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DOI
10.1016/j.jhazmat.2023.131992

Publication date
2023

Document Version
Final published version

Published in
Journal of Hazardous Materials

Journal of Hazardous Materials 458 (2023) 131992

Contents lists available at ScienceDirect

Journal of Hazardous Materials

journal homepage: www.elsevier.com/locate/jhazmat

Simultaneous detection of pesticides and pharmaceuticals in three types of bio-based fertilizers by an improved QuEChERS method coupled with UHPLC-q-ToF-MS/MS

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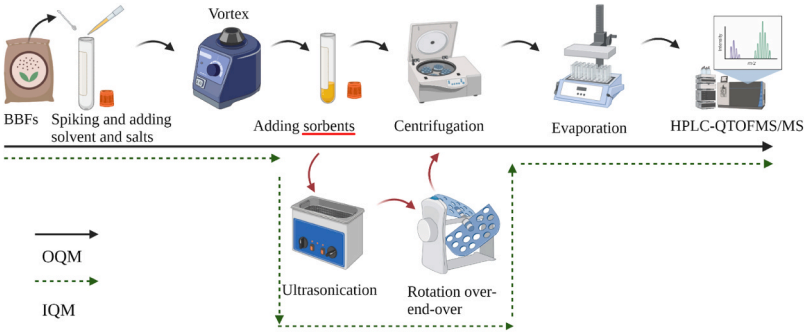
HIGHLIGHTS

- Animal-, plant-, and ash-based BBF were analyzed with QuEChERS for the first time.
- QuEChERS simultaneously recovered pesticides and pharmaceuticals in three BBFs.
- QuEChERS was optimized by incorporating ultrasonication and end-over-end rotation.
- The improved QuEChERS method was successfully applied to analyze 15 different BBFs.

GRAPHICAL ABSTRACT

OQM: original QuEChERS method; IQM: improved QuEChERS method (Created with BioRender.com).



ARTICLE INFO

Editor: Karina S. B. Miglioranza

Keywords:
Pharmaceuticals
Pesticides
Bio-based fertilizers
QuEChERS
Ultrasonication

ABSTRACT

Bio-based fertilizers (BBFs) have the potential to contain both pesticides and pharmaceutical residues, which may pose a threat to soils, crops, and human health. However, no analytical screening method is available currently to simultaneously analyze a wide range of contaminants in the complex origin-dependent matrices of BBFs. To fill this gap, our study tested and improved an original QuEChERS method (OQM) for simultaneously analyzing 78 pesticides and 18 pharmaceuticals in BBFs of animal, plant, and ashed sewage sludge origin. In spiked recovery experiments, 34–58 pharmaceuticals and pesticides were well recovered (recovery of 70–120%) via OQM at spiking concentrations levels of 10 ng/g and 50 ng/g in these three different types of BBFs. To improve the extraction efficiency further, ultrasonication and end-over-end rotation were added based on OQM, resulting in the improved QuEChERS method (IQM) that could recover 57–79 pesticides and pharmaceuticals, in the range of 70–120%. The detection limits of this method were of 0.16–4.32/0.48–12.97 ng/g, 0.03–11.02/0.10–33.06 ng/g,

Abbreviations: BBFs, Bio-based fertilizers; NRSS, Nutrient-rich side streams; quick, easy, cheap, effective, rugged and safe, QuEChERS; MeOH, Methanol; ACN, Acetonitrile; SRE, Spiked recovery experiments; OQM, Original QuEChERS method; IQM, Improved QuEChERS method; ME, Matrix effect; MLOD, Method limit of detection; MLOQ, Method limit of quantification; RSD, Relative standard deviation; UHPLC, Ultra-high performance liquid chromatography; MS, Mass spectrometry; ESI, Electrospray ionization; d-SPE, Dispersive solid-phase extraction; PSA, Primary secondary amine; C_{18}, Octadecyl bonded silica gel.

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https://doi.org/10.1016/j.jhazmat.2023.131992
Received 16 March 2023; Received in revised form 30 June 2023; Accepted 2 July 2023
Available online 4 July 2023

and 0.06–5.18/0.18–15.54 ng/g for animal, plant, and ash-based BBF, respectively. Finally, the IQM was employed to screen 15 BBF samples of various origins. 15 BBFs contained at least one pesticide or pharmaceutical with ibuprofen being frequently detected in at concentration levels of 4.1–181 ng/g. No compounds were detected in ash-based BBFs.

1. Introduction

There is increasing interest in land application of various commercially available bio-based fertilizers (BBFs), produced from nutrient-rich side streams (NRSS) like manure, sewage sludge, food by-products, ash from incarnation facilities, and plant residues. However, NRSS are a reservoir of a wide range of toxic organic compounds [1,2]. Therefore, it is crucial to screen the BBFs for contaminants that may pose a threat to soil, crop and human health.

Pesticides and pharmaceuticals are of particular concern in the context of the agricultural application of BBFs, given their potential persistency and toxicity. Depending on the source of the BBFs, there are various ways in which contamination with pharmaceuticals or pesticides can occur. Farm animals are often given veterinary antibiotics to prevent disease and promote growth [3]. Additionally, insecticides are routinely administered to the feed yards and livestock via multiple routes, such as sprays, pour-on, and injection [4]. As a result, such compounds have been frequently found in the organs, tissue or manure that forms the basis of animal-based BBFs [5–8]. With respect to plant-based BBFs, there is compelling evidence that plants may uptake pesticides and pharmaceuticals from soil or soil with irrigation [9]. In addition, legacy pesticides have been found in BBFs produced from green compost, food byproducts or plants [10,11]. The presence of pharmaceuticals or pesticides in sewage sludge and biowastes has also been reported in numerous studies[12,13]. Therefore, BBFs may pose a risk of introducing both pharmaceuticals and pesticides into the soil and subsequently the food chain[14], regardless of whether they are of animal, plant or sewage sludge origins. To address this issue, analytical techniques are needed to enable a quick, simple and reliable screening of a wide range of these compounds in BBFs.

QuEChERS (quick, easy, cheap, effective, rugged, and safe), ultrasonication-assisted exraction (UAE), and accelerated solvent extraction (ASE) are commonly employed techniques for extracting a wide range of organic pollutants from various matrices [15]. QuEChERS, as its name suggests, offers ease and time efficiency, and is widely applied in the analysis of pesticides or antibiotics in food, vegetables, manure, compost, and sewage sludge [6, 16–18]. ASE utilizes high temperature and pressure to break the strong bond between pollutants and matrix components. However, this method often results in the simultaneous extraction of a higher proportion of matrix components, such as humic and fulvic substances, carbohydrates, proteins, and lipids. It can also lead to thermal degradation of compounds[15]. Moreover, ASE is more costly and time-consuming due to the equipment and in some cases required subsequent clean-up procedures, such as solid-phase extraction (SPE) [15,19]. Consequently, in certain studies, QuEChERS has demonstrated comparable or better recovery rates compared to ASE [20,21]. UAE harnesses energy as well, relying on extraction solvents and sonication cycles, to extract organic pollutants [22]. It offers a favorable balance between extraction efficiency and cost. Notably, UAE is the only technique used in equal proportions for solid sludge, manure, soil, and sediment matrices, accounting for approximately one-third of all available techniques [15]. However, it is important to note that employing multiple rounds of extraction during UAE can result in the extraction of a larger quantity of matrix components. Therefore, QuEChERS or ultrasonication are probably most suitable for the extraction in BBFs.

So far, most of the available analytical screening methodology is limited to measuring only one class of compounds, i.e. either pesticides or pharmaceuticals [2, 5, 23–27]. Using such methodology where pesticides and pharmaceuticals are considered separately, is time-consuming when screening BBFs where both classes of compounds are potentially present. An additional complicating factor is that the complex interactions between organic chemicals and organic matrix.

may lead to problems with the extraction and clean-up, and cause matrix effects (ME) [15], as BBFs are often rich in a variety of organic matter, such as waxes, lipids, and pigments. This is caused by their wide variety of origins, which include plant/fruit/crops residues, struvite, sewage sludge, and various animal products such as meat & bone meal, blood and feather meal [23, 28–32]. Consequently, the ideal screening method must not only be able to simultaneously detect a broad suite of pharmaceuticals and pesticides, but must be able to do so in a wide variety of complex matrices. To our knowledge no such method yet exists.

To fill this gap, the goal of our present study (a part of the overarching EU-funded LEX4BIO research program, www.lex4bio.eu) was to test and develop an analytical methodology for simultaneously analyzing a large suite of pharmaceuticals and pesticides in BBFs with various origins. For this, first an existing short, low-cost QuEChERS method was tested and then further optimized by adding an ultrasonication step and end-over-end rotation. The methods were applied and compared for the simultaneous recovery of 18 pharmaceuticals and 78 pesticides in three BBFs with animal, plant, or ash origins accounting for tvarious types of BBFs. Finally, the optimized method was successfully applied to analyze 15 BBFs with various origins.

2. Materials and methods

2.1. Standards and chemicals

LC-grade solvents methanol (MeOH), acetonitrile (ACN), sodium acetate (CH_3COONa), and calcium sulfate ($MgSO_4$) were supplied by Biosolve (Valkenswaard, The Netherlands). Formic acid and acetic acid were purchased by Merck (Damstadt, Germany). Milli-Q water was purified with an ELGA water purification system (Veolia Water Technologies Netherlands B.V., Ede, the Netherlands).

Analytical grade standards of 18 pharmaceuticals and 78 pesticides, and 20 isotopically labeled compounds used for quantification were purchased from Sigma-Aldrich. Detailed information is provided in Table S1 in the Supporting Information (SI). The stock standard solutions of the individual analytes including standards and labeled standards, were prepared in ACN and stored in amber glass bottles in the dark at 4 °C. Working mixed standards solutions at 200 ng/mL containing all analytes were prepared by appropriate dilution of the individual stock solutions and used for spiking solutions and for the validation study. Calibration curves were constructed by dilution of the working mixed solution using ultra-pure water. Working labeled standard solutions at a concentration of 200 ng/mL were also prepared.

2.2. BBF selection

In this study, the 15 available BBFs from various origins that were selected as part of the LEX4BIO program were considered (Table 1). From these 15 BBFs, a selection was made for the initial spiked recovery experiments (SRE) in the present study to span the range of origins and matrices of the BBFs. Two selected BBF samples (vermicompost (***VAC***) and Bioagenasol (***BA1***)) were from plant residues. Three selected BBFs (AshDec (***ADC***), EcoPlant-humi (***EPH***) and Poultry litter ash (***PLA***)) were ash-based, and one selected BBF (Hühnermist (OPU)) was of

Table 1
Detailed information on the BBFs used in this study.

Acronym	Name of BBFs	Raw material	Technology
VAC[a, *]	Vermicompost, Austria	Green waste or compost	Composting [35]
BA1[a]	Bioagenasol	Wheat and maize	Fermentation and distillation [36]
FEK[b]	Fertikal 4–1–2 organic	Chicken manure	Drying and pressing (extrusion process) [37,38]
CGO[b]	Struvite (Crystal Green)	Wastewater supernatant	Struvite precipitation [39]
OPU[b, *]	Hühnermist (Optisol Universal)	Chicken manure	Pelletising [40]
MO14[b]	Monterra 2–14–4	Animal proteins, vegetable by-products	Pelletising [40]
OG1[b]	Øgro 10–3–1	Meat and bone meal	Pelletising [40]
BIO[b]	Bio 8–4–2	Meat and bone meal (MBM), apatite, vinasse, chicken manure and potassium sulphate	Pelletising [40]
MB1[b]	Meat & bone meal (Biorga Vianos)	Meat and bone meal	Pelletising (Sphero technology) [41]
ECO[b]	Ecolan Agra(r) 13–0–0	Blood and feather meal	Pelletising [40]
OG2[b]	Øgro N15	Horn meal (pig bristles)	Hydrolysis [42]
MO13[b]	Monterra Bio 13–0–0	Feather meal	Pelletising [40]
EPH[c]	EcoPlant-humi	Sunflower husk ash	Granulating [43]
ADC[c, *]	AshDec (Calcinated Phosphate)	Sewage sludge ash[§]	Thermochemical process [44]
PLA[c]	Poultry litter ash	Poultry litter ash	Incineration [45]

[a] is plant-based BBFs; [b] is animal-based BBFs; [c] is ash-based BBFs
*represent BBF selected for spiking recovery experiments

animal origin. The selection of these BBFs allowed for the efficient analysis of a large number of samples, ensuring the validation of the results [33,34]. Subsequently, the optimized method was applied to all 15 BBFs.

2.3. Extraction procedures

Before extraction, BBF samples were freeze-dried and subsequently ground by mortar and pestle and sieved over a 2 mm sieve.

As a starting point for our extraction, we selected an original QuEChERS method that has previously been applied to the extraction of pesticides or pharmaceuticals from various individual matrix types [18, 26, 46, 47]. Based on the results, an improved QuEChERS method was subsequently developed and tested (see Section 3.1). Both methods are henceforth respectively labelled “Original QuEChERS method (OQM)" and ”improved QuEChERS method (IQM)” (the flow is shown in Fig. 1).

The OQM briefly followed the following procedure: 10 g (+/ 0.1 g) homogenized BBF samples were placed into a 50 mL centrifuge tube; 15 mL of ACN (with 2.5% formic acid) were added to the tube, and subsequently the following steps were performed: 1) all tubes were shaken vigorously by hand followed by vortex mixing for 2 min; 2) a mixture of 6 g $MgSO_4$ and 1.5 g CH_3COONa was added to the tube; after shaking by hand for 30 s and vortexing for 30 s; 3) the extract was centrifuged at 4000 rpm for 10 min at room temperature; 4) the aliquot was frozen for 4 h to precipitate interferences and filtered by 0.22 μm PP filter before evaporation with nitrogen gas.

In the development of multiclass methods, the choice of a suitable extraction solvent is of great importance for improving recovery. ACN was used because it can minimize the co-extraction of interferences and improve the recovery of organic pollutants. It was found that recoveries increased for some problematic pharmaceuticals and pesticides when adding acid in organic solvent for extraction [48], for which we used formic acid. Among many dispersive solid-phase extraction (D-SPE) sorbents, the combination sorbents of primary secondary amine (PSA) and Octadecyl bonded silica gel (C18) material had the best purification effect in various solid matrices [49]. PSA is a weak anion exchange agent, and some polar interferences can be retained [50]. C18 material can remove the fats and non-polar compounds [51]. Therefore, the extracts were cleaned up by PSA and C18 in OQM and IQM.

The improved QuECHERS method (IQM) consisted of the same steps as the original method, with the addition of the following steps: the centrifuge tube was ultrasonicated for 15 min and rotated end-over-end at 120 rpm for 30 min after adding $MgSO_4$ and CH_3COONa.

2.4. D-SPE

After application of the OQM or IQM, 1 mL of the filtered organic phase was transferred to a 5 mL tube with 60 mg PSA powder and 60 mg C18 powder; then the tube was vortexed for 30 s and centrifuged for 10 min; Afterwards, all the supernatant was transferred to a 1.5 mL vial and evaporated to dryness under a gentle stream of nitrogen gas; For better dissolution of the hydropholic and hydrophilic target compounds and compatibility with the eluent used in the subsequent liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) analysis, the dry matrix was reconstituted to 1 mL Milli-Q water:MeOH, 90:10 *v/v*. Additionally, the expected concentrations for each analysis in samples were below 50 ppb.

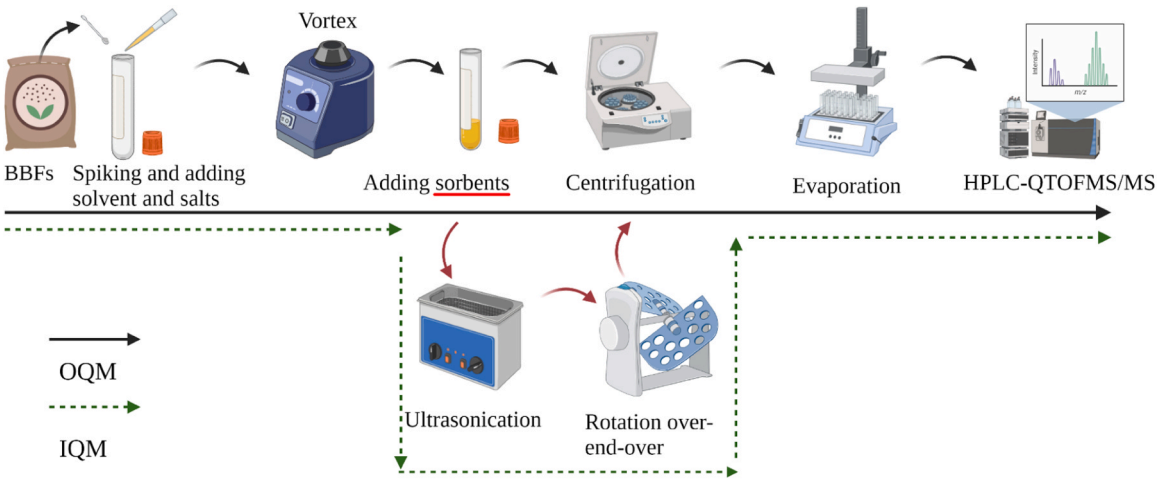

Fig. 1. The flow of OQM and IQM (Created with BioRender.com).

2.5. LC-MS/MS analysis

The analyses were conducted with an ultra-high performance liquid chromatography (UHPLC) system (Nexera, Shimadzu, Den Bosch, The Netherlands) coupled with a Bruker Daltonics maXis 4 G high-resolution quadrupole-time of flight-tandem mass spectrometry (q-ToF-MS/MS) upgraded with an HD collision cell and equipped with an electrospray ionization (ESI) source (Bruker, Leiderdorp, The Netherlands). The analytes were separated on a reversed-phase core-shell Kinetex biphenyl LC column (particle size: 1.7 μm; pore size: 100 Å; dimensions: 150 × 2.1 mm, Phenomenex, Utrecht, The Netherlands). The mobile phase consisted of water with 0.05% acetic acid (mobile phase A) and MeOH (mobile phase B). The LC gradient started at 0% MeOH and increased linearly to 100% at 17 min, remaining at that level until 25 min. The MS detector was internally calibrated before the start of an analysis batch by infusing a 2 mM solution of sodium acetate in a 1:1 volumetric ratio of H_2O and MeOH in both positive and negative ESI mode. The initial conditions were reset over a period of 7 min. A 50 μM solution of sodium acetate in a 1:1 volumetric ratio of H_2O and MeOH was also automatically introduced for m/z recalibration of the system between each sample injection. The column oven was maintained at 40 °C. The system was run in separate positive and negative ESI modes with a resolving power of 30,000–60,000 full width at half maximum. The target screening and quantification method was adapted according to the procedure described by Narain-Ford et al. & Albergamo et al. [52,53].

2.6. Method validation

To evaluate the accuracy and precision of the method, SRE, ME, linearity of calibration curves, method limit of detection (MLOD), and method limit of quantification (MLOQ) were evaluated. Internal and external calibration curves were constructed for 20 analytes with IS and 76 analytes without IS, respectively (Table S2). The spiked recovery experiment of the 96 analytes including 18 pharmaceuticals and 78 pesticides in three types of BBFs was conducted at two concentration levels, 10 and 50 ng/g, in triplicates. For each batch of samples, one type of blank matrix was as quality control sample to check for any possible background concentration of analytes in the sample during SRE. For correcting ME, the recovery was calculated by comparing the concentration difference in extracted samples with and without spiking to the concentration in spiked matrix extract. Linearity was tested in the range of 0.05 − 50 ng/g (0.05, 0.5, 1, 2.5, 5, 10, 15, 25, and 50 ng/g) for 96 analytes. Precision was calculated as relative standard deviation (RSD, %) for each concentration level. ME was calculated using triplicates with the following equation: $ME\ (\%) = 100 * (\frac{\text{concentration in spiked matrix} - \text{concentration in blank matrix}}{\text{concentration in solvent}} - 1)$, where concentration in spiked matrix refers to the concentration of the target compounds that is measured in the matrix after the process of extraction, followed by the addition of the target compound to the extracted matrix. The MLOD and MLOQ were estimated from ratio of standard deviation of the response and the slope in the calibration curve at successive injection of each extract spiked at various analytes at different levels. The accuracy was expressed as $100 * (\frac{\text{spiked concentration in matrix} - \text{concentration in blank matrix}}{\text{spiked concentration in solvent}})$, where spiked concentration in matrix refers to the concentration of target compounds that is measured in the matrix after the spiking process, followed by the extraction steps, in three types of BBFs was conducted at two concentration levels, 10 and 50 ng/g, in triplicates.

2.7 Measurement of organic matter content in BBFs.

The organic matter content of ***OPU***, ***VAC***, and ***ADC*** was determined using the loss on ignition method, with triplicate measurements. Five grams of BBFs samples were placed in a crucible and dried in an oven at 105 °C for 24 h to obtain the dry BBFs. Subsequently, the samples were subjected to combustion in the oven at 375 °C for 16 h to obtain the burned BBFs. The weight difference between the dry and burned BBFs, relative to the initial dry BBFs weight, represents the organic matter content.

3. Results and discussion

3.1. Results of SRE with original QuEChERS method

During the processing of raw materials of various origins into BBFs, sorption to matrix components (via cation exchange, surface complexation, electrostatic interaction, and hydrogen bonding), or sequestration may happen [54–57], which could mainly influence the extraction efficiency. In addition, sorption depends on the molecular characteristics of the pollutants of interest and the composition of the matrix of the BBFs [58]. Therefore, the SREs were conducted in a representative animal-based (***OPU***), plant-based (***VAC)***, and ash-based BBF (***ADC***) matrix. The experiments were performed at spiked concentrations of 10 and 50 ng/g via OQM, as shown in Table S2.

The number of recovered compounds varied in the three types of BBFs. In ***OPU*** 34 (at 10 ng/g) and 38 (at 50 ng/g) out of 96 of the spiked targets exhibited an acceptable recovery (70–120%) of which 8 and 9 out of 18 pharmaceuticals, and 26 and 29 out of 78 pesticides at spiked concentrations of 10 and 50 ng/g, respectively. However, 9 and 6 pesticides were below the MLOD at spiked concentrations of 10 and 50 ng/g, respectively. In ***VAC***, 33 targets, including four pharmaceuticals and 29 pesticides, exhibited an adequate recovery of 70–120% at a spiked concentrations of 10 ng/g. Nine pharmaceuticals and 47 pesticides, had an acceptable recovery of 70–120% at a spiked concentration of 50 ng/g. Also in ***VAC***, both six compounds were below the MLOD at spiked concentrations of 10 and 50 ng/g. In ***ACD***, 54 and 58 targets, of which 9 and 10 pharmaceuticals and 45 and 48 pesticides, were in the acceptable range at spiked concentrations of 10 and 50 ng/g, respectively, and all compounds were recovered. Therefore, the OQM performed the best for ***ADC***.

When interacting with the matrix, the compounds can be adsorbed. The components within the matrix can therefore be categorized based on their sorption capacity towards pharmaceuticals and pesticides. These categories include: (1) components with poor sorption capacity, such as sand; (2) components with medium sorption capacity, such as iron oxide; and (3) components with strong sorption capacity, such as organic matter and montmorillonite, an important natural clay mineral. ***ADC*** consists entirely of inorganic matter and given its origin (sewage sludge) does not contain any clay minerals. As a result it can be expected to display relatively weak or medium sorption between the matrix and compounds. As a result, the compounds could easily be dissociated from ***ADC*** using organic solvents. In contrast, ***OPU*** and ***VAC*** are rich in organic matter (***OPU***, 62%; ***VAC***, 35%). There are several interaction forms between pesticides or pharmaceuticals and organic matter, such as H-bonds, π-π bonds and cation bridges, [59]. Pesticides such as dichlorodiphenyltrichloroethane and hexachlorocyclohexane may be sequestered in organic matter in soil [60,61]. Sulfonamide can form non-extractable residues in association with organic matter via these chemical bonds [62,63]. This explains the difference in the extraction efficiency between ***ADC*** on the one hand, and ***OPU*** and ***VAC*** on the other, for most compounds. Furthermore, the extraction difference between ***OPU*** and ***VAC*** is likely caused by the difference in molecular organic matter composition, which affects the degree and type of interaction between the organic molecules and the pollutant in question [64,65]. Similarly, the various extraction effects observed with the OQM in SRE can be explained by interactions of pollutants and the BBF matrix, as OQM is unlikely to break the strong interactions between the targets and organic matter in ***OPU*** and ***VAC***.

In summary, the OQM was capable of adequately extracting only 34–54 and 38–58 out of the 96 pesticides and pharmaceuticals tested at spiking concentrations levels of 10 and 50 ng/g, respectively, in three types of BBFs: ***OPU***, ***VAC***, and ***ADC*** (Table S2). However, there is the possibility to improve the suboptimal outcomes. Therefore, further optimization of the OQM was undertaken.

3.2. The results of the SRE with the improved QuEChERS method

Increasing the input energy may be a better way to obtain a complete extraction than changing buffers, such as the EDTA-McIlvaine buffer, or the mixture of organic solvents due to the limitation of partition via solvents in the case of extraction of a wide range of organic chemicals [66]. Ultrasonication is a technique that is used equally for the extraction of solid sludge, manure, soil, and sediment matrices, and also is a good compromise between extraction efficiency and cost [15]. Therefore, we added an ultrasonication step to the OQM. In addition, the samples were rotated end-over-end to improve contact between the matrix and organic solvent after ultrasonication. This combination is in-line with previous studies of the extraction of pharmaceuticals and PFAS (perfluoroalkyl substances) at trace level from a solid matrix [67,68]. To test the potential improvement over the OQM, spiked recovery experiments were performed at spiked concentration of 10 ng/g via the improved QuEChERS method (IQM).

The results are presented in Table S3 and show that for ***OPU***, ***VAC***, and ***ADC*** the recovery of 57 (11 pharmaceuticals and 46 pesticides), 69 (9 pharmaceuticals and 60 pesticides), and 65 compounds (10 pharmaceuticals and 55 pesticides) was in the acceptable range of 70–120%, respectively, compared to respectively 34, 44, and 54 compounds via the OQM at a spiking concentration level of 10 ng/g. Therefore, the extraction efficiency of both pesticides and pharmaceuticals was significantly improved when extracted via the IQM compared to the OQM, which is in line with results reported elsewhere that ultrasonication improved the recovery from a complex matrix [69,70]. In previous studies, pharmaceuticals and antibiotics such as naproxen, carbamazepine, and tetracyclines were poorly recovered via OQM, whereas their recovery improved via adding an ultrasonication method [57,70]. Song, et. al. (2015) considered the polybrominated diphenyl ethers was too strongly sorbed to sediment and vegetables to achieve satisfactory extraction. Therefore, QuEChERS assisted with ultrasonication improved the extraction efficiency as compared to conventional QuEChERS[71]. There is considerable literature data that indicates that QuEChERS followed by ultrasonication could significantly improve the recoveries of a large suite of pesticides in soil, sewage sludge or crops [72–74]. Therefore, we considered the IQM as an option in this study to improve the extraction efficiency due to dissociation of the strong interaction between organic pollutants and organic matter.

To perform a rigorous test, SRE was subsequently performed at a spiking concentration of 50 ng/g via the IQM, as shown in Table S3. From ***OPU***, ***VAC*** and ***ADC*** 61 compounds (12 pharmaceuticals and 49 pesticides), 68 compounds (12 pharmaceuticals and 56 pesticides), and 79 compounds (16 pharmaceuticals and 63 pesticides) were recovered in the range of 70–120%, respectively. At 50 ng/g the results also improved compared to the OQM, thus showing that the IQM also proved suitable for compounds at higher concentration levels.

In summary, the IQM indeed significantly improved the combined extraction of pharmaceuticals and pesticides as compared to OQM, and was therefore subsequently applied to all 15 BBFs.

3.3. Validation parameters

Linearity of calibration curves evaluated for 96 analytes were at a concentration range of 0.05–50 ng/g. The results, presented in Table S4, demonstrated linearity with R^2 values of 0.991–0.999. MLOD (Table S4) ranged from 0.16 to 4.32 ng/g, 0.03–11.02 ng/g, and 0.06–5.18 ng/g for ***OPU***, ***VAC*** and ***ADC***, respectively. MLOQ (Table S4) was found to be 0.48–12.97, 0.10–33.06 ng/g, and 0.18–15.54 ng/g for ***OPU***, ***VAC*** and ***ADC***, respectively. The occurrence of ME was classified into three categories: "no ME" (ME $<\pm$20%), "medium ME" (ME of 20–50%), and "strong ME" (ME $> \pm$ 50%). As shown in Table S5, the majority of compounds displayed low to medium ME at spiking level of 10 and 50 ng/g in three BBFs via IQM. Specifically, 30 (at 10 ng/g) and 33 (at 50 ng/g) compounds showed no ME, 59 and 50 compounds showed a medium ME, and 7 and 13 compounds showed a strong ME in ***OPU*** at spiking concentrations of 10 and 50 ng/g, respectively; in ***VAC*** 43 and 40 compounds showed no ME, 49 and 46 compounds showed a medium ME, and 33 and 28 compounds showed a strong ME at spiking concentrations of 10 and 50 ng/g, respectively; in ***ADC*** 74 and 28 compounds showed no ME, 20 and 52 compounds showed a medium ME, and 2 and 16 compounds showed a strong ME at spiking concentrations of 10 and 50 ng/g, respectively. These results suggest that ME remains a significant issue in the extraction of complex matrices, as previously reported in the literature [75–77]. Accuracy results were found to be excellent, with 48–64 compounds falling within the range of 70–120% in three BBFs at two concentration levels (Table S6).

3.4. Quantification

The IQM combined with LC-MS/MS analysis was employed to determine pharmaceuticals and pesticide residues simultaneously in the 15 BBFs samples (Table 1). The results are shown in Table 2 and showed that most BBFs contained at least one pesticide or pharmaceutical, although some were below MLOQ. None of the compounds were detected in the ash-based BBFs, which may be due to the production process effectively degrading all targeted compounds through incineration. The concentrations of the compounds ranged from 4.1 to 181 ng/g, but most were below MLOD and some were below MLOQ (Table 2).

Ibuprofen is a commonly prescribed non-steroidal anti-inflammatory drug that has been frequently detected in environmental matrices such as water, soil, sediment, and sewage sludge due to its high mobility [78–81]. In this study, ibuprofen was detected in veterinary-based BBFs and plant-based BBFs at the highest concentration of all compounds detected (181 ppb: Table 2). This suggests that ibuprofen may be becoming ubiquitous and warrants attention in BBFs. Antipyrine is another compound that has been frequently detected in aquatic environments, sediment, and wastewater treatment plants, but is rarely found in solid matrices such as BBFs and soil [82,83]. However, it was also detected in 7 BBFs in this study, although at levels below MLOD (Table 2). This may be due to its use in treating diseases in livestock, which can retain the compound in their bodies and excrete it into their manure [84,85]. Additionally, its degradation resistance is similar to carbamazepine, which may contribute to the trace levels found in BBFs.

4. Conclusions

In order to screen 15 BBFs derived from various origins for the presence of pharmaceuticals and pesticides, we tested and improved a QuEChERS method for the simultaneous extraction of a large suite of such compounds. In spiked recovery experiments with animal-based (***OPU***), plant-based (***VAC***), and ash-based BBFs (***ADC***), only 34–58 compounds, both pharmaceuticals and pesticides, were well recovered (i.e. between 70% and 120% recovery) at concentrations levels of 10 and 50 ng/g using the original QuEChERS method. To improve the extraction efficiency, an improved QuEChERS method (IQM) was tested at two concentration levels (10 and 50 ng/g) and found to increase the number of compounds extracted with an acceptable recovery to 57–77. Therefore, the IQM was subsequently used to screen 15 BBFs of various origins. Most BBFs contained at least one pesticide or pharmaceutical, with concentrations ranging from 4.1 to 181 ng/g. Most compounds were below LOD and some were below LOQ. Ibuprofen was frequently detected in animal- and plant-based BBFs, indicating that some compounds may be becoming ubiquitous. No compounds were detected in any of the ash-based BBFs, likely due to the degradation of most compounds during incineration.

CRediT authorship contribution statement

Yan Dong played a significant role as the first author, providing the majority of the contributions. This included conducting the experiments,

Table 2
Mean concentrations of pesticides and pharmaceuticals in 15 BBFs, ng/g.

	VAC	*BA1*	*FEK*	*CGO*	*OPU*	*MO14*	*OG1*	*BIO*	*MB1*	*ECO*	*OG2*	*MO13*	*EPH*	*ADC*	*PLA*
Antipyrine	-	<MLOQ	-	-	<LOQ	5	<MLOQ		<MLOQ	<MLOQ	<MLOQ	-	-	-	-
Atenolol	-	-	MLOQ	-	<MLOQ		-	-	<MLOQ	13.3	-	-	-	-	-
Atrazine	-	-	-	-		<MLOQ	-	-	-	-	-	-	-	-	-
Climbazole	<MLOQ	-	-	<MLOQ		-	-	-	-	-	-	-	-	-	-
Fenuron	-	-	50.0	-	<MLOQ	<MLOQ	-	-	-	-	-	-	-	-	-
Ketoprofen	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lincomycin	-	-	46.4	-			-	-	-	-	-	-	-	-	-
Methylpirimifos	<MLOQ	<MLOQ	<MLOQ	-			-	-	<MLOQ	-	-	-	-	-	-
Metoprolol	-	-	-	<MLOQ		-	-	-	-	-	-	-	-	-	-
Naproxen	-	-	-	-	-	<MLOQ	-	-	-	-	-	-	-	-	-
Propoxur	-	-	-	<MLOQ	-	-	-	-	<MLOQ	-	-	-	-	-	-
Sotalol	-	-	-	<MLOQ	-	-	-	-	-	-	-	-	-	-	-
Bentazon	-	-	-	-	<MLOQ	-	-	-	-	-	-	-	-	-	-
BiphenolA	-	-	-	-	-	<MLOQ	-	-	-	-	-	-	-	-	-
Gemfibrozil	-	-	<MLOQ	-	<MLOQ	-	-	-	-	-	-	-	-	-	-
Ibuprofen	-	102	109.0	<MLOQ	12.5	181	-	<MLOQ	-	-	8.2	4.1	-	-	-

- indicates a concentration level below MLOD; other compounds were not shown were below MLOD

analyzing the data, interpreting the results, and writing the manuscript. **Supta Das**, the second author, was involved in the experimental design of the manuscript. **John R. Parsons**, the third author, contributed to the work by assisting in overseeing the project, involving experimental design, and providing critical revisions to the manuscript. **Antonia Praetorius**, the fourth author, primarily focused on reviewing and revising the manuscript. **Eva de Rijke**, the fifth author, focused on reviewing and revising the manuscript. **Rick Helmus**, the sixth author, contributed to the work through reviewing and critical revisions of the manuscript. **J. Chris Slootweg,** the seventh author, primarily focused on reviewing the manuscript. **Boris Jansen**, the eighth author, was involved in monitoring the whole project, reviewing the manuscript for content, construction, and clarity, designing the experiments, and providing critical revisions to the manuscript. All authors have read and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Yan Dong reports financial support was provided by European Union. Yan Dong reports financial support was provided by Chinese Scholarship Council.

Data Availability

Data will be made available on request.

Acknowledgements

We gratefully acknowledge funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 818309 (www.lex4bio.eu) as well as funding from the China Scholarship Council (CSC). The views expressed in this study are those of the authors alone and do not necessarily reflect the position of the European Union. We also extend our sincere thanks to the LEX4BIO project partners for their contribution of soil samples and standards, as well as lab support from Samira Absalah, Rutger van Hall, and Bram Ebben in the Institute for Biodiversity and Ecosystem Dynamics (IBED).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhazmat.2023.131992.

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