five wastewater treatment processes, Sci. Total Environ. 473–474 (2014) 235–243. doi:10.1016/j.scitotenv.2013.12.008.

[42] Q. Yan, X. Gao, Y.P. Chen, X.Y. Peng, Y.X. Zhang, X.M. Gan, C.F. Zi, J.S. Guo, Occurrence, fate and ecotoxicological assessment of pharmaceutically active compounds in wastewater and sludge from wastewater treatment plants in Chongqing, the Three Gorges Reservoir Area, Sci. Total Environ. 470–471 (2014) 618–630. doi:10.1016/j.scitotenv.2013.09.032.

[43] B. Subedi, S. Lee, H.B. Moon, K. Kannan, Emission of artificial sweeteners, select pharmaceuticals, and personal care products through sewage sludge from wastewater treatment plants in Korea, Environ. Int. 68 (2014) 33–40. doi:10.1016/j.envint.2014.03.006.

[44] A. Garcia-Rodríguez, E. Sagristà, V. Matamoros, C. Fontàs, M. Hidalgo, V. Salvadó, Determination of pharmaceutical compounds in sewage sludge using a standard addition method approach, Int. J. Environ. Anal. Chem. 94 (2014) 1199–1209. doi:10.1080/03067319.2014.921292.

[45] H. Zhou, Q. Zhang, Q. Zhang, L. Ma, .B. Tu, H. Li, Y. Zhou, Removal of clofibric acid and diclofenac during anaerobic digestion of sewage sludge, Environ. Prot. Eng. 39 (2013) 63–77. doi:10.5277/epe130406.

[46] A.S. Stasinakis, N.S. Thomaidis, O.S. Arvaniti, A.G. Asimakopoulos, V.G. Samaras, A. Ajibola, D. Mamais, T.D. Lekkas, Contribution of primary and secondary treatment on the removal of benzothiazoles, benzotriazoles, endocrine disruptors, pharmaceuticals and perfluorinated compounds in a sewage treatment plant, Sci. Total Environ. 463–464 (2013) 1067–1075. doi:10.1016/j.scitotenv.2013.06.087.

[47] A. Lajeunesse, S.A. Smyth, K. Barclay, S. Sauvé, C. Gagnon, Distribution of antidepressant residues in wastewater and biosolids following different treatment processes by municipal wastewater treatment plants in Canada, Water Res. 46 (2012) 5600–5612. doi:10.1016/j.watres.2012.07.042.

[48] Q. Huang, K. Zhang, Z. Wang, C. Wang, X. Peng, Enantiomeric determination of azole antifungals in wastewater and sludge by liquid chromatography–tandem mass spectrometry, Anal. Bioanal. Chem. 403 (2012) 1751–1760. doi:10.1007/s00216-012-5976-9.

[49] M. Shafrir, D. Avisar, Development method for extracting and analyzing antibiotic and hormone residues from treated wastewater sludge and composted biosolids, Water. Air. Soil Pollut. 223 (2012) 2571–2587. doi:10.1007/s11270-011-1049-5.

[50] Y. Yu, L. Wu, Analysis of endocrine disrupting compounds, pharmaceuticals and personal care products in sewage sludge by gas chromatography-mass spectrometry, Talanta. 89 (2012) 258–263. doi:10.1016/j.talanta.2011.12.023.

[51] J. Cristale, S. Lacorte, Development and validation of a multiresidue method for the analysis of polybrominated diphenyl ethers, new brominated and organophosphorus flame retardants in sediment, sludge and dust, J. Chromatogr. A. 1305 (2013) 267–275. doi:10.1016/j.chroma.2013.07.028.

[52] A.G. Asimakopoulos, A. Ajibola, K. Kannan, N.S. Thomaidis, Occurrence and removal efficiencies of benzotriazoles and benzothiazoles in a wastewater treatment plant in Greece, Sci. Total Environ. 452–453 (2013) 163–171. doi:10.1016/j.scitotenv.2013.02.041.

[53] C. Schoeman, M. Dlamini, O.J. Okonkwo, The impact of a Wastewater Treatment Works in Southern Gauteng, South Africa on efavirenz and nevirapine discharges into the aquatic environment, Emerg. Contam. 3 (2017) 95–106. doi:10.1016/j.emcon.2017.09.001.

[54] A. Luque-Muñoz, J.L. Vílchez, A. Zafra-Gómez, Multiclass method for the determination of pharmaceuticals and personal care products in compost from sewage sludge using ultrasound and salt-assisted liquid–liquid extraction followed by ultrahigh performance liquid chromatography-tandem mass spectrometry, J. Chromatogr. A. 1507 (2017) 72–83. doi:10.1016/j.chroma.2017.05.051.

[55] N. Dorival-García, A. Zafra-Gómez, F.J. Camino-Sánchez, A. Navalón, J.L. Vílchez, Analysis of quinolone antibiotic derivatives in sewage sludge samples by liquid chromatography-tandem mass spectrometry: Comparison of the efficiency of three extraction techniques, Talanta. 106 (2013) 104–118. doi:10.1016/j.talanta.2012.11.080.

[56] X. Yuan, Z. Qiang, W. Ben, B. Zhu, J. Liu, Rapid detection of multiple class pharmaceuticals in both municipal wastewater and sludge with ultra high performance liquid chromatography tandem mass spectrometry, J. Environ. Sci. (China). 26 (2014) 1949–1959. doi:10.1016/j.jes.2014.06.022.

[57] N. Vakondios, A.A. Mazioti, E.E. Koukouraki, E. Diamadopoulos, An analytical method for measuring specific endocrine disruptors in activated sludge (biosolids) using solid phase microextraction-gas chromatography, J. Environ. Chem. Eng. 4 (2016) 1910–1917. doi:10.1016/j.jece.2016.03.018.

[58] C. Abril, J.L. Santos, J.L. Malvar, J. Martín, I. Aparicio, E. Alonso, Determination of perfluorinated compounds, bisphenol A, anionic surfactants and personal care products in digested sludge, compost and soil by liquid-chromatography-tandem mass spectrometry, J. Chromatogr. A. 1576 (2018) 34–41. doi:10.1016/j.chroma.2018.09.028.

[59] B. Subedi, K. Balakrishna, D.I. Joshua, K. Kannan, Mass loading and removal of pharmaceuticals and personal care products including psychoactives, antihypertensives, and antibiotics in two sewage treatment plants in southern India, Chemosphere. 167 (2017) 429–437. doi:10.1016/j.chemosphere.2016.10.026.

[60] C.S. Eskilsson, E. Björklund, Analytical-scale microwave-assisted extraction, J. Chromatogr. A. 902 (2000) 227–50. http://www.ncbi.nlm.nih.gov/pubmed/11192157.

[61] A. Morales-Toledo, C. Afonso-Olivares, S. Montesdeoca-Esponda, R. Guedes-Alonso, Z. Sosa-Ferrera, J.J. Santana-Rodríguez, Optimization and development of SPE and MAE combined with UHPLCFD for the determination of acetylsalicylic acid, naproxen, ibuprofen and gemfibrozil in sewage and sludge samples, Curr. Anal. Chem. 12 (2016) 545–552. doi:10.2174/1573411012666160113235153.

[62] B. Petrie, J. Youdan, R. Barden, B. Kasprzyk-Hordern, Multi-residue analysis of 90 emerging contaminants in liquid and solid environmental matrices by ultra-high-performance liquid chromatography tandem mass spectrometry, J. Chromatogr. A. 1431 (2016) 64–78. doi:10.1016/j.chroma.2015.12.036.

[63] N. Dorival-García, C. Labajo-Recio, A. Zafra-Gómez, B. Juárez-Jiménez, J.L. Vílchez, Improved sample treatment for the determination of 17 strong sorbed quinolone antibiotics from compost by ultra high performance liquid chromatography tandem mass spectrometry, Talanta. 138 (2015) 247–257. doi:10.1016/j.talanta.2015.03.011.

[64] S.E. Evans, P. Davies, A. Lubben, B. Kasprzyk-Hordern, Determination of chiral pharmaceuticals and illicit drugs in wastewater and sludge using microwave assisted extraction, solid-phase extraction and chiral liquid chromatography coupled with tandem mass spectrometry, Anal. Chim. Acta. 882 (2015) 112–126. doi:10.1016/j.aca.2015.03.039.

[65] A. Azzouz, E. Ballesteros, Combined microwave-assisted extraction and continuous solid-phase extraction prior to gas chromatography-mass spectrometry determination of pharmaceuticals, personal care products and hormones in soils, sediments and sludge, Sci. Total Environ. 419 (2012) 208–215. doi:10.1016/j.scitotenv.2011.12.058.

[66] T. wang, Z. Sosa-Ferrera, J.J. Santana-Rodríguez, Determination of various estradiol mimicking-compounds in sewage sludge by the combination of microwave-assisted extraction and LC-MS/MS, Talanta. 85 (2011) 1825–1834. doi:10.1016/j.talanta.2011.07.051.

[67] M.L. Svoboda, J.-J. Yang, P. Falletta, H.-B. Lee, A microwave-assisted extraction method for the determination of synthetic musks in sewage sludge, Water Qual. Res. J. Canada. 42 (2007) 11–19.

[68] S.F. Wu, W.H. Ding, Fast determination of synthetic polycyclic musks in sewage sludge and sediments by microwave-assisted headspace solid-phase microextraction and gas chromatography-mass spectrometry, J. Chromatogr. A. 1217 (2010) 2776–2781. doi:10.1016/j.chroma.2010.02.067.

[69] S. Morales, P. Canosa, I. Rodríguez, E. Rubí, R. Cela, Microwave assisted extraction followed by gas chromatography with tandem mass spectrometry for the determination of triclosan and two related chlorophenols in sludge and sediments, J. Chromatogr. A. 1082 (2005) 128–135. doi:10.1016/j.chroma.2005.05.059.

[70] A. Nieto, F. Borrull, E. Pocurull, R.M. Marcé, Pressurized liquid extraction: A useful technique to extract pharmaceuticals and personal-care products from sewage sludge, TrAC - Trends Anal. Chem. 29 (2010) 752–764. doi:10.1016/j.trac.2010.03.014.

[71] C. vom Eyser, T.C. Schmidt, J. Tuerk, Fate and behaviour of diclofenac during hydrothermal carbonization, Chemosphere. 153 (2016) 280–286. doi:10.1016/j.chemosphere.2016.03.051.

[72] Z. Křesinová, L. Linhartová, K. Petrů, L. Krejčová, K. Šrédlová, O. Lhotský, Z. Kameník, T. Cajthaml, Method for analysis of psychopharmaceuticals in real industrial wastewater and groundwater with suspended organic particulate matter using solid phase extraction disks extraction and ultra-high performance liquid chromatography/time-of-flight mass spectro, J. Chromatogr. A. 1440 (2016) 15–22. doi:10.1016/j.chroma.2016.02.035.

[73] C. Vom Eyser, K. Palmu, R. Otterpohl, T.C. Schmidt, J. Tuerk, Determination of pharmaceuticals in sewage sludge and biochar from hydrothermal carbonization using different quantification approaches and matrix effect studies, Anal. Bioanal. Chem. 407 (2015) 821–830. doi:10.1007/s00216-014-8068-1.

[74] A. Jelic, F. Fatone, S. Di Fabio, M. Petrovic, F. Cecchi, D. Barcelo, Tracing pharmaceuticals in a municipal plant for integrated wastewater and organic solid waste treatment, Sci. Total Environ. 433 (2012) 352–361. doi:10.1016/j.scitotenv.2012.06.059.

[75] P. Gao, Y. Ding, H. Li, I. Xagoraraki, Occurrence of pharmaceuticals in a municipal wastewater treatment plant: Mass balance and removal processes, Chemosphere. 88 (2012) 17–24. doi:10.1016/j.chemosphere.2012.02.017.

[76] E. Barón, E. Eljarrat, D. Barceló, Gas chromatography/tandem mass spectrometry method for the simultaneous analysis of 19 brominated compounds in environmental and biological samples, Anal. Bioanal. Chem. 406 (2014) 7667–7676. doi:10.1007/s00216-014-8196-7.

[77] P. Gao, M. Munir, I. Xagoraraki, Correlation of tetracycline and sulfonamide antibiotics with corresponding resistance genes and resistant bacteria in a conventional municipal wastewater treatment plant, Sci. Total Environ. 421–422 (2012) 173–183. doi:10.1016/j.scitotenv.2012.01.061.

[78] Y. Chen, Q. Cao, S. Deng, J. Huang, B. Wang, G. Yu, Determination of pharmaceuticals from various therapeutic classes in dewatered sludge by pressurized liquid extraction and high performance liquid chromatography and tandem mass spectrometry (HPLC-MS/MS), Int. J. Environ. Anal. Chem. 93 (2013) 1159–1173. doi:10.1080/03067319.2012.717271.

[79] ‡ Petros Dimitriou-Christidis,†,‡ Alex Bonvin,† Saer Samanipour,† Juliane Hollender,‡,§ Rebecca Rutler,† Jimmy Westphale,† Jonas Gros,† and J. Samuel Arey*,†, GC×GC Quantification of Priority and Emerging Nonpolar Halogenated Micropollutants in All Types of Wastewater Matrices: Analysis Methodology, Chemical Occurrence, and Partitioning, Appl. Phys. 49 (2015) 7914–7925.

[80] Y. Chen, G. Yu, Q. Cao, H. Zhang, Q. Lin, Y. Hong, Occurrence and environmental implications of pharmaceuticals in Chinese municipal sewage sludge, Chemosphere. 93 (2013) 1765–1772. doi:10.1016/j.chemosphere.2013.06.007.

[81] M. Gorga, S. Insa, M. Petrovic, D. Barceló, Analysis of endocrine disrupters and related compounds in sediments and sewage sludge using on-line turbulent flow chromatography-liquid chromatography-tandem mass spectrometry, J. Chromatogr. A. 1352 (2014) 29–37. doi:10.1016/j.chroma.2014.05.028.

[82] A. Jelic, M. Gros, A. Ginebreda, R. Cespedes-Sánchez, F. Ventura, M. Petrovic, D. Barcelo, Occurrence, partition and removal of pharmaceuticals in sewage water and sludge during wastewater treatment, Water Res. 45 (2011) 1165–1176. doi:10.1016/j.watres.2010.11.010.

[83] J. Radjenović, A. Jelić, M. Petrović, D. Barceló, Determination of pharmaceuticals in sewage sludge by pressurized liquid extraction (PLE) coupled to liquid chromatography-tandem mass spectrometry (LC-MS/MS), Anal. Bioanal. Chem. 393 (2009) 1685–1695. doi:10.1007/s00216-009-2604-4.

[84] A.M. Difrancesco, P.C. Chiu, L.J. Standley, H.E. Allen, D.T. Salvito, Dissipation of Fragrance Materials in Sludge-Amended Soils, Environ. Sci. Technol. 38 (2004) 194–201. doi:10.1021/es034618v.

[85] C.C. Teo, S.N. Tan, J.W.H. Yong, C.S. Hew, E.S. Ong, Pressurized hot water extraction (PHWE), J. Chromatogr. A. 1217 (2010) 2484–2494. doi:10.1016/j.chroma.2009.12.050.

[86] R.M. Smith, Extractions with superheated water, J. Chromatogr. A. 975 (2002) 31–46. doi:10.1016/S0021-9673(02)01225-6.

[87] J.M. Cortés, E. Larsson, J.Å. Jönsson, Study of the uptake of non-steroid anti-inflammatory drugs in wheat and soybean after application of sewage sludge as a fertilizer, Sci. Total Environ. 449 (2013) 385–389. doi:10.1016/j.scitotenv.2013.01.061.

[88] A. Saleh, E. Larsson, Y. Yamini, J.Å. Jönsson, Hollow fiber liquid phase microextraction as a preconcentration and clean-up step after pressurized hot water extraction for the determination of non-steroidal anti-inflammatory drugs in sewage sludge, J. Chromatogr. A. 1218 (2011) 1331–1339. doi:10.1016/j.chroma.2011.01.011.

[89] A.L. Capriotti, C. Cavaliere, P. Giansanti, R. Gubbiotti, R. Samperi, A. Laganà, Recent developments in matrix solid-phase dispersion extraction, J. Chromatogr. A. 1217 (2010) 2521–2532. doi:10.1016/j.chroma.2010.01.030.

[90] S.A. Barker, Matrix solid phase dispersion (MSPD), J. Biochem. Biophys. Methods. 70 (2007) 151–162. doi:10.1016/j.jbbm.2006.06.005.

[91] S. Triñanes, M.C. Casais, M.C. Mejuto, R. Cela, Matrix solid-phase dispersion followed by liquid chromatography tandem mass spectrometry for the determination of selective ciclooxygenase-2 inhibitors in sewage sludge samples, J. Chromatogr. A. 1462 (2016) 35–43. doi:10.1016/j.chroma.2016.07.044.

[92] M. Li, Q. Sun, Y. Li, M. Lv, L. Lin, Y. Wu, M. Ashfaq, C. ping Yu, Simultaneous analysis of 45 pharmaceuticals and personal care products in sludge by matrix solid-phase dispersion and liquid chromatography tandem mass spectrometry, Anal. Bioanal. Chem. 408 (2016) 4953–4964. doi:10.1007/s00216-016-9590-0.

[93] M.B.R. Cerqueira, K.L. Soares, S.S. Caldas, E.G. Primel, Sample as solid support in MSPD: A new possibility for determination of pharmaceuticals, personal care and degradation products in sewage sludge, Chemosphere. 211 (2018) 875–883. doi:10.1016/j.chemosphere.2018.07.165.

[94] G. Castro, M. Roca, I. Rodríguez, M. Ramil, R. Cela, Identification and determination of chlorinated azoles in sludge using liquid chromatography quadrupole time-of-flight and triple quadrupole mass spectrometry platforms, J. Chromatogr. A. 1476 (2016) 69–76. doi:10.1016/j.chroma.2016.11.020.

[95] T. Ruan, Y. Lin, T. Wang, R. Liu, G. Jiang, Identification of novel polyfluorinated ether sulfonates as PFOS alternatives in municipal sewage sludge in China, Environ. Sci. Technol. 49 (2015) 6519–6527. doi:10.1021/acs.est.5b01010.

[96] C. Sánchez-Brunete, E. Miguel, J.L. Tadeo, Analysis of polybrominated diphenyl ethers in sewage sludge by matrix solid-phase dispersion and isotope dilution GC-MS, J. Sep. Sci. 32 (2009) 109–117. doi:10.1002/jssc.200800479.

[97] M.J. Martínez Bueno, C. Boillot, H. Fenet, S. Chiron, C. Casellas, E. Gómez, Fast and easy extraction combined with high resolution-mass spectrometry for residue analysis of two anticonvulsants and their transformation products in marine mussels, J. Chromatogr. A. 1305 (2013) 27–34. doi:10.1016/j.chroma.2013.06.071.

[98] A.V. Marta-Sanchez, S.S. Caldas, A. Schneider, S.M.V.S. Cardoso, E.G. Primel, Trace analysis of parabens preservatives in drinking water treatment sludge, treated, and mineral water samples, Environ. Sci. Pollut. Res. 25 (2018) 14460–14470. doi:10.1007/s11356-018-1583-4.

[99] N. Muhammad, Q. Subhani, F. Wang, D. Guo, Q. Zhao, S. Wu, Y. Zhu, Application of a simple column-switching ion chromatography technique for removal of matrix

interferences and sensitive fluorescence determination of acidic compounds (pharmaceutical drugs) in complex samples, J. Chromatogr. A. 1515 (2017) 69–80. doi:10.1016/j.chroma.2017.07.007.

[100] W. Peysson, E. Vulliet, Determination of 136 pharmaceuticals and hormones in sewage sludge using quick, easy, cheap, effective, rugged and safe extraction followed by analysis with liquid chromatography-time-of-flight-mass spectrometry, J. Chromatogr. A. 1290 (2013) 46–61. doi:10.1016/j.chroma.2013.03.057.

[101] M.B.R. Cerqueira, J.R. Guilherme, S.S. Caldas, M.L. Martins, R. Zanella, E.G. Primel, Evaluation of the QuEChERS method for the extraction of pharmaceuticals and personal care products from drinking-water treatment sludge with determination by UPLC-ESI-MS/MS, Chemosphere. 107 (2014) 74–82. doi:10.1016/j.chemosphere.2014.03.026.

[102] S. Ramos, V. Homem, L. Santos, Development and optimization of a QuEChERS-GC–MS/MS methodology to analyse ultraviolet-filters and synthetic musks in sewage sludge, Sci. Total Environ. 651 (2019) 2606–2614. doi:10.1016/j.scitotenv.2018.10.143.

[103] P. Campíns-Falcó, A. Sevillano-Cabeza, R. Herráez-Hernández, C. Molins-Legua, Y. Moliner-Martínez, J. Verdú-Andrés, Solid-Phase Extraction and Clean-Up Procedures in Pharmaceutical Analysis, Encycl. Anal. Chem. (2012). doi:10.1002/9780470027318.a1920.pub2.

[104] V. Camel, Solid phase extraction of trace elements, Spectrochim. Acta - Part B At. Spectrosc. 58 (2003) 1177–1233. doi:10.1016/S0584-8547(03)00072-7.

[105] L. Vallecillos, E. Pocurull, F. Borrull, A simple and automated method to determine macrocyclic musk fragrances in sewage sludge samples by headspace solid-phase microextraction and gas chromatography-mass spectrometry, J. Chromatogr. A. 1314 (2013) 38–43. doi:10.1016/j.chroma.2013.09.033.

[106] K. Bester, Triclosan in a sewage treatment process - Balances and monitoring data, Water Res. 37 (2003) 3891–3896. doi:10.1016/S0043-1354(03)00335-X.

[107] T.Y. Chiu, Y.K.K. Koh, N. Paterakis, A.R. Boobis, E. Cartmell, K.H. Richards, J.N. Lester, M.D. Scrimshaw, The significance of sample mass in the analysis of steroid estrogens in sewage sludges and the derivation of partition coefficients in wastewaters, J. Chromatogr. A. 1216 (2009) 4923–4926. doi:10.1016/j.chroma.2009.04.019.

[108] T.A. Ternes, H. Andersen, D. Gilberg, M. Bonerz, Determination of estrogens in sludge and sediments by liquid extraction and GC/MS/MS, Anal. Chem. 74 (2002) 3498–3504. doi:10.1021/ac015717z.

[109] B. Wang, T. Ezejias, H. Feng, H. Blaschek, Sugaring-out: A novel phase separation and extraction system, Chem. Eng. Sci. 63 (2008) 2595–2600. doi:10.1016/j.ces.2008.02.004.

[110] A. Kaleta, M. Ferdig, W. Buchberger, Semiquantitative determination of residues of amphetamine in sewage sludge samples, J. Sep. Sci. 29 (2006) 1662–1666. doi:10.1002/jssc.200500465.

[111] R. Céspedes, S. Lacorte, A. Ginebreda, D. Barceló, Occurrence and fate of alkylphenols and alkylphenol ethoxylates in sewage treatment plants and impact on receiving waters along the Ter River (Catalonia, NE Spain), Environ. Pollut. 153 (2008) 384–392. doi:10.1016/j.envpol.2007.08.026.

[112] M. Taleuzzaman, S. Ali, S. Gilani, I. Imam, A. Hafeez, Ultra Performance Liquid Chromatography (UPLC) - A Review, Austin J Anal Pharm Chem. Austin J Anal Pharm Chem. 2 (2015) 1056–6. http://austinpublishinggroup.com/analytical-pharmaceutical-chemistry/fulltext/ajapc-v2-id1056.php#Advantages of UPLC.

[113] R. Iberoamericana, Boletín Boletín, (2009).

[114] G. Alvarez-Rivera, M. Llompart, C. Garcia-Jares, M. Lores, Identification of halogenated photoproducts generated after ultraviolet-irradiation of parabens and benzoates in water containing chlorine by solid-phase microextraction and gas chromatography-mass spectrometry, J. Chromatogr. A. 1349 (2014) 105–115. doi:10.1016/j.chroma.2014.05.009.

[115] M. Vila, J. Pablo Lamas, C. Garcia-Jares, T. Dagnac, M. Llompart, Ultrasound-assisted emulsification microextraction followed by gas chromatography-mass spectrometry and gas chromatography-tandem mass spectrometry for the analysis of UV filters in water, Microchem. J. 124 (2016) 530–539. doi:10.1016/j.microc.2015.09.023.

[116] M. Vila, M. Celeiro, J.P. Lamas, C. Garcia-Jares, T. Dagnac, M. Llompart, Simultaneous in-vial acetylation solid-phase microextraction followed by gas chromatography tandem mass spectrometry for the analysis of multiclass organic UV filters in water, J. Hazard. Mater. 323 (2017) 45–55. doi:10.1016/j.jhazmat.2016.06.056.

[117] J. Regueiro, M. Llompart, E. Psillakis, J.C. Garcia-Monteagudo, C. Garcia-Jares, Ultrasound-assisted emulsification-microextraction of phenolic preservatives in water, Talanta. 79 (2009) 1387–1397. doi:10.1016/j.talanta.2009.06.015.

[118] E. Becerril-Bravo, J. Pablo Lamas, L. Sanchez-Prado, M. Lores, C. Garcia-Jares, B. Jimenez, M. Llompart, Ultrasound-assisted emulsification-microextraction of fragrance allergens in water, Chemosphere. 81 (2010) 1378–1385. doi:10.1016/j.chemosphere.2010.09.028.

[119] R. López-Serna, B. Kasprzyk-Hordern, M. Petrović, D. Barceló, Multi-residue enantiomeric analysis of pharmaceuticals and their active metabolites in the Guadalquivir River basin (South Spain) by chiral liquid chromatography coupled with tandem mass spectrometry, Anal. Bioanal. Chem. 405 (2013) 5859–5873. doi:10.1007/s00216-013-6900-7.

[120] B. Petrie, J. Mrazova, B. Kasprzyk-Hordern, K. Yates, Multi-residue analysis of chiral and achiral trace organic contaminants in soil by accelerated solvent extraction and

enantioselective liquid chromatography tandem–mass spectrometry, J. Chromatogr. A. 1572 (2018) 62–71. doi:10.1016/j.chroma.2018.08.034.

[121] S.S. Patil, U.U. Shedbalkar, A. Truskewycz, B.A. Chopade, A.S. Ball, Nanoparticles for environmental clean-up: A review of potential risks and emerging solutions, Environ. Technol. Innov. 5 (2016) 10–21. doi:10.1016/j.eti.2015.11.001.

[122] FDA, Draft Guidance for Industry Use of Nanomaterials in Food for Animals, (2014) 10.http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM401508.pdf.

[123] Georgia Miller, Lisa Archer, Erich Pica, D.R.S. and G.K. Dick Bell, Nanomaterials, sunscreens and cosmetic: small ingredients, big risks, Friends Earth Aust. Friends Earth United States. (n.d.).

[124] Y. Hao, R. Gao, L. Shi, D. Liu, Y. Tang, Z. Guo, Water-compatible magnetic imprinted nanoparticles served as solid-phase extraction sorbents for selective determination of trace 17beta-estradiol in environmental water samples by liquid chromatography, J. Chromatogr. A. 1396 (2015) 7–16. doi:10.1016/j.chroma.2015.03.083.

[125] J. Zhang, B. Sun, X. Xiong, N. Gao, W. Song, E. Du, X. Guan, G. Zhou, Removal of emerging pollutants by Ru/TiO2-catalyzed permanganate oxidation, Water Res. 63 (2014) 262–270. doi:10.1016/j.watres.2014.06.028.

[126] A. Ballesteros-Gómez, M.D. Sicilia, S. Rubio, Supramolecular solvents in the extraction of organic compounds. A review, Anal. Chim. Acta. 677 (2010) 108–130. doi:10.1016/j.aca.2010.07.027.

[127] A. Beiraghi, K. Pourghazi, M. Amoli-Diva, Mixed supramolecular hemimicelles aggregates and magnetic carrier technology for solid phase extraction of ibuprofen in environmental samples prior to its HPLC-UV determination, Chem. Eng. Sci. 108 (2014) 103–110. doi:10.1016/j.ces.2013.12.044.

[128] E. Aguilera-Herrador, R. Lucena, S. Cárdenas, M. Valcárcel, The roles of ionic liquids in sorptive microextraction techniques, TrAC - Trends Anal. Chem. 29 (2010) 602–616. doi:10.1016/j.trac.2009.11.009.

[129] L. Vallecillos, F. Borrull, E. Pocurull, Determination of musk fragrances in sewage sludge by pressurized liquid extraction coupled to automated ionic liquid-based headspace single-drop microextraction followed by GC-MS/MS, J. Sep. Sci. 35 (2012) 2735–2742. doi:10.1002/jssc.201200326.

[130] M. Schlabach, Non-target screening – A powerful tool for selecting environmental pollutants, Trondheim NILU – Nor. Inst. Luftforskning. 1st ed (2013).

[131] A.K. Huba, Going Beyond the Analysis of Common Contaminants : Target , Suspect , and Non-Target Analysis of Complex Environmental Matrices by High-Resolution Mass Spectrometry, (2016). doi:10.25148/etd.FIDC001186.

[132] P. Gago-Ferrero, E.L. Schymanski, A.A. Bletsou, R. Aalizadeh, J. Hollender, N.S. Thomaidis, Extended Suspect and Non-Target Strategies to Characterize Emerging Polar Organic Contaminants in Raw Wastewater with LC-HRMS/MS, Environ. Sci. Technol. 49 (2015) 12333–12341. doi:10.1021/acs.est.5b03454.

[133] A. Jakimska, M. Śliwka-Kaszyńska, J. Reszczyńska, J. Namieśnik, A. Kot-Wasik, Elucidation of transformation pathway of ketoprofen, ibuprofen, and furosemide in surface water and their occurrence in the aqueous environment using UHPLC-QTOF-MS Euroanalysis XVII, Anal. Bioanal. Chem. 406 (2014) 3667–3680. doi:10.1007/s00216-014-7614-1.

[134] C.P. Higgins, J.A. Field, C.S. Criddle, R.G. Luthy, Quantitative determination of perfluorochemicals in sediments and domestic sludge, Environ. Sci. Technol. 39 (2005) 3946–3956. doi:10.1021/es048245p.

[135] A. Göbel, A. Thomsen, C.S. McArdell, A. Joss, W. Giger, Occurrence and sorption behavior of sulfonamides, macrolides, and trimethoprim in activated sludge treatment, Environ. Sci. Technol. 39 (2005) 3981–3989. doi:10.1021/es048550a.

[136] P. Gago-Ferrero, M.S. Díaz-Cruz, D. Barceló, Occurrence of multiclass UV filters in treated sewage sludge from wastewater treatment plants, Chemosphere. 84 (2011) 1158–1165. doi:10.1016/j.chemosphere.2011.04.003.

[137] B.M. Validation, Bioanalytical Method Validation Guidance, Cder. (2001) 25.

[138] B. Magnusson, The Fitness for Purpose of Analytical Methods, 2014. doi:10.1016/S0014-2999(99)00500-2.

[139] and P.B. Jay Breaux , Kevin Jones, Understanding and Implementing Efficient Analytical Methods Development and Validation, Pharm. Technol. (2003) 6–13. doi:10.1542/peds.2011-1215.

[140] A. Jelić, M. Petrović, D. Barceló, Multi-residue method for trace level determination of pharmaceuticals in solid samples using pressurized liquid extraction followed by liquid chromatography/quadrupole-linear ion trap mass spectrometry, Talanta. 80 (2009) 363–371. doi:10.1016/j.talanta.2009.06.077.

[141] W. Chenxi, A.L. Spongberg, J.D. Witter, Determination of the persistence of pharmaceuticals in biosolids using liquid-chromatography tandem mass spectrometry, Chemosphere. 73 (2008) 511–518. doi:10.1016/j.chemosphere.2008.06.026.

[142] M. Khoshkhoo, Research Report Sustainable and energy efficient leaching of Örjan Johansson, Taraka Pamidi, Mohammad Khoshkhoo, Åke Sandström, (2017).

[143] A. Klančar, J. Trontelj, R. Roškar, Development of a Multi-Residue Method for Monitoring 44 Pharmaceuticals in Slovene Surface Water by SPE-LC-MS/MS, Water. Air. Soil Pollut. 229 (2018). doi:10.1007/s11270-018-3845-7.

[144] O. Svahn, E. Björklund, Extraction Efficiency of a Commercial Espresso Machine Compared to a Stainless-Steel Column Pressurized Hot Water Extraction (PHWE) System for the Determination of 23 Pharmaceuticals, Antibiotics and Hormones in Sewage Sludge, Appl. Sci. 9 (2019) 1509. doi:10.3390/app9071509.

1 **Figure legends**

2 Fig.1. Extraction techniques for PPCPs in sewage sludge

3 Fig.2. Clean-up techniques for PPCPs in sewage sludge

4 Fig.3. Instrumental analysis techniques for PPCPs in sewage sludge

5 Fig.4. Calibration methods used in the quantification of PPCPs in sewage sludge

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Table 1: Determination of PPCPs in sewage sludge based on traditional extraction techniques (Soxhlet and UAE)

Analyte	Sample type	Extraction technique	Clean-up	Analysis	Quantification technique	LOQ (ng/g)	Recovery (%)	Precision (%)	Ref.
3 NPE: NP, NP2EO, NP1EO	Primary and secundary sludge. (Freeze-dried 1g)	Soxhlet MeOH by DCM Overnight	The remaining extract was solvent-exchanged into cyclohexane for further cleanup prior to LC/MS analysis	LC-MS	Labeled internal standard (3) Non-labeled internal standard (2)	(0.4 (NP) 1.3 (NP1EO) 0.2 (NP2EO))[e] mg/kg	94 (NP) 94 (NP1EO) 112 (NP2EO)	1.3 (NP) 4.1 (NP1EO) 10.9 (NP2EO)	[20]
2 PhACs (1-stearoyl-1h-1,2,4-triazole)	Sewage sludge (200 g d.w)	Soxhlet 300 mL DCM/acetone (1:1) 8 h	a	GC-MS	Qualification	d	d	d	[21]
9 PBDE congeners: (BDE congeners 28, 47, 99, 100, 153, 154, 183, and 209) 2,2',4,4',5,5'Hexabromobiphenyl (BB-153)	Dewatered sludge (Oven dried 50ºC) (10g)	Soxhlet N-hexane and acetone (3:1) 16h	Draft Method 1614 for PBDE determination in wastewater and biosolid was employed with some modifications (USEPA 2007)	GC-ECD	d	d	>85% absolute recoveries	d	[22]
6 Flame retardants (TBECH, BTBPE, DBDPE, EBTPI, TBBPA AE, TBBPA DBPE)	Sewage sludge (Freeze-dried)	Soxhlet MeOH 15 h	a	The extracts were divided in two parts, one for GC–MS analysis and one for HPLC–MS analysis.	Labeled (^{13}C) internal standard	0.02 - 1.6	d	d	[23]
4 Benzotriazole UV stabilizers (UV 320, UV326, UV 327, UV 328)	Sewage sludge (Freeze-dried 2g)	Soxhlet (DCM:Hexane) (8:1) 6 h	SPE (Oasis HLB)	GC-MS	d	(0.0021-0.0087)[b]	(98-115)%	d	[24]
12 PPCPs (PhACs (IBP, NPX, DCF, SA, RAM) and PCPs (MP, EP, PP, CA, TCS, PHBA, BQ)	Digested sludge (0.8g)	UAE (2 cycles) 15 mL MilliQ water pH 9 30 min	a	Online DI-SPME – On-Fiber Derivatization – GC – MS	Matrix-matched Isotopically labelled internal standard (6)	<10[b]	(5.69-103.59)% absolute recoveries	< 10%	[28]

Table 1 (Continued)

10 EDCs and PPCPs (CBZ, SMX, TCS, 4-NP, BPA, OBZ), four estrogens (E1, E2, E3, EE2)	(Freeze-dried 0.5g) (Before and after anaerobic digestion)	UAE (2 cycles) 4 mL MeOH/Acetone (1:1)10 min	SPE (Oasis HLB)	LC-MS	Isotopically labelled internal standard (1)	1.6-100 (pg absolute))	(75-106)%	< 20%	[29]
29 PPCPs (NSAIDs, antibiotics,stimulant, preservatives)	Return sludge (0.1g)	USEPA SPE method 1694[f]	SPE (Oasis HLB)	LC- MS/MS	Isotopic standards (5)	0.1-5.0[c]	(31-93)%	<20%	[30]
1 NSAID (DCF)	Wastewater sludge (Primary sludge, secondary sludge) (Lyophilized 0.5 g)	UAE MeOH 20 mL 15 min	SPE (Sep-Pak C18 plus Short Cartridges)	LDTD-APCI-MS/MS	Isotopically labelled internal standards (1)	75[c]	(86 ± 4)%	8.6% (repeatability) and 9.8% (reproducibility)	[31]
18 Antibiotics (sulfonamides, tetracyclines, quinolones, macrolides, and β-lactams)	Dewatered sludge (Lyophilized and sieved sludge 0.5 g)	UAE 10 mL MeOH-EDTA-citrate buffer (3:1:2)	SPE (Oasis HLB)	UPLC-MS/MS	Standard addition Internal standard (1)	0.3-3.2	(60.1–92.7)%	(0.5-4.7)%	[32]
8 PhACs (DCF, APh, NPX, GEM, CA, PH, CAF, Chol)	Sludge sample (dewatered) (25 g)	UAE MeOH 20 mL 30 min	SPE	Derivatization-GC-MS/MS	Internal standard (1)	(1.7-9.4) ng/L	(73-95)%	(8.9-20.4)%	[33]
34 PhACs (antibiotics, analgesic and/or anti-inflammatory drugs, antiepileptics, benzodiazepines, antipsychotics, and antidepressants)	Freeze-dried sewage sludge (0.1g)	UAE 2 mL MeOH-MilliQ water 15 min 50°C	a	LC-MS/MS	Standard additions Isotopically labeled internal standard (10)	< 55[e]	(16-119)% absolute recoveries	<20%	[34]
153 compounds: pharmaceuticals, herbicides, antioxidants, intermediates, organic solvents and chemical raw materials	Sludge samples	UAE (3 cycles) DCM 20 min	Gel permeation chromatography (GPC) and a silica gel column	GC-MS	d	d	d	(5.8-14.9) %	[35]

Table 1 (Continued)

13 PhACs (4-AA, 4-AAA, 4-FAA, BZE, TBZ, VNF, CBZ, IRB, VAL, DCF, SA, ACE, FA)	Lyophilized sewage sludge (0.1g)	USE MeOH-MilliQ water 15 min 50ºC	a	(AMDIS) LC-MS/MS	Isotopically-Labeled Internal Standards (ILIS) (6)	50-2000	(70-120)%	< 20 %	[36]
30 Steroidal compounds (androstanes, pregnanes, estrone, cholestanes)	Compost Dry sludge (0.05g)	USE (2 cycles) 6 mL AcCN 60 min	SPE (cartridges Strata-X and Florisil)	Derivatization-GCXGC-TOFMS	Internal standard (1)	d	>90%	d	[37]
12 PhACs (ACE, FA, VAL, IRB, SA, DCF, CBZ, 4-AA, 4-AAA, 4-FA, VNF, BZE)	Lyophilized sludge (after anaerobic digestion) (0.1 g)	USE 2 mL MeOH-MilliQ water 15 min 50ºC	a	LC-MS/MS	Isotopically-Labeled Internal Standards (ILIS) (8)	<50	(70-120)%	< 20 %	[38]
1 NSAID (DCF)	Freeze dried sludge (0.1g)	UAE (2 cycles) 10 mL MeOH/Acetone (1:1)	SPE (Oasis HLB;MCX)	LC-MS/MS	Isotope labeled internal standard (ILIS) (1)	5	>80%	<20%	[39]
21 compounds: PhACs (analgesics (IBP, DCF, ACM), sulfonamide antibiotics (SDZ, SM1, SM2, TMP), macrolide antibiotics (ERY, ROX, AZM), quinolone antibiotics (OFX, NOR, MOX), antiepileptics (MTP, ALP), cholesterol lowering statin drugs (ATT, SVT), lipid regulators (BZB, CA, GFB), and antihypersensitives (CBZ)	Dewatered sludge (Freeze-dried 2g)	UAE (3 cycles) 10 mL MeOH/Citric acid/ Na_2EDTA (2:1:1) 15 min	SPE (Oasis HLB)	LC-MS/MS	Non-labeled internal standard (2) and labeled internal standard (2)	0.17 - 5.83	(46 –139)%	< 15 %	[40]
62 PhACs (antibiotic, analgesic/anti-inflammatory, and antifungal compounds)	Dry biosolids (0.5 g)	UAE EPA method 1694	SPE	LC-MS/MS	Isotopically labeled internal standard (16)	d	(20 – 150)%	< 22 %	[41]
18 PhACs (antibiotics, analgesics, antiepileptics, antilipidemics and antihypersensitives)	Primary and secondary sludge (EPA Method (1694 USEPA, 2007 with some modifications)	UAE 10 mL MeOH/citric acid/ Na_2EDTA (2:1:1) 15 min <40ºC	SPE (Oasis HLB)	LC-MS/MS	Non-labeled internal standard (1) and labeled internal standard (2)	0.17 - 5.83	(54 – 139)%	< 13 %	[42]

Table 1 (Continued)

15 compounds: 5 artificial sweeterners and 10 PPCPs (analgesics, antibiotics and PCPs)	Digested sludge (Freeze dried 0.1g)	UAE 6 mL MeOH/water (5:3) 30 min	SPE (C_{18} cartridges)	HPLC-MS/MS	Isotopically labeled internal standard (4)	5-50	(103 ± 24)%	< 14 %	[43]
8 PhACs: NSAIDs (NPX, DCF, and IBP), lipid regulators (CA), and antibiotics (SFT, SP, SMT, and SMX)	Urban biosolids (Freeze-dried 0.2g)	UAE (3 cycles) 2 mL MeOH/water (1:1) 15 min	0.2 µm nylon syringe filter	LC-MS/MS	Standard addition	2 -12[b] ($ng.g^{-1}dw$)	(76-131)% absolute recoveries	5-15%	[44]
2 compounds: Lipid regulator (CA), and NSAID (DCF)	Raw mixed sludge (Oven dried 60-70º C; 0.02g)	UAE 8 mL MeOH/wáter (5:3) 5 mL MeOH (3 times) 30 min 50ºC	SPE	GC-MS	No internal standard or surrogate used	d	101.8-105 % (CA) 98–104.3% (DCF)	d	[45]
36 emerging contaminants (BTRs; BTHs; PFCs; NSAIDs and EDCs)	Dewatered sludge	UAE 5 mL MeOH/MilliQ water (1:1) 45 min	SPE	GC-MS (for EDCs and NSAIDs) UHPLC -MS/MS (for PFCs, BTRs and BTHs)	Non-labeled internal standard (3) Labeled internal standard (6)	From 0.14 (MTBTH) to 108 ng g−1 dw (BPA)	(64–115) % for most of the target compounds. Lower recoveries (26.4%–59.8%) were observed for longer PFCAs and PFASs	< 15 %	[46]
15 compounds: 14 antidepressants along with their respective N-desmethyl metabolites and the anticonvulsive drug (CBZ)	Biosolids (Freeze dried 0.2g)	UAE 8 mL MeOH/acetic acid buffer solution (1:1) 15 min	SPE (cartridges Strata X-C)	LC-MS/MS	Standard addition Labeled internal standard (1) Non-labeled internal standard (1)	0.2 ng g-[1](CBZ), 0.4 ng g [-1](FLX), 0.1ng g [-1](PAR)	71 %, (CBZ), 97 % (FLX), 63% (PAR)	d	[47]

Table 1 (Continued)

5 Chiral azole antifungals	Secundary sludge. Lyophilized and homogenized sludge	UAE 4 mL MeOH (0.1% formic acid) 10 min	SPE (Oasis HLB)	LC-MS/MS	Isotope-labeled internal standard (ILIS) (4)	(3–29) ng g^{-1} d.w	(71-95)%	< 20%	[48]
6 compounds: 4 antibacterial agents (SMX, SDM, TET, OXY) and 2 natural estrogens (E1, E2)	Secondary sludge and compost (Freeze-dried 2g)	UAE (2 cycles) 10 mL MeOH/water 20 min	SPE Antibiotics (Strata SAX; Oasis HLB) Natural strogens (CarboPrep/NAX)	HPLC-MS/MS (ESI) source for antibiotics and (APCI) source for estrogens)	Standard addition	1.1 - 17.1	(17-59)% absolute recoveries for sludge (11-50)% absolute recoveries for compost	d	[49]
14 compounds: 4 EDCs (BPA, E1, NP and OP) and 10 PPCPs (ASA, CBZ, CA, DCF, GEM, IBP, KET, NPX, APAP, TCS)	Sewage sludge (1g)	UAE 5 mL MeOH (1% formic acid) 20 min	SPE (Oasis HLB)	Derivatization-GC-MS	Isotopically internal standard (2)	4.7 -39	(57.9-103.1)% absolute recoveries	(1.3–9.5)%	[50]
27 BFRs	Sludge samples (primary treatment: primary sludge; secondary treatment or anaerobic digestion: biological sludge) (Freeze dried 0.1g)	UAE 30 mL EtAc/cyclehexane (5:2) 10 min	Florisil cartridges	GC-MS/MS	Non-labeled internal standard (2)	28-575[c]	(79 -125)%	(3-26)%	[51]
8 compounds: 4 BTRs and 4 BTHs	Dewatered sewage sludge. Additional sludge samples from the primary and secondary settlement tanks were also collected (0.1g)	UAE 5 mL of acidified MeOH/Milli-Q water (1:1) 45 min	SPE (C_{18} cartridges)	LC-MS/MS	Internal standard method (labeled internal standard (2)) and with a matrix-matched calibration standard prepared by spiking target analytes into a matrix prior to extraction	0.04-13[b] ng/g d.w	Recoveries relative to BTR-d4 (64–116)% and to BTR-d5 (50–106)%.For 2-Me-S- BTH, the recovery values relative to BTR-d4 (>64%) both matrices	<15%	[52]

Table 1 (Continued)

2 Pharmaceutical drugs (EFV and NVP)	Dried sludge (oven-dried for 48 h at 40 ºC ± 3ºC) (Dried sludge 1g)	UAE 15 ml EtAc 45 min 50ºC	QuEChERS	GC-TOFMS	External standard Internal standard (1)	12900 (EFV) 11400 (NVP)	104.6%(EFV) 80.9 %(NVP)	3.3 % (EFV) 4.5 % (NVP)	[53]
16 PPCPs: NSAIDs (DCF, FLU, NAP, KET), liquid regulators (BEZ, FEN, GEM), parabens (MP, EP, PP, BP), benzophenones (4-OH-BP, BP1, BP3, BP6, BP8)	Compost from sewage sludge (Freeze-dried 0.5g)	UAE (2 cycles) 5 mL ACN:EtAc (1:1) containing 10% (v/v) of acetic acid 10 min	SALLE	UHPLC-MS/MS	Matrix–matched Surrogates (4)	2 - 13	(93-111)%	< 11%	[54]
13 Quinolones (PIP , ENO, NOR, CIP, OFL, ENR, LOM, MOX, CIN, NAL, OXO, FLU, PIR)	Dried sewage sludge (Oven dried 60ºC; 0.5g)	UAE (2 cycles) 5 mL MeOH/McIlvaine buffer, (50:50) 15 min	a	LC-MS/MS	Matrix-matched Surrogates (2)	4 - 18	(97.9-104.8)%	The inter-and intra-day variability was >7%	[55]
23 PhACs (sulfonamides, fluoroquinolones, tetracyclines, macrolides, trimethoprim, bet-blockers, anti-epileptics, lipid regulators, and stimulants)	Suspended solids (Freeze-dried sludge 0.5g)	UAE (3 cycles) 10 mL extraction solvent MilliQ water 10 min	SPE (Oasis HLB)	UHPLC-MS/MS	Isotopically labeled internal standard (3) Non-labeled internal standard (1)	0.02 - 1.00	(54–130)%	Intraday <11% Interday <13%	[56]
10 PhACs and ECDs (triclosan, 2,4-dichlorophenol, 2,3,4-trichlorophenol, bisphenol A, estrone, 17-beta-estradiol, 17-alpha-ethinylestradiol, androsterone, 5α-androstan-17β-ol-3-one and 19-norethindrone)	Activated sludge (1g dry solids)	UAE 6 mL MeOH 10 min	SPME	GC-MS	Matrix-matched	4-50	d	(2.19-12.10)%	[57]

Table 1 (Continued)

6 Perfluorinated compounds (5 perfluorocarboxylicacids and perfluorooctanesulfonic acid), the plasticizer BPA, four anionic surfactants (sodiumalkylsulfates), four preservatives (parabens), two antimicrobial agents (TCS and triclocarban TCC) and six UV-filters (benzophenones)	Digested sludge and compost (freeze-dried 1g)	UAE 3 mL MeOH: acetic acid (95:5) 7 min	d-SPE C_{18}	LC-MS/MS	Isotopically-labelled internal standards (4) Matrix-matched	(0.01-6.2)[d]	(70-120)%	<21%	[58]
29 PPCPs: 2 antischizophrenics 3 sedatives-hypnotics-anxiolytics, 3 antidepressants, 4antihypertensions, 1antimicrobial, 6 antibiotics, 4 analgesics,1 antihistamine, 1 antiplatelet, 1 UV-filter, 1 antihypercholesterolemic, and 1 stimulant	Activated sludge samples (0.1g freeze-dried)	UAE 6 mL MeOH:water (5:3) 30 min	SPE (Oasis HLB)	HPLC-MS/MS	Isotopically-labeled standards (7)	(0.5-50)ng/g	(77-122)%	d	[59]

Abbreviations: Acesulfame (ACE), acetonitrile (ACN), 4-acetylaminoantipyrine (4-AAA), acetylphenylhydrazine (APh), acetylsalicylic acid (ASA), 4-aminoantipyrine (4-AA), amlodipine (ALP), atmospheric-pressure chemical ionization (APCI), automated mass spectral deconvolution -identification system (AMDIS), atorbastatin (ATT), azithromycin (AZM), bezafibrate (BZB), benzophenone 1 (BP1), benzophenone 3 (BP·), benzophenone 6 (BP6), benzophenone 8 (BP8), p-benzoquinone (BQ), benzothiazoles (BTHs), benzotriazoles (BTRs), benzotriazole UV stabilizers (BUVSs), benzoylecgonine (BZE), bezafibrate (BEZ), bisphenol A (BPA), 1,2-bis(2,4,6-tribromophenoxy) ethane (BTBPE), butylparaben (BP), brominated flame retardants (BFRS), caffeine (CAF), carbamazepine (CBZ), cholesterol (Chol), cinoxacin,(CIN), ciprofloxacin (CIP), clofibric acid (CA), decabromodiphenylethane (DBDPE), 1,2-dibromo-4-(1,2-dibromoethyl) cyclohexane (TBECH), diclofenac (DCF), dichloromethane (DCM), dispersive solid-phase extraction (d-SPE), efavirenz (EFV), electrospray ionization (ESI), endocrine disruptor compounds (EDCs), enoxacin (ENO), enrofloxacin (ENR), erythromycin-H_2O (ERY), estrone (E1), 17β-estradiol (E2), estriol (E3), ethyl acetate (EtAc), ethylene bis(tetrabromophthalimide) (EBTPI), ethylparaben (EP), fenofibrate (FEN), fenofibric acid (FA), flumequine (FLU), 4-formyl aminoantipyrine (4-FAA), 4-formyl antipyrine (4-FA), gas chromatography - electron capture detector (GC-ECD), gas chromatography - mass spectrometry (GC-MS), gas chromatography -tandem mass spectrometry (GC-MS/MS), gas chromatography-time-of-flight mass spectrometry (GC-TOFMS), gel permeation chromatography (GPC), gemfibrozil (GEM), p-hydroxybenzoic acid (PHBA), 2,2',4,4',5,5' Hexabromobiphenyl (BB-153), 4-hidroxy-benzophenone (4-OH-BP), high-performance liquid chromatography – tandem mass spectrometry (HPLC–MS/MS), ibuprofen (IBP), irbesartan (IRB), ketoprofen (KET),), liquid chromatography – tandem mass spectrometry (LC-MS/MS), , laser diode thermal desorption—atmospheric pressure chemicalionization—tandem mass spectrometry (LDTD-APCI-MS/MS), limit of quantification (LOQ), liquid chromatography –triple quadrupole-tandem mass spectrometry (LC-QqQMS), lomefloxacin (LOM), methanol (MeOH), methylparaben (MP), moxifloxacin (MOX), nalidixicacid (NAL), naproxen (NPX), nevirapine (NVP), non-steroidal anti-inflammatory drugs (NSAIDs), nonylphenol (NP), nonylphenol ethoxylates (NPE), nonylphenol diethoxylate (NP2EO), nonylphenol monoethoxylate (NP1EO), norfloxacin (NOR), octylphenol (OP), ofloxacin (OFL), oxolinic acid (OXO), oxytetracycline (OXY), paracetamol (APAP), perfluorinated compounds (PFCs), pharmaceuticals (PhACs), pharmaceutical and personal-care products (PPCPs), phenacetin (PH), pipemidic acid (PIP), piromidicacid (PIR), polibrominated diphenyl ethers (PBDEs), propylparaben (PP), quick, easy, cheap, effective, rugged and safe extraction (QuEChERS), roxithromycin (ROS), salicylic acid (SA), salt-assisted liquid–liquid extraction (SALLE), solid-phase extraction (SPE), sulfadimethoxine (SDM), sulfamethazine (SMT), sulfamethoxazole (SMX), sulfapyridine (SP), sulfathiazole (SFT), symvastatin (SVT), tetrabromobisphenol A diallyl ether (TBBPA AE), tetrabromobisphenol A bis(2,3-dipropyl ether) (TBBPA DBPE), triclocarban (TCC), triclosan (TCS), ultra-high performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS), ultra-high-performance liquid chromatography – tandem mass spectrometry (UPLC-MS/MS), ultrasound-assisted extraction (UAE), valsartan (VAL),

[a] Not clean-up

[b] Limits of detection (LOD)

[c] Method detection limit (MDL)

[d] Not reported

[e] Method quantification limit (MQL)

[f] Englert, B., 2007. Method 1694: Pharmaceuticals and Personal Care Products in Water, Soil, Sediment, and Biosolids by HPLC/MS/MS. US Environmental Protection Agency (EPA), EPA-821-R-08-002, pp. 1-72

Table 2: Determination of PPCPs in sewage sludge based on extraction techniques (MAE, PLE, MSPD and QuEChERS)

Analyte	Sample type	Extraction technique	Clean-up	Analysis	Quantification technique	LOQ (ng/g)	Recovery (%)	Precision (%)	Ref.
4 PhACs (ASA, NPX, IBP and GEM)	Sludge samples	MAE 5 mL MeOH 500 W 6 min	Oasis HLB	UHPLC-FLD	d	(1.16-86.4)[b]	69% absolute recoveries	d	[61]
52 PPCPs: 40 PhACs (steroid estrogens, antibacterials/antibiotics, hypertension, NSAIDs, lipid regulators, B-blockers, anti-cancer, anti-depressans, anti-epileptics, analgesics), and 12 PCPs (UV-filters, parabens, plasticizers)	Digested sludge (Freeze-dried 0.5 g)	MAE 25 mL water/MeOH (50:50) 110ºC 30 min	SPE (Oasis MCX, MAX)	UPLC-MS/MS	Isotopically labeled internal standard (38)	< 25 ng/g[e]	<45% absolute recoveries for majority of compounds	< 10%	[62]
17 Antimicrobials (quinolone antibiotics)	Sewage sludge (freeze-dried 1g)	MAE 15 mL ACN:m-phosphoric acid (7:3) 5 min 120 °1000W	SALLE and d-SPE sorbent (dispersive SPE sorbent.)	UHPLC-MS/MS	Matrix matched Internal standard (1)	0.5-1.5	(95.3-106.2)%	<7 %	[63]
11 Chiral pharmaceuticals (AM, MA, MDMA, MDA, VNF, DVF, CTP, MTL, PPL, SOT, ALPR)	Digested sludge (1g and 3g)	MAE 20 mL MeOH:water (1:1) 120 ºC 30 min.	SPE (Oasis HLB, MCX, MAX)	LC-MS/MS	Isotopically labeled internal standard (9)	0.08-25.2	(65-140)%	< 30%	[64]
22 compounds: 18 PhACs (analgesics, antibacterials, anti-epileptics, β-blockers, lipid regulators and non-steroidal anti-inflammatories), 1 personal care product and 3 hormones	Sewage sludge. (Freeze-dried sludge 1g)	MAE 10 mL MeOH/water (3:2) 500W 6 min	Continuos SPE (Oasis HLB)	Derivatization-GC-MS	Non-labeled internal standard (1)	(0.0008 - 0.0051)[b]	(91 – 101)%	<7%	[65]
13 Quinolones (PIP, ENO, NOR, CIP, OFL, ENR, LOM, MOX, CIN, NAL, OXO, FLU, PIR)	Dried sewage sludge (Oven dried 60ºC; 0.5g)	MAE 10mL MeOH/McIlvaine's Buffer (50:50) 1000 W 87ºC 17 min	a	LC-MS/MS	Matrix matched Surrogates (2)	4-18	(97.9 - 104.8)%	The inter- and intra-day variability was >7%	[55]
28 PhACs (analgesics and anti-inflammatory drugs, antihypertensive, anthelmintic, anti-H_2, calcium channel blockers, antibiotics, antiplatelet drug, contrast medium, diuretics, Psychiatric drugs)	Membrane biological reactor (MBR) Sludge (Lyophilized 0.2g)	ASE MeOH/water (1:2) 3 cycles 15min 100ºC	SPE (Oasis HLB)	UPLC-MS	Matrix matched Isotopically labelled internal standards (1)	d	d	d	[13]

Table 2 (Continued)

1 NSAIDs (DCF)	Sewage sludge (Lyophilized 1g)	PLE MeOH 15 min 100ºC 100 bar	SPE	LC-MS/MS	Standard addition	1.2-68	(81.0±7.7- – 94.8±9.6)	5-17%	[71]
9 PhACs (psychopharmaceuticals)	Raw influent (Freeze dried sludge 2 g)	PLE MeOH 5 min 3 cycles 80ºC 1500 psi	ENVI C18-DSK SPE disk	UHPLC-TOFMS	External matrix-matched	2.0-25.0[e]	> 80% absolute recoveries	< 20%	[72]
12 PhACs (2 analgesics (DCF, PNZ), 1antirheumatic agent (IBP), 1 antiepilepticdrug (CBZ), 4 antibiotics (SMX, CLR, RXM, ERY), 2 fibrates (BEZA, FA), 2 β-blockers (MTL, PPL)	Sewage sludge (Lyophilized 1g)	PLE MeOH 15 min 100ºC 100 bar	d	LC-MS/MS	Standard addition	1.2-68	(22-106)% absolute recoveries	(5-17)%	[73]
42 PhACs (analgesics and anti-inflammatory drugs, anti-ulcer agent, psychiatric drugs, antiepileptic drug, antibiotics, ß-blockers, diuretics, lipid regulator and cholesterol lowering statin drugs and anti-histamines)	Thickened, digested and dewatered (treated) sludge (Freeze dried)	PLE MeOH/water (1:2) 3 cycles 15min 100ºC	SPE (Oasis HLB)	LC-MS/MS	Isotopically labeled internal standard (28)	0.2–16 (thickened) 0.2–14 (digested) 0.3–18 (treated) sludge	(31–136)% thickened; (35–126)% digested and (35–133)% treated sludge	20%	[74]
15 PhACs (TC, DMC, CTC, OTC, DOC, MCC, SDZ, SMR, SMZ, TYL, AMP, ERY, LCM, CBZ, CAF)	Sludge samples (primary sludge, waste sludge) (Freeze-dried sludge 0.5g))	PLE ACN/water (70:30) 15 min 100ºC 1500 psi	SPE (Oasis HLB)	LC-MS/MS	External standard	2 - 487	(49 – 95)% absolute recoveries	<10%	[75]

Table 2 (Continued)

19 Brominated compounds: 8 PBDEs, 8 MeO-PBDEs, BFRs (HBB, PBEB, DBDPE)	Digested sludge (Freeze-dried 1.5 g d.w)	PLE 22 mL Hexane: DCM (1:1) 2 cycles 10 min 100ºC 1500 psi	SPE (Silica cartridges and alumina cartridges)	GC-MS/MS	d	0.17 and 9.26 ng/g dw	PBDEs (52 to 67) % MeO-PBDEs (53 to 68) % Finally, HBB, PBEB, and DBDPE (52 to 66)% absolute recoveries	<20%	[76]
7 Antibiotics (4 tetracyclines, 3 sulfonamides)	Primary sludge (after primary clarifier), waste sludge (after secondary clarifier) and dewatered sludge (after dewatering system) (Freeze-dried 0.5g)	PLE ACN/water (7:3) 3 cycles 15 min 100ºC 100 bar	SPE (Oasis HLB)	LC-MS/MS	External standard	0.6 µg/kg d.w (sulfonamide)[b] and 146 µg/kg dw (tetracycline)[b]	(49 -95)% absolute recoveries	(1.1-5.4)%	[77]
14 PhACs (antibiotic, anti-inflammatory, antilipidemic, anti-hypertensive, anticonvulsant)	Dewatered sludge	PLE MeOH/McIlvaine buffer (1 :1) 2 cycles 15 min 100ºC 100 bar	SPE	HPLC-MS/MS	Isotopically labelled internal standard (6)	0.6–19.4	(70-120)%	<19%	[78]
59 Emerging nonpolar halogenated micropollutants	Primary sludge, and secondary sludge matrices (freeze-dried 1g)	PFE U.S. EPA Method 3545A.	SPE	GC-TOFMS	Non-labeled internal standard (2)	< 10	(70-130)%	< 30 %	[79]
30 PhACs (anti-infective, antiperitic, analgesics)	Dewatered sewage sludge	PLE Methanol/EDTA-McIlvaine buffer (50/50) 2 cycles 15 min 100ºC 100 bar	SPE (Oasis HLB)	HPLC-MS/MS	Isotopically labeled internal standard (22)	1-30	(64.0±6.1–324.5±44.1)%	d	[80]

Table 2 (Continued)

ECDs: Natural and synthetic estrogens and their conjugates, antimicrobials, parabens, bisphenol A, alkylphenolic compounds, benzotriazoles, organophosphorus flameretardants	Sewage sludge (Lyophilized samples 1g d.w)	PLE water:methanol:acetone (1:2:1) 25 min 50 ºC 1500 psi	SPE (Oasis HLB)	TFC–LC–MS/MS	Isotopically labeled Internal standard (7)	0.10-125)	(64-115)%	<10%	[81]
13 Quinolones (PIP, ENO, NOR, CIP, OFL, ENR, LOM, MOX, CIN, NAL, OXO, FLU, PIR)	Dried sewage sludge (Oven dried 60ºC; 0.5g)	PLE MeOH/McIlvaine buffer (50:50, pH = 3) 5 cycles 5 min 86ºC 1000 psi	a	LC-MS/MS	Matrix matched Surrogates (2)	4 - 18	(97.9-104.8)%	The inter- and intra-day variability was >7%	[55]
4 NSAIDs (NPX, KET, DCF, IBP)	Digested sludge (0.5g)	PHWE NaOH in water 5 cycles 5 min 120ºC 100 bar	HF-LPME	LC-MS	Standard addition	1.5–12.2	(101-109)% spiked; (38.9 - 90.3)% native; absolute recooveries	<13.1%	[87]
23 Pharmaceuticals, antibiotics and hormones	Sewage sludge (Lyophilized sludge 0.2g)	The PHWE system consisted of a Waters Alliance 2690 HPLC system (Waters, Milford, MA, USA).	SPE (HLB cartridges)	UPLC-MS/MS	Isotopic Labelled internal standard (8)	d	(17-45)%	<25%	[144]
5 NSAIDs (Valdecoxib, Etoricoxib, Parecoxib, Celecoxib and 2,5-Dimethylcelecoxib)	Sewage sludge (Freeze dried 0.2g)	MSPD Florisil (1g) Silica (3g) Hexane (acetone (1:2) 15 mL	d	LC-QTOF-MS	Standard additions	0,005-0,05	(86-105)% absolute recoveries	< 4%	[91]
45 PPCPs: 34 PhACs (antibiotics, nonsteroidal anti-inflammatory drugs, β-blockers, antidepressants), 11 PCPs (antimicrobial agents, preservatives, UV filters)	Sewage sludge (Dewatered sludge) (Freeze-dried 0.1g)	MSPD C_{18}-bonded silica (0.4g) 6 mL MeOH and 10 mL ACN /5 % oxalic acid (8/2)	d	LC-MS/MS	Matrix-matched	0,117-5,55	(50.3-107)% absolute recoveries	< 15 %	[92]

Table 2 (Continued)

23 PPCPs: 19 PhACs and 4 PCPs	Sewage sludge (Freezed-dried 2g)	MSPD Maceration of the sample for 5 min. Addition 5 mL MeOH and vortexing for 1 min. Centrifugation for 5min.	d	HILIC-MS/MS	Matrix-matched	1,25-1250	(50-120)% absolute recoveries	<20%	[93]
4 Antimycotic drugs (tioconazole, sertaconazole, fenticonazole, and itraconazole), the fungicide imazalil	(Freeze-dried sludge 0.5g)	MSPD C_{18} (2g) 20 mL MeOH: formic acid, (99:1).	SPE (SCX sorbent)	LC-QTOF/MS	Isotope-labeled internal standard (1)	2 ng/g	(75-124)% absolute recoveries	13%	[94]
9 compounds: PFAESs (PFSAs, Cl-PFAESs, FTSAs)	Freshly digested sludge (lyophilized 0.5g)	DSPE with slight modifications 3 mL of ACN and 160 µL NaOH 50ºC 120 min	d	UPLC-MS/MS	External standard with correction of 2 isotope-labeled internal standards	0.043	(84-137)%	<20%	[95]
9 Parabens (MP, EP, PP, BP, PhP, IsBP, IsPP, BzP, PeP)	Drinking water sludge samples (10g)	QuEChERS 10 mL ACN 1% formic acid. 4 g $MgSO_4$ and 1 g NaCl	$MgSO_4$	LC-MS/MS	Matrix-matched	5-500	(62-119)% absolute recoveries	<20%	[98]
5 Acid pharmaceutical drugs (CA, IBP, ASA, NPX, FLB)	Sewage sludge (2g)	QuEChERS/automated online 2.0 mL deionized water and 10 mL polypropilene 1.2 g NaCl	a	IC-FLD	Matrix-matched	0.082-29	(81.1-112.7)% absolute recoveries	< 17,8%	[99]

Table 2 (Continued)

136 compounds: 119 PhACs, 17 hormonal steroids.	Sewage sludge (Freeze-dried 2g)	QuEChERS 10 mL EDTA and 10 mL ACN + acetic acid 1% 1 mL heptane and 10 metal balls Acetate buffer (1.5 g NaOAc and 6 g $MgSO_4$, whereas the citrate buffer contained 1 g sodium citrate, 4 g $MgSO_4$, 1 g NaCl and 0.5 g disodium citrate sesquihydrate)	a	LC-TOF/MS	Standard addition	1-2500	(15-131)% absolute recoveries	Intra-day (< 20%) Inter-day (<28%)	[100]
27 PPCPs (21 PhACs, 6 PCPs)	Drinking-water sludge samples (10g)	QuEChERS 10 mL ACN acidified with 100 µL acetic acid. 4 g $MgSO_4$ and 1 g NaCl	SPE (PSA)	UPLC-MS/MS	Standard addition	(0.5-10)[e]	(50-93)% absolute recoveries	<10%	[101]
13 SMCs (6 polycyclic, 2 macrocyclic and 5 nitromusks) and 6 ultraviolet-filters (UVFs)	Sewage sludge (Freeze dried 0.5g)	QuEChERS 10 mL ACN 15 min in a 420W ultrasonic bath 500 mg $MgSO_4$, 315 mg PSA and 410 mg C_{18}	d-SPE	GC-MS/MS	Isotopically labeled internal standard (3)	(0.003-25) pg	(75-122)%	<10%	[102]
8 PCPs (macrocyclic musk fragrances)	Mixture of primary and secondary sewage sludge (freeze-drying 0.25g d.w)	HS-SPME 0.5 mL ultrapure water 45 min 750rpm 80ºC	d	GC-MS	Matrix-matched	0.89pg/g[c]	d	1-15%	[105]

Abbreviations: accelerated solvent extraction (ASE), acetaminophen (AMP), acetonitrile (ACN), acetylsalicylic acid (ASA), alprenolol (ALPR), amphetamine (AM), bezafibrate (BEZA), brominated flame retardants (BFRS), butylparaben (BP), caffeine (CAF), carbamazepine (CBZ), chlortetracycline (CTC), cinoxacin,(CIN), ciprofloxacin (CIP), citalopram (CTP), clarithromycin (CLR), chlorinated Polyfluoroalkyl Ether Sulfonates (Cl-PFAESs) clofibric acid (CA), cyclooxygenase-2 (COX-2) cyclooxygenase inhibitors (COXIBs), decabromodiphenylethane (DBDPE), demeclocycline (DMC) o-desmethylvenlafaxine (DVF), diclofenac (DCF), dispersive solid-phase extraction (d-SPE), doxycycline (DOC), emerging contaminants (ECs), endocrine disruptors (EDCs) enoxacin (ENO), enrofloxacin (ENR), erythromycin (ERY), ethylparaben (EP), fenofibric acid (FA), flumequine (FLU), flurobrofen (FLB), luotelomer Sulfonates (FTSAs), gas chromatography-mass spectrometry (GC-MS), gas chromatography- tandem mass spectrometry (GC-MS/MS), gas chromatography-time-of-flight mass spectrometry (GC-TOFMS), gemfibrozil (GEM), hexabromobenzene (HBB), high performance liquid chromatography –tandem mass spectrometry (HPLC-MS/MS),

hollow fibre liquid-phase microextraction (HF-LPME), ibuprofen (IBP), ionic-chromatography-fluorescence detector (IC-FLD), ketoprofen (KET), liquid chromatography–hybrid quadrupole time-of-flight mass spectrometry (LC-QTOF-MS), liquid chromatography – mass spectrometry (LC-MS), liquid chromatography -tandem mass spectrometry (LC–MS/MS), liquid chromatography- time-of-flight (LC-TOF), liquid chromatography –triple quadrupole (LC-QQQ), lomefloxacin (LOM), matrix solid-phase dispersion (MSPD), meclocycline (MCC), methamphetamine (MA), metanol (MeOH), methoxylated-polybrominated diphenyl ethers (MeO-PBDEs), 3,4-methylenedioxyamphetamine (MDA), methylenedioxymethamphetamine (MDMA), methylparaben (MP), 2-methylpropyl paraben (IsBPB) metoprolol (MTL), microwave-assisted extraction (MAE), moxifloxacin (MOX), nalidixicacid (NAL), naproxen (NPX), non-steroidal anti-inflammatory drugs (NSAIDs), norfloxacin (NOR), octadecyl□silica (C18), ofloxacin (OFL), oxolinic acid (OXO), oxytetracycline (OTC), pentabromoethyl benzene (PBEB), perfluoroalkyl Sulfonates (PFSAs) personal care products (PCPs), pentyl paraben (PePB), pharmaceuticals (PhACs), pharmaceutical and personal-care products (PPCPs), phenazone (PNZ), phenylparaben (PhP), pipemidic acid (PIP), piromidicacid (PIR), polybrominated diphenyl ethers (PBDEs), polyfluorinated ether sulfonates (PFAESs),), pressurized fluid extraction (PFE), pressurized hot water extraction (PHWE), pressurized liquid extraction (PLE), primary and secondary amine exchange bonded silica sorbent (PSA) propan-2-yl paraben (IsPPB), propranolol (PPL), propylparaben (PP), quick, easy, cheap, effective, rugged and safe extraction (QuEChERS), roxithromycin (RXM), solid-phase extraction (SPE), sotalol (SOT), sulfadiazine (SDZ), sulfamerazine (SMR), sulfamethoxazole (SMX), syntheticmusk compounds (SMCs), flow chromatographyfollowed by liquid chromatography coupled to tandem mass spectrometry (TFC-LC-MS/MS), , tylosin (TYL), ultra-high-performance liquid chromatography-fluorescence detector (UHPLC-FLD), ultra-high performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS), SALLE (salt-assisted liquid–liquid extraction), ultra-high performance liquid chromatography –mass spectrometry (UPLC-MS), ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UHPLC-TOF-MS), ultraviolet-filters (UVFs), venlafaxine (VNF).

[a] Not clean-up

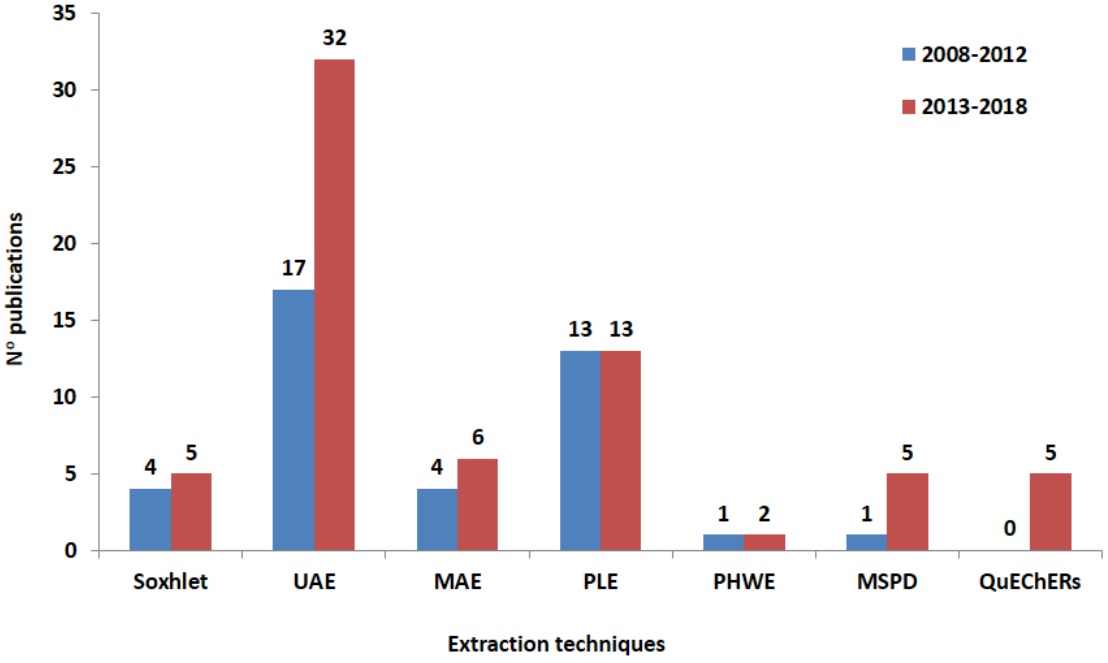
[b] Limits of detection (LOD)

[c] Method detection limit (MDL)

[d] Not reported

[e] Method quantification limit (MQL)

[f] Englert, B., 2007. Method 1694: Pharmaceuticals and Personal Care Products in Water, Soil, Sediment, and Biosolids by HPLC/MS/MS. US Environmental Protection Agency (EPA), EPA-821-R-08-002, pp. 1-72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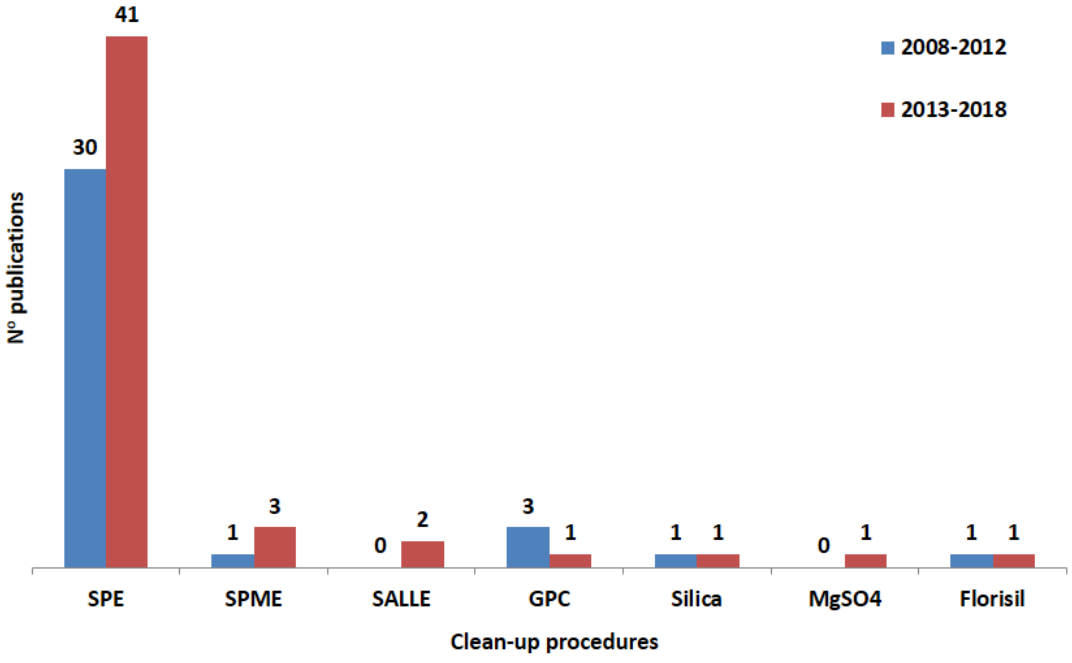
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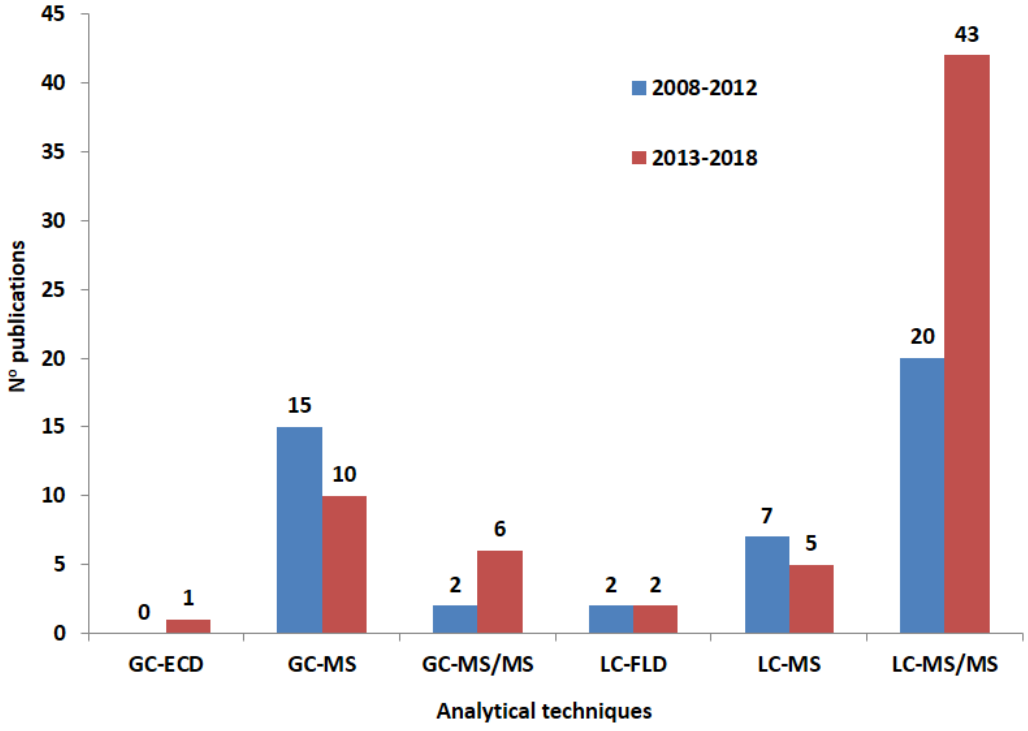
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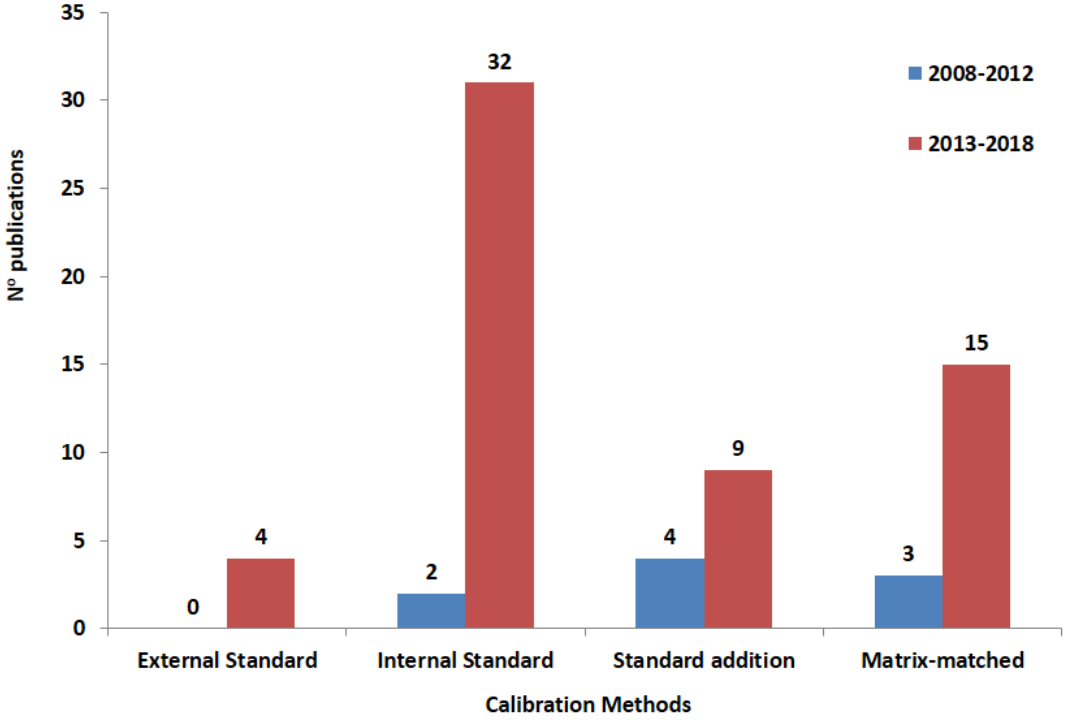
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External Standard
Internal Standard
Standard addition
Matrix-matched
Calibration Methods

HIGHLIGHTS

- A critical review on the determination of PPCPs in sewage sludge is presented
- Analytical methodologies are discussed involving extraction, clean-up and instrumental analysis
- UAE represents more than a half of the publications using extraction techniques
- LC-MS/MS is the analysis technique more used to determinate PPCPs in sludge
- Miniaturization and automation of analytical techniques is becoming a trend to analyze environmental

Enrique Barrado, is Professor of Analytical Chemistry at the University of Valladolid (Spain). He has authored around 150 scientific publications in international journals. His research interests focus around: a) The pollution by heavy metals and its impact on the environment and the food chain. b) Methods to obtaining magnetic particles used as stationary phases in batch and flow separation techniques (HPLMC). c) Electrochemical studies of the behavior of different Lanthanide and Transition Metals and Metalloids ions in Molten Salts, Ionic Liquids and NADES (Natural Deep Eutectic Solvents). He current research interests lie also in the development of experimental designs to sludge characterization and treatment and also the analysis of emergent contaminants in these samples.

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Conflict of interest

The authors declare no conflicts of interest

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