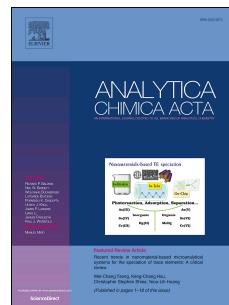


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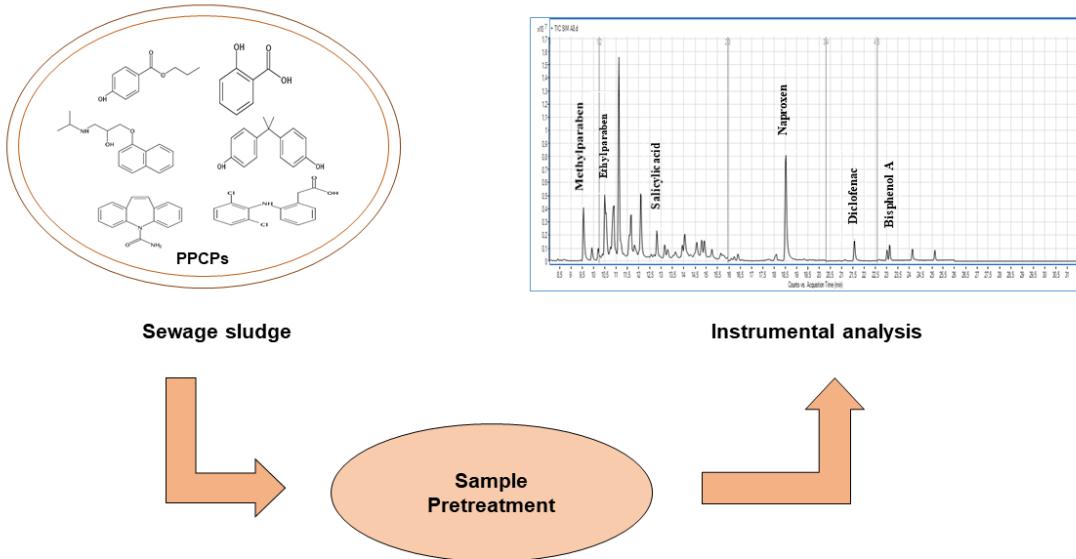
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1 **Analytical methodologies for the determination of pharmaceuticals**
2 **and personal care products (PPCPs) in sewage sludge: a critical review**

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10 Keywords: PPCPs, Sewage Sludge, Sample pretreatment, Gas Chromatography, Liquid
11 Chromatography, Mass spectrometry

12

13 **ABSTRACT**

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

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

3

4 **1. Introduction**

5 Emerging pollutants (EPs) are a great concern because of their detrimental effects on the
6 health of human beings as well as aquatic and terrestrial life [1]. EPs include pharmaceuticals
7 and personal care products (PPCPs) whose presence in the environment has not been yet
8 regulated as stated in Directive 2013/39/EU on priority substances in the field of water policy
9 [2].

10 PPCPs represent a large number of chemicals used in daily life including medicines, cosmetic
11 and personal hygiene products. The active ingredients of PPCPs are products such as non-
12 steroidal drugs like analgesics, antibiotics, antiepileptics, β -blockers, blood-lipid regulators,
13 antiretroviral drugs and steroid drugs (hormones). As an example, non-steroidal anti-
14 inflammatory drugs (NSAIDs) are among the most commonly prescribed pain medications.
15 NSAIDs are used for the treatment of osteoarthritis, rheumatoid arthritis, inflammation, fever
16 and sever and chronic pain and therefore improve quality of daily life [3]. Personal care
17 products include cosmetic and personal hygiene products such as antimicrobials, fragrances,
18 UV filters, and surfactants, among others. For instance, endocrine disrupting compounds such
19 as parabens, are widely used as preservatives in PPCPs because their toxicity levels are
20 theoretically low [4]. These drugs (active ingredients and preservatives), excreted in the
21 environment via urine, feces, wastewater, sewage sludge and manure [5–6], are known to be
22 persistent, bio-active and bio-accumulative as they are cleared at a faster rate than that of their
23 natural degradation. These agents can pose a threat to drinking water supplies [7] and may be
24 a health risk due to their estrogen activity and effects on the endocrine system [1,4,8,9].
25 PPCPs have been detected in water bodies throughout the world, even in Antarctic waters
26 [10]. Moreover, in Europe, the rate of increase in the consumption and production of PPCPs
27 has grown markedly in the last 20 years. Several studies examining the impacts of a
28 wastewater treatment plant (WWTP) in Spain have shown that PPCPs contribute to water
29 toxicity in a greater measure than traditional priority pollutants [11]. Conventional WWTPs
30 are not designed to remove organic micropollutants. In fact, effluents from such plants are
31 now considered to be a major point source of endocrine disrupting compounds and PPCPs in

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

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

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

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

27

28 **2. Analysis of sewage sludge samples**

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

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

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

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

19 Despite similar analytical protocols (extraction, clean-up and analysis), differences did exist
20 in terms of the quantity of sample treated or the amount of solvent in each matrix. Some of the
21 studies reviewed used different amounts of sample and extraction solvent for different types
22 of sludge with ultrasound as the extraction technique: Kopperi et al. [37] used 0.05 g of
23 sample and 6 mL of solvent (acetonitrile) in composted sludge samples; Abril et al. [58] used
24 1 g of sample and 3 mL of solvent (methanol: acetic acid (1:1)) in digested sludge samples;
25 Shafrir [49] used 2 g of sample and 10 mL of solvent (methanol: water (1:1) in secondary
26 sludge samples; Lonappan et al. [31] used 0.5 g of sample and 20 mL of solvent (methanol) in
27 primary sludge samples; and Yan et al. [40] used 2 g of sample and 10 mL of solvent
28 (methanol/citric acid/Na₂EDTA (2:1:1)) in dewatered sludge samples.

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

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

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

10

11 **2.1. Sample pretreatment**

12 The sampling of different types of sludge is particularly important to assess the distribution of
13 PPCPs along the sludge line. According to Tables 1 and 2, sampling sludge locations within
14 WWTPs depends on the type of sewage sludge sample required for the subsequent analysis.
15 In the literature reviewed, a large number of studies preferred sampling sewage sludge
16 [92,100] (suspension with a dry solids content of 3 to 4 % weight arising from the purification
17 of wastewaters). Some authors sample the sludge after the final dewatering step to obtain a
18 representative bulk product [22,78]. Other researchers carry out their sampling after the
19 anaerobic digestion step in which some of the organic matter is removed [43,64]. However,
20 few publications considered sampling in primary and secondary tanks [42,77].

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

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

1 plastic bags after sewage sludge dewatering [34] were also utilized for sample collection.
2 These samples were then transported to the laboratory where they were frozen and lyophilized
3 [53, 59, 88] or dried in air to room temperature [50], and passed through a 2 mm Ø sieve and
4 homogenized [50] or were macerated in a glass mortar for some minutes [93]. Finally, the
5 lyophilized samples were stored at –20 °C [65] until their analysis.

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

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

14

15 **2.1.1. Extraction**

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

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

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

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

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

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

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

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

1 solvents [86] and its low cost. In the future, this green extraction technique is expected to help
2 manipulate large sample sizes for industrial applications. Despite these commented
3 advantages, only two references of the use of PHWE as the extraction technique was found in
4 the last 6-years reviewed [87,144] along with one more [88] in the previous five-year period
5 [14].

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

13 MSPD for the extraction of PPCPs in sewage sludge was introduced in 1989 and applied to
14 the extraction of solid, semisolid or viscous samples. It consists of homogenizing the sample
15 with a dispersing agent (abrasive solid) onto a solid support, allowing the disruption of the
16 sample and the extraction of target analytes by means of a suitable elution solvent [89]. The
17 great interest in MSPD may be attributed to the advantages it offers and its simplicity and
18 flexibility which have contributed to its choice over more classical sample preparation
19 methods [90]. MSPDE is rapid, scarcely manual-intensive and eco-compatible. After
20 extraction, depending on the nature of target analytes and the instrumentation used for their
21 detection, a clean-up procedure may or not be needed. This technique and PLE have
22 sometimes been employed together as the solvents used at high pressures and temperatures
23 increase analyte recoveries when interactions of the analytes with the solid matrix are really
24 strong. The method's selectivity is related to the elution solvent utilized and the nature of the
25 sorbent materials. Lipophilic sorbent materials such as C₁₈-bonded silica or C₈-bonded silica
26 are employed in numerous applications, although the latter is used less frequently [90]. The
27 solvents chosen for elution depend on the nature of the solid material. Organic solvent
28 mixtures are mainly used, however, hot water offers excellent results in certain applications
29 (mostly in PLE procedures). MSPD extraction has several benefits such as reduced amounts
30 of solvents and sample, short extraction times, low cost and good performance at room
31 temperature and atmospheric pressure with acceptable yields and selectivity. The technique is
32 suitable for a great variety of analytes and environmental matrices due to its flexibility and

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

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

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

14 Overall, as depicted in **Figure 1**, UAE emerges as the most popular extraction technique
15 (49%), followed by PLE (19%) and MAE (9%). Thus, the trend observed until 2012 reviewed
16 by [14] has been maintained in the last six years. Nonetheless, UAE seems to have lately
17 experienced a boost, most probably because of its simplicity and high performance as well as
18 affordability and availability at most of laboratories around the world.

19

20 **2.1.2. Clean-up**

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

28 C₁₈ is a clean-up agent commonly used to remove interfering lipids and lipophilic compounds
29 in extracts contained in organic solvents. PSA (primary and secondary amine) has also proved

1 effective for the removal of acidic interferences such as humic and fulvic acids (main
2 components of compost) among others [55]. C₁₈ and PSA (primary and secondary amine) are
3 examples of some clean-up agents commonly used in dispersive solid-phase extraction (d-
4 SPE) [102]. Thus, the choice of sorbent must be adequate to retain interferences present in
5 each particulate sludge matrix. Deficiencies in the extraction process have been also attributed
6 to the presence of co-extracted matrix components [34].

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

11 There are three general extraction mechanisms used in SPE: polar, non-polar and ion
12 exchange. More than half of the works found in the literature during the last 6 years have
13 employed reverse-phase SPE (63%). The retention mechanism is the interaction of non-polar
14 groups of the analytes of interest and the non-polar functional groups on the sorbent (Van der
15 Waals forces) [104]. In many cases, extraction was performed in a polar solvent [13,24,39-
16 43,45-48,50,52,56,59,62,64,74,75,77,80,81]. Mixed-mode SPE is an extraction approach
17 involving sorbents which are designed to exhibit two or more primary interactions for analyte
18 retention. Most mixed-mode sorbents include hydrophobic functional groups in combination
19 with ion-exchange functional groups. In some cases, Oasis MCX (Mixed-Mode Cation-
20 eXchange) has been used for the clean-up of extracts containing acidic pharmaceuticals
21 [39,62,64]. Oasis MAX (Mixed-Mode Anion-eXchange) has been also used in other cases
22 [62,64]. However, the reverse phase sorbent patented in Oasis HLB (Hydrophilic-Lipophilic
23 Balanced) has been the preferred option over the last six years [13,24,29,30,32,39,40,42,48-
24 50,56,59,64,74,75,77,80,81]. It is a universal polymer reversed-phase sorbent that was
25 developed for the extraction of a wide range of acidic, basic and neutral compounds from
26 various matrices. Another type of adsorbent is based on C₁₈-silica and used to adsorb analytes
27 of even weak hydrophobicity from aqueous solutions [43,52]. In the 1990s, a miniaturized
28 variation of SPE emerged as a solid-phase microextraction technique (SPME). This method
29 involves an alternative preconcentration technique to LLE or SPE. It consists of a silica fiber
30 coated with a thin layer of an extractant polymer, which can be placed in the head space (HS-
31 SPME) or subjected to direct immersion (DI-SPME) in solid, liquid or gaseous samples. As
32 the fiber is desorbed in the injection port of a gas chromatography system, the use of solvents

1 is eliminated and possible losses of analytes and contamination of the samples are reduced.
2 [28,57] are examples found in the literature reviewed here.

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

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

22 Overall, the vast majority of publications, 60% of the reports reviewed here, chose SPE as the
23 clean-up approach, as shown in **Figure 2**. Only isolated examples of other techniques have
24 been found such as florisil [51], silica [90] or MgSO₄ [98].

25

26 **2.2. Instrumental analysis**

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

1 acylation (acetylation), alkylation [33] and silylation [28,37,50,65]. GC is a relatively
2 inexpensive instrumental technology which enables this kind of analysis to be carried out by a
3 wide range of laboratories around the world, including those in developing countries [20,53].
4 Overall, 25% of the reports reviewed chose GC-based on instrumental techniques. In
5 comparison to the period reviewed by [14], there seems to have been a decline in the
6 popularity of GC (**Figure 3**). Most GC approaches are coupled to mass spectrometry (MS)
7 detection in both a single and tandem (MS/MS) modality. Other detection approaches were
8 found coupled to GC such as electron capture detector (ECD) [22]. Triple quadrupole (QqQ)
9 is the most common analyzer mainly used in selected reaction monitoring (SRM) mode for
10 quantitative analysis [51,76]. However, some examples of target analysis in high resolution
11 by quadrupole to time-of flight (Q-TOF) couplings have been also found in the literature
12 [37,53,79]. As pointed out in the previous section, SPME is a pretreatment technique which
13 allows automation when coupled to GC and was employed by [28] and [129] for the analysis
14 of 12 PPCPs and 8 macrocyclic musk fragrances in sewage sludge respectively. This
15 constitutes the only examples of pretreatment coupling to instrumental analysis in our realm.
16 However, despite the above, LC-based on instrumental analysis has become the most popular
17 technique (**Figure 3**) in the determination of PPCPs in environmental matrices including
18 sewage sludge. This is probably because of its higher versatility as a larger spectrum of
19 compounds can be readily analyzed with no prior derivatization or alike. Again, mass
20 spectrometry is the preferred detection option, but some examples (2) of coupling to
21 fluorescence detection have been also found [61,99]. This repeats the scenario as in the period
22 reviewed by [14] where a single example of this coupling was cited [110]. In contrast,
23 ultraviolet (UV) detection cited years ago [111] is no longer an interesting option. Within MS
24 modalities, MS/MS was found to have the greatest applicability, in particular using QqQ in
25 SRM mode for target analysis. Hence, 63% of the LC works reviewed fit this classification.
26 Nevertheless, interest in the use of other tandem combinations such as Q-TOF has been
27 recently sparked due to improvements in the dynamic range and sensitivity of TOF. In
28 addition, TOF analyzers offer a high resolution capacity. This ensures high selectivity and
29 reduces the probability of false positive results. In addition, they open the possibility of
30 qualitative analysis of un-known compounds, which is not readily available in QqQ.
31 Electrospray ionization (ESI) is the most commonly used ionization approach as it allows
32 mild ionization of the target analyte and molecular ions usually remain un-fragmented
33 [47,75,100]. Nonetheless, apolar compounds might undergo poor ionization by ESI, and

1 atmospheric pressure chemical ionization (APCI) is then recommended as in [31,49]. Weak
2 acids and bases such as formic acid and ammonium acetate are usually used as mobile phase
3 modifiers when working at +ESI and -ESI respectively. Moderate acidic (~3) and basic pHs
4 (~8) are provided by formic acid and ammonium acetate respectively. In this regard, a larger
5 number of PPCPs contain basic functional groups (such as amines) with pKa values above pH
6 3 rather than acidic functional groups (such as alcohols) with pKa values below pH 8.
7 Therefore, PPCPs are more prone to be positively ionized and are more efficiently analyzed
8 by +ESI rather than -ESI.

9 Within LC, fast chromatography has emerged as an improved modality over high
10 performance liquid chromatography (HPLC). The ultra-high version (UHPLC) was
11 introduced under the trade mark UPLCTM in 2004 and triggered many advances in
12 instrumentation and column technology, which have led to a significant increase in resolution,
13 speed and sensitivity. Column efficiency increases with reduction of stationary phase particle
14 size (usually <1.7µm) and mobile phase delivery is done at <15,000 psi (about 1000 bar)
15 [112]. Separations are mostly completed in less than 10 min and some even in under 2 min
16 [32,62,72]. UHPLC often provides narrow peaks (in few seconds or even less) offering a
17 high-speed detection response (> 100Hz) [112].

18 Over these past 6 years, out of 47 of the applications using LC, 14 were fast chromatography.
19 This in comparison to the previous 5-year period reviewed by [14], in which only 8% of
20 studies examined this kind of liquid chromatography, reveals a clear upward trend in the use
21 of UHPLC likely attributable to its many benefits mentioned. Overall, as depicted in **Figure**
22 **3**, LC has been the most popular instrumental technique (73%) for the determination of
23 PPCPs in environmental matrices including sewage sludge. Hence, the trend observed up until
24 2012 and reviewed by [14] has been maintained over the last six years.

25

26 **2.3. Current trends and future perspectives in the determination of PPCPs in sewage** 27 **sludge**

28 The concept of "green chemistry", otherwise known as sustainable chemistry, was introduced
29 20 years ago and refers to the design of chemicals and processes that reduce and eliminate the
30 use or generation of hazardous substances. When applying and proposing new methods and
31 processes of analysis, sustainability should be considered a necessary characteristic. By

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

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

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

1 Future perspectives related to the development of new sample preparation methods differ
2 depending on the type of the pollutant. There is increasing interest in nanotechnology in
3 important sectors of science and technology such as engineering, medicine or agriculture,
4 among others. Nanotechnology is making progress in technologies for protecting the
5 environment too. However, nanotechnology's unique characteristics can lead to unforeseen
6 environmental problems [121]. In parallel, the use of novel solid and liquid phase materials
7 has increased in the last years including nanomaterials (NMs), ionic liquids (ILs) or
8 supramolecular solvents (SUPRAS) used in the analysis of environmental samples.
9 Engineered nanomaterials (ENMs) are materials or chemical substances with particle sizes
10 between 1 to 100 nanometers in at least one dimension [122]. There is great interest in
11 innovations produced in the industrial, commercial and medical sectors due to the physical
12 and chemical properties of these materials. However, some of their properties (chemical
13 reactivity, surface area and particle size) pose a risk to health and the environment [123].
14 Some works have described applications of nanoadsorbents in environmental water samples
15 [124,125]. In the near future, NMs could be applied to sewage sludge samples. SUPRAS are
16 nanostructured liquids generated from compounds with both hydrophilic and lipophilic
17 properties (amphiphiles) [126]. SUPRAS have been employed for the extraction and
18 preconcentration of emerging pollutants in environmental water samples [127]. However,
19 there are still no reports of applications of SUPRAS to sewage sludge. ILs are salts whose
20 ions are poorly coordinated, which makes these solvents liquid at temperatures below 100°C,
21 or even at room temperature (room temperature ionic liquids) [128]. One publication reports
22 on the determination of musk fragrances in sewage sludge based on IL-HS-SPME followed
23 by GC-MS/MS [129].

24

25 **3. Data processing**

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

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

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

1 may make up for matrix effects although it does not eliminate the underlying cause because
2 the effect intensity may differ from one matrix or sample to another, and can be also affected
3 by the matrix concentration. In fact, matrix-matched calibration is a particular type of external
4 calibration in which the calibration standards are prepared using a simulated sample that
5 initially does not contain the analyte. Of the reports reviewed, 22% chose matrix-matched as
6 calibration method (Tables 1 and 2), which represents an increase in comparison with the
7 period reviewed by [14], in which only 6% of the publications selected the matrix-matched
8 method [134-136]. Another calibration alternative is based on standard addition. This method
9 is more accurate and precise and overcomes more matrix effects than external and matrix-
10 matched calibration approaches, as it uses the sample itself to build the calibration curve.
11 However, it entails the preparation of a different calibration curve per sample. It is therefore
12 labor intensive, time-consuming, and requires large sample amounts, which is usually in
13 disagreement with green chemistry principles. Overall, 14% of the publications reviewed here
14 used this calibration method (Tables 1 and 2). In contrast, previous publications reviewed by
15 [14] reported this calibration approach less frequently (9%). Finally, an internal standard (IS)
16 is a reference species with similar physicochemical properties and similar analytical behavior
17 to the compounds of interest not expected to be found in the samples. This calibration method
18 is not as useful for GC and HPLC methods involving non-MS detectors unless the internal
19 standards can be separated from target compounds chromatographically. The advantage of
20 this calibration method is that fluctuations are monitored in every sample. It assumes that the
21 behavior of the IS is identical to that of the analyte. Thus, the selection of a suitable IS is
22 mandatory. The use of internal standard calibration approaches has experienced a boom in the
23 last few years. In effect, 47% of the reports reviewed selected this procedure (Tables 1 and 2)
24 versus 4% reported in the prior review [14]. In particular, the use of stable-isotope-labeled
25 analogues of the analytes has become popular because of its efficiency and reliability to
26 compensate for any alteration in the signal due to casualties across the whole analytical
27 process. However, for highly multi-component applications, it requires a significant economic
28 investment, unaffordable for many laboratories.

29 **Figure 4** depicts the frequency of each calibration method used in the reports reviewed. The
30 use of isotopically labeled analogues in internal standard calibrations has been the most
31 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%

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

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

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

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

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

27

28 **5. Impacts of sewage sludge analytical procedures on validation parameters**

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

1 Extraction and clean-up steps are thought to be the main contributors to absolute recovery
2 [55]. In the literature reviewed, various studies have addressed the determination of PPCPs
3 both in sewage sludge and sewage. In many of those cases, methodology was common for
4 both matrices but an extraction step was added at the beginning of the protocol for the sludge
5 samples. For instance, Křesinová et al. [72] used PLE followed by SPE with ENVI C18-DSK
6 SPE disk and LC-ToFMS for the determination of PPCPs in sludge. The same methodology
7 was employed when these PPCPs were determined in water samples, but a PLE extraction
8 step did not precede the protocol. This extra step for the solid samples led to lower absolute
9 recoveries for most of the compounds, indicating how extraction influences method accuracy.
10 Accordingly, amitriptyline, 2-chloroprothioxanthen-9-one and melitracene carbinol rendered
11 recoveries of 97.6%, 96.7%, 88.1%, respectively. These percentages decreased to 92.8%, 89.5
12 % and 86.8%, for the same compounds in solid samples [72]. Additionally, López-Serna et al.
13 [28] showed how dramatic the impact of the extraction step can be on the accuracy. These
14 authors employed a fully automated method based on online extraction by DI-SPME followed
15 by on-fiber derivatization coupled to GC-MS for sewage samples. In sewage sludge samples,
16 UAE preceded the sewage methodology. The absolute recoveries reported in this paper for
17 compounds such as ibuprofen, salicylic acid and diclofenac were 77.77%, 21.43%, and
18 83.07%, respectively, in sewage samples. However, in sludge, these recoveries dropped to
19 18.18% for ibuprofen, 17.92% for salicylic acid, and 65.89% for diclofenac. Among the
20 different extraction techniques discussed in the present paper, UAE, MAE and PLE seem the
21 most popular. PLE is considered to be much more effective at extracting analytes from solid
22 samples than UAE or MAE, leading to higher real recoveries. However, PLE is also described
23 to extract more components of the matrix along with the analytes of interest. This means the
24 associated matrix effect diminishes the given absolute recovery rate [70]. Nonetheless, PLE
25 and MAE are usually shown to be slightly more efficient than UAE for extracting PPCPs
26 from sludge as observed by Dorival-García et al. [55]. For instance, Gao et al. [77] tested a
27 method based on PLE-SPE-LC-MS/MS and the absolute recoveries reported for compounds
28 such as sulfamethoxazole, tetracycline and oxytetracycline in sludge samples were 78%, 54%,
29 and 52%, respectively. Similarly, Shafrir et al. [49] used a method based on UAE-SPE-LC-
30 MS/MS and reported absolute recoveries such as 17%, 22%, and 17% for sulfamethoxazole,
31 tetracycline and oxytetracycline, respectively. Gago-Ferrero et al. [34] developed a method
32 that combined UAE and LC-MS/MS, and absolute recoveries reported in this paper for
33 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

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

5 Precision (expressed as repeatability) is usually affected by the number of stages included in
6 the analytical procedure. A strategy to achieve good precision has been to automatize some of
7 the method stages (e.g., PLE, SMPE) to minimize the human error impact. In the literature,
8 two fully automated methods DI-SPME – on fiber derivatization-GC-MS [28] and HS-SPME-
9 GC-MS [129] have been used to determine PPCPs and PCPs in sewage sludge, respectively.
10 López-Serna et al. [28] reported satisfactory intra-day repeatability (expressed as %RSD)
11 values such as 0.87% for propylparaben, 1.59% for naproxen and 2.99% for triclosan, among
12 others. Vallecillos et al. [129] also reported good intra-day repeatability results such as 1% for
13 exaltone, 8% for muscone, and 9% for exaltolide, among others. However, SPME fibers used
14 for a large number of samples might lead to significant carry over effects. López-Serna et al.
15 [28] reported carry over rates of up to 10% and 13% for diclofenac and triclosan, respectively.

16 Sensitivity is mainly affected by the instrumental analysis technique employed [28]. In the
17 revised literature, different groups have examined the use of similar methods with different
18 detectors such as FL [61], Q-MS [13], QqQ-MS [62], or QToF-MS [72] for the determination
19 of PPCPs in sludge samples. For instance, Morales-Toledo et al. [61] developed a method
20 based on MAE and SPE combined with UHPLC-FLD for the determination of
21 pharmaceuticals in sludge samples, and reported method LODs for naproxen and ibuprofen
22 below 86.5 ng/g. Much lower LODs were observed by Petrie et al. [62] for a similar method
23 based on MAE and SPE followed by UHPLC-MS/MS. In particular, they reported method
24 LODs of 0.07 ng/g for ibuprofen and 0.60 ng/g for naproxen. Among the analyzers used in
25 mass spectrometry, QqQ has usually provided lower LODs than QToF. Hence, Peysson et al.
26 [100] made use of a method based on QuEChERS followed by UPLC-QToF and reported
27 LODs as low as 17 ng/g for sulfamethoxazole and 3 ng/g for propranolol, among others. Even
28 lower limits of 0.6 ng/g and 0.3 ng/g respectively for the same compounds were reported by
29 Cerqueira et al. [101] for a similar pretreatment method followed by UHPLC-QqQ-MS. The
30 use of GC usually leads to higher LODs in comparison to LC, even when the detection
31 method is MS. This is usually attributed to incomplete derivatization of the non-volatile
32 PPCPs and/or a poorer ionization rate of the resulting substance. UHPLC provides narrower

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

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

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

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

26

27 **6. Conclusions**

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

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

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

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

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

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

27

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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 secondary 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 50°C) (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 ^e	(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 ^e	(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 50°C	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-GCXC-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 50°C	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 antihypersensitivities (CBZ)	Dewatered sludge (Freeze-dried 2g)	UAE (3 cycles) 10 mL MeOH/Citric acid/ Na ₂ EDTA (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 antihypersensitivities)	Primary and secondary sludge (EPA Method (1694 USEPA, 2007 with some modifications)	UAE 10 mL MeOH/citric acid/Na ₂ EDTA (2:1:1) 15 min <40°C	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 sweeteners 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 60-70° C; 0.02g)	UAE 8 mL MeOH/water (5:3) 5 mL MeOH (3 times) 30 min 50°C	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	Secondary 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 BTNs	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- BTN, 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 °C ± 3°C) (Dried sludge 1g)	UAE 15 ml EtAc 45 min 50°C	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 60°C; 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-ethynodiol, 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 perfluorocarboxylic acids 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, 4 antihypertensions, 1 antimicrobial, 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-acetylaminooantipyrine (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), atorvastatin (ATT), azithromycin (AZM), bezafibrate (BZB), benzophenone 1 (BP1), benzophenone 3 (BP₃), 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-H₂O (ERY), estrone (E1), 17 β -estradiol (E2), estriol (E3), ethyl acetate (EtAc), ethylene bis(tetrabromophthalimide) (EBTP), 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 chemical ionization—tandem mass spectrometry (LDTD-APCI-MS/MS), limit of quantification (LOQ), liquid chromatography –triple quadrupole-tandem mass spectrometry (LC-QQMS), 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), roxitromycin (ROS), salicylic acid (SA), salt-assisted liquid–liquid extraction (SALLE), solid-phase extraction (SPE), sulfadimethoxine (SDM), sulfamethazine (SMT), sulfamethoxazole (SMX), sulfapyridine (SP), sulfathiazole (SFT), simvastatin (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-depressants, anti-epileptics, analgesics), and 12 PCPs (UV-filters, parabens, plasticizers)	Digested sludge (Freeze-dried 0.5 g)	MAE 25 mL water/MeOH (50:50) 110°C 30 min	SPE (Oasis MCX, MAX)	UPLC-MS/MS	Isotopically labeled internal standard (38)	< 25 ng/g ^c	<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 °C 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 60°C; 0.5g)	MAE 10mL MeOH/McIlvaine's Buffer (50:50) 1000 W 87°C 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 100°C	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 100°C 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 80°C 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), 1 antirheumatic agent (IBP), 1 antiepileptic drug (CBZ), 4 antibiotics (SMX, CLR, RXM, ERY), 2 fibrates (BEZA, FA), 2 β- blockers (MTL, PPL))	Sewage sludge (Lyophilized 1g)	PLE MeOH 15 min 100°C 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, β-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 100°C	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 100°C 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 100°C 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 100°C 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 100°C 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 100°C 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 °C 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 60°C; 0.5g)	PLE MeOH/McIlvaine buffer (50:50, pH = 3) 5 cycles 5 min 86°C 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 120°C 100 bar	HF-LPME	LC-MS	Standard addition	1.5-12.2	(101-109)% spiked; (38.9 - 90.3)% native; absolute recoveries	<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). MSPD Florisil (1g) Silica (3g) Hexane (acetone (1:2) 15 mL	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 50°C 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 polypropylene 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%)	[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 80°C	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), meclocline (MCC), methamphetamine (MA), metanol (MeOH), methoxylated-polybrominated diphenyl ethers (MeO-PBDEs), 3,4-methylenedioxymphetamine (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), octadecylsilica (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), pipemicid 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)

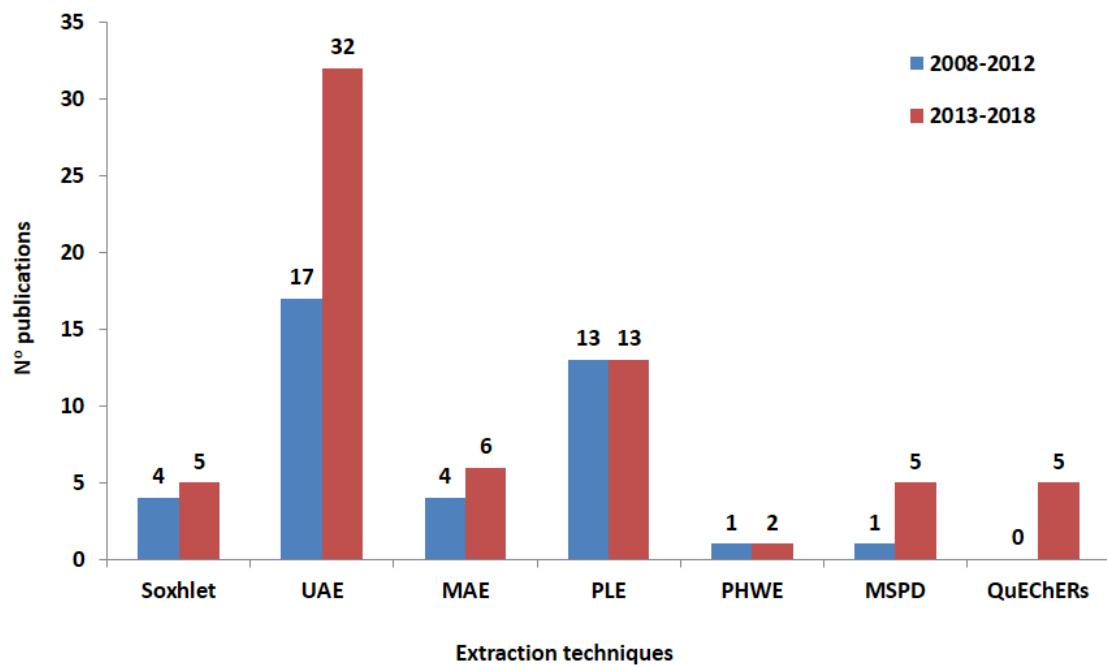
^d Not reported

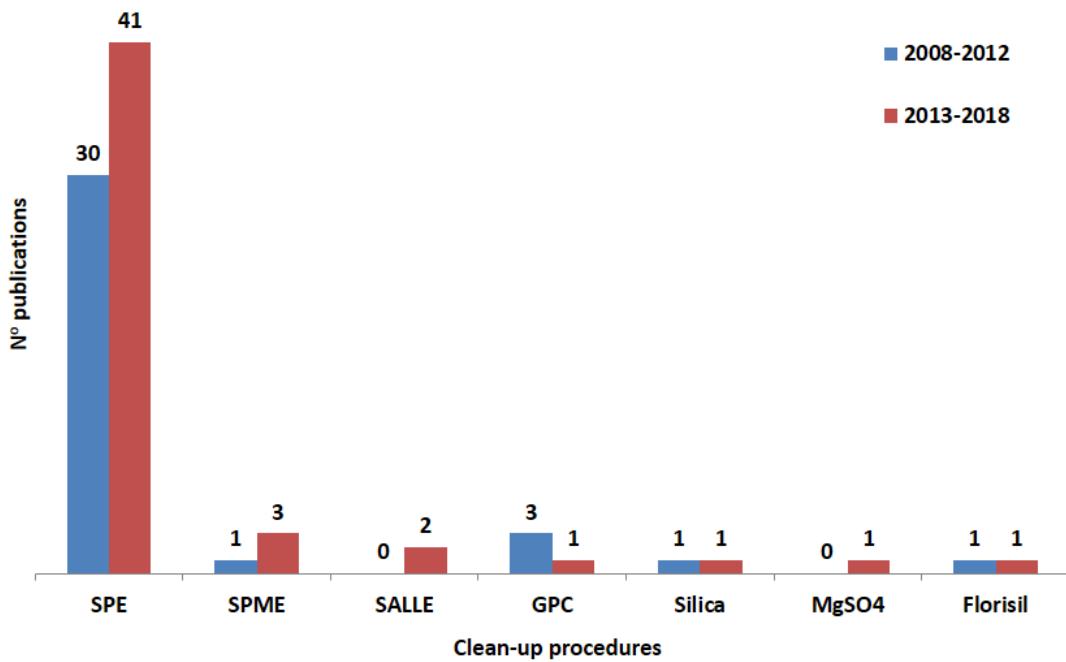
^eMethod quantification limit (MQL)

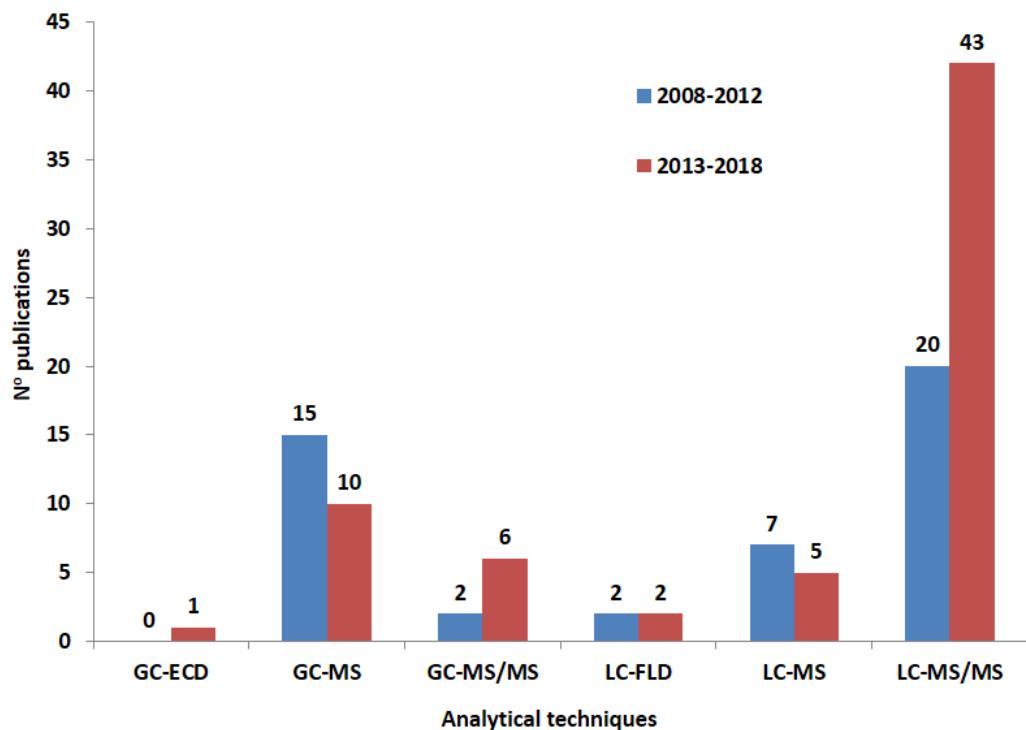
^fEnglert, B., 2007. Method 1694: Pharmaceuticals and Personal Care Products in Water, Soil, Sediment, and Biosolids by HPLC/MS/MS. US Environmental Protection Agency (EPA), EPA-821-R-08-002, pp. 1-72

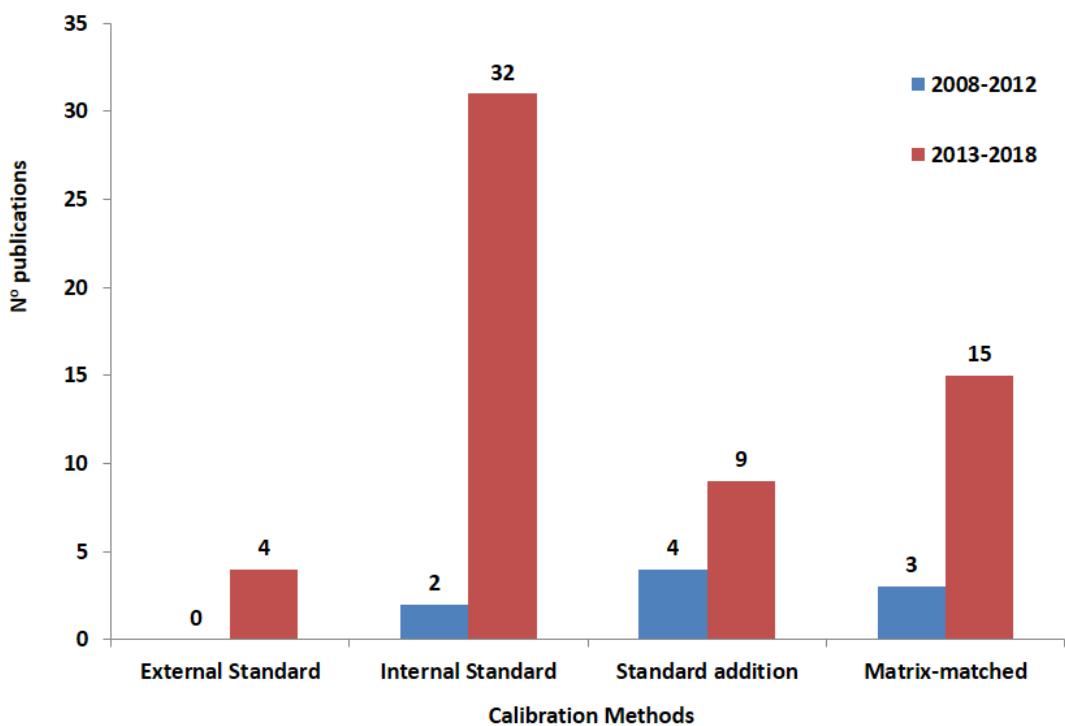


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HIGHLIGHTS

- 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

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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:
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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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