Innovative approach to increase sensibility and selectivity in analytical chemistry: QuEChERS method

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Abstract

The QuEChERS method, acronym of quick, easy, cheap, effective, rugged and safe is one of the pre-treatment techniques that has gained great popularity among researchers for analysis of different analytes such as drugs, pesticides, mycotoxin, etc. The QuEChERS method involved different steps: liquid-liquid extraction (LLE) with minimum use of organic solvent, followed by salting-out and clean-up step using dispersive-Solid Phase Extraction (d-SPE). In the last years, all these steps have been optimized in order to increase sensibility and selectivity. This method allows to reduce the sample manipulation, avoiding loss of target analytes and increasing the recovery. Furthermore, the method is considered to be more environmentally friendly, respecting the green analytical chemistry (GAC) principles. The QuEChERS method has already been applied for extraction of different compounds and it is expected that will be more used in the next years. In this review the main advantages and recent applications of this procedure have been reported.

Keywords: QuEChERS, Analytical methods, Chromatographic procedures, Sample preparation, Complex matrices, Green Chemistry.

1.0 Introduction

Nowadays, a challenge that analytical chemists are called to solve is to develop methods that should be easy to perform, faster, more environmentally friendly, precise, accurate, without complicated cleaning steps and that allow the analysis of a wide range of analytes. To resolve this challenge, the Quick, Easy, Cheap, Effective, Rugged and Safe (QuEChERS) method has been developed as one of the most promising friendly, multiclass and multiresidue analytical approach [1-4]. The QuEChERS method was presented for the first time at the European Pesticide Residue Workshop (EPRW) in Rome in 2002 by Anastassiades, Lehotay, Stajnbaher and Schenck and then published in 2003 [1]. The approach proposed by Anastassiades et al. was developed to extract pesticide residues from fruit and vegetables [5,6].

Abbreviations

LLE: liquid-liquid extraction; d-SPE: dispersive-solid phase extraction; GAC: green analytical chemistry; DLLME: dispersive liquid-liquid microextraction; PSA: primary and secondary amine exchange material; GCB: graphitized carbon black; HPLC: High-Performance Liquid Chromatography; GC: Gas chromatography; DAD: diode array detector; MS: mass spectrometry; MRL: maximum residual level; OPP: organophosphorus pesticide; OCP: organochlorine pesticide; PAH: polycyclic aromatic hydrocarbons; PCB: polychlorinated biphenyl; GPC: gel permeation chromatography; PPCP: pharmaceuticals and personal care products; SCDT: Sodium Citrate Tribasic Dihydrate; SCDS: Sodium Citrate Dibasic Sesquihydrate.
This method rapidly gained the attention of the scientific community due to the ability of extract a broad analyte spectrum, ranging from non-polar to very polar pesticides. Based on its great versatility, recently the QuEChERS approach has become popular over the scientific community, expanding its field of application outside its classical domain into different analytes (e.g. environmental pollutants, amines, polyphenols pharmaceuticals) from different matrices including food, biological fluids and environmental samples [7,8]. In short, the QuEChERS method involved two steps: in the first step acetonitrile (ACN) is added to a solid matrix and a partitioning between the aqueous and organic layer is obtained after adding salts (usually sodium chloride or magnesium chloride); in the second step a combination of salts and porous sorbents is added to the ACN solution obtained before in order to remove matrix interfering substances by dispersive solid phase extraction (d-SPE) [9]. A scheme of standard QuEChERS method is reported in Figure 1.

Before the extraction phase it is necessary to homogenize the sample; it is important to pay attention to the degree of shredding and the quantity of sample as these factors influence the contact surface between the sample and the extracting solvent. Then proceed with the extraction by adding a solvent suitable for the homogenized sample. Several water-miscible solvents were tested for the salting out extraction/partitioning such as: acetone, acetonitrile, ethanol, ethyl acetate. Different degrees of phase separation were obtained using different concentrations of different salts [10]. Among these solvents, acetonitrile was chosen as best solvent for the first step of QuEChERS method, due to its better phase separa-

Figure 1. Scheme of standard QuEChERS method.
tion after the addition of salts and its selectivity. Acetonitrile also ensures a low solubility of lipids, thus lipid co-extraction with this technique is relatively limited, but extraction of pesticides from lipids may occur [11]. In this review paper, QuEChERS methods in several matrices, including food, biological and environmental matrices is reviewed. Whenever possible, the advantages and disadvantages of each extraction method are critically reviewed. Potential readers can gain practical information about QuEChERS method and its possible modification in order to optimize procedures as a function of their research.

2.0 QuEChERS method and its evolution
Since its introduction by Anastassiades et al., in 2003 [1], other two QuEChERS procedures have been developed:

Standard QuEChERS method:
in this method the extraction process involves the addition of 10 mL of ACN to 10 g of powdered sample and shake vigorously. The mixture of salts (MgSO₄ and NaCl in a 4:1 ratio) is added to obtain the LLE, it is stirred again for 1 minute and centrifuged at 6000 rpm for 5 minutes. The supernatant is transferred to an Eppendorf containing 150 mg of MgSO₄ and 50 mg of PSA (clean-up), shaken for 1 min and centrifuged for 1 min at 6000 rpm. The supernatant is used for analyte research.

AOAC method (the acetate-buffering version):
15 mL of 1% acetic acid in acetonitrile are added to 15 g of homogenized and hydrated sample [12]. The mixture is stirred and 6 g of MgSO₄ and 1.5 g of Sodium acetate (strong buffering capacity) were added. It is stirred again and centrifuged for 1 min at 1500 rpm. One mL of supernatant is transferred into Eppendorf containing MgSO₄ and PSA (C18 and GCB) for the clean-up phase [13], shake for 30 seconds and spin for 1 min at 1500 rpm. The purified sample is conserved in toluene for GC/MS and in formic acid 6.7 mM for LC-MS/MS.

CEN method (citrate buffer version):
15 mL of 1% acetic acid in ACN were added to 15 g of sample. MgSO₄ and NaCl were added in a 4:1 ratio [14] and also citrate buffer (low buffering capacity) to create a pH suitable for inducing LLE. It is stirred for 1 min and is centrifuged for 5 min at 3000 rpm. As sorbent phases of d-SPE are used PSA, C18 and anhydrous MgSO₄. It is stirred and centrifuged; the supernatant was preserved in 5% formic acid in ACN and analyzed with GC/MS or LC-MS/MS.

These methods differ for the extraction salts and solvents used. In fact, a first improvement introduced to the QuEChERS method was the optimization of salts amount and their combination based on chemical properties of investigated analytes. Furthermore, CEN and AOAC methods differ from Standard QuEChERS in the use of buffered salts which enhance the recovery of compounds that may be degraded at high or low pH values [9,15]. Salts also play a key role for the liquid-liquid partitioning, due to their interaction with the H₂O molecules. The original salts used by Anastassiades were MgSO₄ and NaCl although MgCl₂, NaNO₃, LiCl are options which could be investigated [1]. Magnesium sulphate in contact with the aqueous solution containing the analytes causes an exothermic reaction which leads to an increase in the temperature of the sample and facilitates the extraction of non-polar analytes [16]. Moreover, although magnesium sulphate is a good choice to achieve phase separation, a combination of magnesiu sulphate and sodium chloride leads to a better phase separation and it has been also demonstrated that fewer co-extractives were obtained using this combination of salts [17,18]. For this reason, Anastassiades and coworkers developed a non-buffered QuEChERS method using in the first step 10 g of sample, 10 mL of acetonitrile, 4 g of MgSO₄ and 1 g of NaCl. The buffered salts have been introduced in the QuEChERS method in order to avoid the degradation of pesticides at high or low pH values. For this reason, the CEN method and the AOAC method has been developed [19-24]. The AOAC method use a combination of 1.5 g of sodium acetate which has a strong buffer capacity and 6 g of MgSO₄ in the first step while the CEN methods use 1 g of trisodium citrate dihydrate and 0.5 g of disodium hydrogen citrate sesquihydrate which were added to the standard salt combination (4 g of MgSO₄ and 1 g of NaCl). Nowadays, in several laboratories these two methods are widely used as they ensure a sample solution with a pH 5, which is the optimal condition for extracting pH dependent analytes. Moreover, a limitation of AOAC and CEN method may be encountered when samples with a high content of fats are extracted, this is due a higher extraction of interferents which could be less retained by the sorbents in the clan-up step at this pH level.

The second step of QuEChERS method is the clean-up of the extract by using dispersive solid phase extraction (d-SPE). For this purpose, several sorbents have been reported in literature used alone or in combination among primary secondary amine (PSA) octadecyl silica (C18) and graphitized
carbon black (GCB) [25]. Historically, the first sorbent used by Anastassiades and coworkers for the cleaning phase was MgSO$_4$ with PSA which ensures effective elimination of fatty acids and organic acids without interfering with the analytes present in the solution. Magnesium sulphate, in this case, was used as drying agent in order to eliminate the water residual in the ACN extract obtained in the first step. Subsequently, both GCB and C18 have been introduced as sorbents. They ensure an efficient removing of fats and pigments such as chlorophyll and carotenoid which could reduce the column life and the efficiency of detectors in the LC or GC systems [26]. Although GCB ensure a high removal of fats, it should be used with caution because GCB remove also analytes with planar structure due to its affinity for planar compounds. Recently, the Enhanced Matrix Removal-Lipid (EMR-Lipid) has been developed by Agilent in order to selectively extract interferents from sample matrix. EMR-Lipid mechanism differs from classical sorbents because it acts through hydrophobic and size exclusion interactions between the sorbent and lipids. Furthermore, unlike classical sorbents which are used after the ACN-Water partitioning, EMR-lipid is used in the first step and subsequently in the second step the EMR-lipid polish was used to achieve the partitioning between ACN and water. This difference is due to the need by EMR-lipid of samples with high water content to achieve an efficient removal of lipids from matrix, in fact a high-water content is impossible to obtain after the ACN-water partitioning [27-29]. Despite the theoretical potential of EMR lipid in the elimination of lipids, other sorbents have been developed that can overcome the lipid removal issue. Another sorbent introduced recently is CarbonX, which remove efficiently more interferents without loss in the analyte recovery compared to GCB sorbent [18].

Finally, thanks to research on graphene-based materials, the Cleanert NANO sorbent based on functionalized carbon nanotubes has been developed. Cleanert NANO allows compared to other sorbent a better removal of fatty acids and pigments. Furthermore, compared to other sorbents, only few milligrams of Cleanert NANO (10-15 mg) are sufficient for the sample clean-up giving to the sorbent the possibility of being packaged as a filter format cartridge.

The most used analytical techniques for the separation and identification of pesticides and organic pollutants are GC and LC coupled with mass spectrometry. In recent years, also ultra-high-performance liquid chromatography (UHPLC) coupled with mass spectrometry has become more popular and widely applied to the analysis of food and environmental samples giving the possibility to the laboratories to increase their workflow. LC is more suitable for the multiresidue analysis of pesticides because it allows the possibility to separate and detect a wide range of compounds while GC is limited to volatile analytes. However, the development of analytical techniques has led to the achievement of rapid analysis due to the tandem MS detection. In fact, the use of GC-MS/MS and LC-MS/MS has increased the use of QuEChERS method giving the possibility to perform the simultaneous analysis of hundreds of compounds [30].

3.0 QuEChERS applications

3.1 Food safety

Food safety and preservation have always been the first goal of the scientific community avoiding contamination and adulteration in order to protect human health. In this field the QuEChERS method represent an alternative tool to conventional analytical methods, due to the possibility of rapid and economic control of different food matrices. The main changes of the standard method mainly concern the extraction solvent, or the mix of salts used. An example is given by Tomas Tuzimski and coworkers [32], a QuEChERS/d-SPE method coupled with HPLC-DAD was optimized for the detection of bisphenols in milk samples both from a can and breast milk. In this work six different sorbent phases and their mixtures (PSA, C18, Z-Sep, Z-Sep Plus, Chitin and EMR LIPID) were evaluated to obtain the best analyte recovery and minimize matrix interferents. In fact, milk samples, due to their generally oily consistency (6% fat content), require special attention during the clean-up phase (d-SPE). Among the various sorbent phases evaluated, Z-Sep (Zirconium dioxide modified silica particles) and Z-Sep Plus were the best because they can adsorb majority of fatty non-polar interferences. Moreover, the introduction of a pre-concentration step before the chromatographic analysis showed an increase in the sensitivity of the method. Another example showing the versatility of the QuEChERS technique is reported from Parvin Eslami Shahrbabki et al. [33], where a method has been optimized to determine the acrylamide content in some types of Tha-Dig, a typical meal of Iranian cuisine based on rice, meat and potatoes. Acrylamide, recognized as a human carcinogen by the International Agency for Research on Cancer, can be produced by the reaction of asparagine with sugars at high temperatures; therefore, carbohydrate-rich foods like Tha-Dig are an important source. In this work the authors used a mixture of deionized water, acetonitrile and n-hexane in the extraction phase, while for the clean-up phase the ACN layer was transferred to a falcon containing the sorbent phase
(MgSO$_4$ and PSA). Another variant of the QuEChERS method is promoted by Fontana et al. [34]. In their work the analysis of 3-isopropyl-2-methoxy pyrazine, 3-sec-butyl-2-methoxy pyrazine, and 3 isobutyl-2-methoxy pyrazine in red and white wine, was carried out using toluene as an extraction solvent in the preparation phase of the sample, followed by GC-MS analysis for the determination of different compounds. As reported in the literature, the QuEChERS method was introduced for the first time for the determination of pesticides in fruit and vegetables. These compounds are widely used in agriculture to eliminate all that damages the cultivated plants and compromises productivity but, if their quantity is higher than the maximum residual level (MRL) imposed by European Union, they could create different health damages; their determination is therefore fundamental in terms of food safety.

Among the various articles on pesticides research in the agricultural sector, the one published by Narenderan et al. [35], reports a modification of the original QuEChERS method; in this work the authors evaluate the presence of five organophosphorus pesticides (OPPs) in some types of fruit and vegetables grown in Nilgiris (South India) by adding to the homogenized sample ACN acidified with 8% of formic acid in order to obtain greater selectivity towards the analytes. A new method for pesticides research but in a different matrix was developed by Stremel et al. [36]. In this work a QuEChERS method was applied for the organochlorine pesticides (OCPs) determination in the tissues of various fish trying to optimize the various parameters present in the preparation phase of the sample and using low quantities of sample (0.5 g). The best results in terms of recovery were obtained using acetone and hexane (1:1, v:v) as extracting solvents, MgSO$_4$, NaCl and Na$_2$SO$_4$ in salting-out step and MgSO$_4$, C18 and PSA as sorbent phases for d-SPE. In addition, Chen et al. [37] analyzed plants and soil samples looking for afidopyropen and its metabolites, using a mixture of H$_2$O:ACN (3:10, v:v) for the extraction phase, maintaining MgSO$_4$ and NaCl for the salting-out, but reducing the ratio to 2:1, and using C18, GCB and MgSO$_4$ as sorbent phases. Always for a tight control of the foods that arrive on our tables, the evaluation of contaminants present in the meat represents a further possibility of application of the QuEChERS method. In fact, it was quickly applied for searching both veterinary drugs and prohibited pharmacologically active substances (substances with hormonal and beta-agonist activities), potentially dangerous for animals and humans health. An example is the work reported by Yen-ping Li et al. [38], in this paper the QuEChERS method was applied applying the acidification of the extracting phase (ACN + 1% of acetic acid) for the determination of -agonists in two different breeding tissues (muscles and viscera). The acidification of the extracting solvent allowed a better recovery of non-polar analytes in the organic phase while the polar impurities of the matrix remained in the aqueous layer. Oliveira et al. (2017) developed a QuEChERS method followed by LC-MS analysis for the detection of various pesticides present in beef. The method was effective for the quantitative determination of more than 150 compounds. The extractive phase was performed with acetonitrile and 1% acetic acid and ethyl acetate (70:30, v:v %), while MgSO$_4$, C18 and PSA were used for the clean-up phase [39].

### 3.2 Biological samples

Another important application of QuEChERS method is in biological field. This other application includes the determination of antibiotics, veterinary and pharmaceuticals drugs but also pesticides, toxic substances and every kind of contaminant that could be present in biological fluid or human tissues. In literature you can find several works that show the applicability of QuEChERS on both conventional and unconventional matrices, confirming the wide versatility of this preparation method. An example is the study conducted by Admin Wurta et al. [40], to identify methamphetamine from 71 years old man who died of a heart attack [41]. They used centrifuge tubes with PSA, end-capped octadecyl silane and magnesium sulfate for the clean-up step and Captiva nondrip (ND) Lipids cartridge for filtration. The method of standard addition [42] allowed to minimize the matrix effect and exploit advantage of the atomic absorption spectroscopy to the full. Twenty-one solid tissue samples were analyzed like brain, kidney, liver, pancreas, hearth muscle, adipose tissue, as well as different bodily fluids, such as blood. Attention was paid to the location of blood samples analyzed, linking it to post-mortem redistribution of blood. Additionally, it has been seen that, despite the concentration of xenobiotic in the femoral vein, it could reflect that at the time of death (with minimal changes in the post mortem), however it needs taking in consideration the partial loss of xenobiotic through the thin wall of venous vessel, especially in long post mortem range. In 2016, M. Licata et al. [43], conducted a study on patients suffering acute migraines attacks undergoing therapy, 234 real samples were analyzed with modified QuEChERS method coupled with LC-MS/MS. The study was also widely acknowledged in the toxicological field: as based on the length
of the hair, it is possible to make a retrospective assessment about drugs, therapeutic adherence or abuse drugs used up to seven months before, finding a broad consensus in legal and clinical field. In this regard, about fifty psychoactive substances and their metabolites were analyzed, belonging to different pharmacokinetic classes; antidepressants, anxiolytics, mood stabilizers, opioids, and triptans. The authors used methanol instead acetonitrile in the extraction step, then they skipped the partitioning step and only used MgSO₄ in the clean-up to extract psychoactive substances. Some particular studies have found variants in the QuEChERS method. Xiao Qian Jia et al. (2019) [44], focused their attention on organic pollutants, especially polycyclic aromatic hydrocarbons (PAHs), organochlorine pesticides (OCPs), and polychlorinated biphenyls (PCBs) which are very harmful for human health, whose presence in serum was searched. During this study different methods of purification were applied to eliminate matrix interferents, (proteins, lipids, carbohydrates, and pigments). A comparison was made between traditional GPC and QuEChERS method, both of them following by a second clean-up step obtained with a combined column of neutral silica gel and neutral alumina oxide (AlO/SiG). The results obtained from the two method are comparable and, only in the case of polychlorinated biphenyls (PCBs) with high molecular weight, the association gel-permeation chromatography and Al₂O₃/SiG column proved to be convenient after analysis in GC/MS. Instead the work of Lehmann et al. [45] on the exposure of man to pesticides in areas where intensive cultivation of vegetables takes place, is conducted using a non-conventional matrix; the matrix used is human hair that, after a phase of careful homogenization, undergoes extraction using the QuEChERS method and subsequent analysis in GC-MS. The optimized procedure involves the use of ACN and H₂O (1:1, v:v) in the extractive phases while, for d-SPE, Z-Sep Plus was used as sorbent phase. The study showed high human exposure to locally used pesticides and the optimized protocol was sensitive, accurate and robust.

Another important example of the QuEChERS used on biological samples was carried out by Alves et al., in 2016 [4], for the identification and quantitative determination of fluoxetine, ciprofloxacin and their active metabolites in twelve human urine samples of patients being treated with these antidepressants. In this study, the use of ethyl acetate as extraction solvent has showed good results for extraction potential of non-polar compounds, because it ensures the maximum contact efficiency between sample and solvent that allowed satisfying analysis in HPLC. The search for different drugs in the blood through the QuEChERS technique has been exploited by various authors. Pouliopoulos et al. [46] use the traditional method for identifying 15 psychotropic drugs in post-mortem whole blood and serum, while Mizuno et al. [47] use it for testing for valproate only in whole blood. What differs between the two works is the sorbent phase used; in fact the first one used MgSO₄ and PSA for d-SPE step, while in the other one MgSO₄ and C18 are used.

3.3 Environmental samples
The analysis of soils, sediments, wastewater and surface water represents another large field of application of the QuEChERS technique for the detection of contaminants that could be found in foods of both plant and animal origin. The complexity of the environmental matrix has led to the development of numerous modifications to the standard method. In this sense Fernandes et al. (2013) [48], in their work modified the QuEChERS version based on the citrate buffer for the determination of 36 pesticides used in organic farming and for the management of pesticides in the soil. These changes mainly concerned the amount of sample used, the adsorbents required and the addition of water at the beginning of the extraction in order to obtain better recoveries. Furthermore, the authors used ultrasound in the extraction step to improve the degree of homogenization of the sample and consequently to have a better extraction.

Another development was that proposed by Wang et al. [49] that in their work for the determination of PAH in the upper, middle and lower layers of soils they used dichloro-methane as the extracting solvent, Na₂SO₄ as salt, PSA, C18 and Na₂SO₃ as adsorbents for the purification step. A further application of the QuEChERS acidified method in the environmental field is reported from Kachawaha and coworkers [50] for the analysis of pharmaceutical and personal care products (PPCPs) in surface water and sewage. In this work ACN acidified with formic acid as extraction solvent, MgSO₄ and NH₄CH₃CO₂ for the breakdown were used, but the purification phase was not performed.

3.4 Mycotoxins
Mycotoxins are chemicals with potential toxicity, produced by fungi, molds and various microscopic species. Environmental and food contamination due to the spread of these substances can generate even chronic toxicity phenomena, putting human and animal health at risk. Therefore, the identification of such substances is indispensable to limit poisoning phenomena. The QuEChERS method fits into this field thanks
to its extreme versatility and, although with different modifications compared to the traditional method, is a fast and advantageous technique. In the literature there are several works in which the QuEChERS technique has been used for the determination of mycotoxins. An example is the work of Martins et al. [51] in which the research of twelve mycotoxins and their respective metabolites in breakfast cereals was conducted using ACN as extraction solvent, MgSO₄ and NaCl (4:1) in the salting-out phase and MgSO₄ and PSA as sorbent phases for d-SPE. Also, in the food field, Huang et al. [52] have researched different mycotoxins present in lico-
rice using a QuEChERS method modified by the addition of formic acid to the acetonitrile and using MgSO₄, NaCl, SCTD and SCDS (4:1:0.5:1) as salts. Wang et al. [53], instead they modified the standard QuEChERS method by acidifying aceto-
nitrile with citric acid for the research of various mycotoxins in dried fruit. In addition to the applications abovementioned, QuEChERS method was applied also for different other drugs, mycotoxins, various environmental contaminants, samples of animal origin like beef, pork, sheep meat, but also eggs, honey, aquatic organism (Table 1). Then it could be applied for multi-classes analysis, for the detention of large range of contaminants with a single analysis.

4.0 Comparison with other extraction methods
Due to the wide range of application of QuEChERS method, its comparison with other extraction techniques is allowed. A comparison between QuEChERS, Soxhlet and solid-liquid extraction (SLE) is presented by Durovic-Pejcev et al. for the analysis of multiclass pesticides in soil samples. The traditional techniques are SLE and Soxhlet which are time consuming, tedious, expensive and require large quantities of organic solvents. Among these techniques QuEChERS showed much better results in terms recovery, LOD values and relative standard deviations (RSDs) clearly indicating that SLE and soxhlet extraction still needs improvements for the determination of multiclass pesticides in soil samples [74]. Chen et al. on the contrary, reported that micellar extraction combined with ionic liquid-based vortex-assisted liquid liquid microextraction (ME-IL-VALLME) achieved better analytical performance with higher enrichment factor compared with QuEChERS for the analysis of difeconazole in cowpea [75]. An interesting comparison was made by Pawliszyn et al. between solid-phase microextraction, solvent extraction (SE) and QuEChERS for the quantitative analysis of veterinary drug residues in chicken and beef matrices. In terms of time required to perform extraction SE requires two min/sample, QuEChERS requires 3 min/sample and SPME less than 1 min/sample. Furthermore, SPME, can be easily automated eliminating a significant source of variation. The low con-
sumption of organic solvent is clearly an advantage of solid phase microextraction, in fact the SPME protocol requires only 0.3 mL of organic solvent compared to the QuEChERS method which requires 10 mL of ACN. However, a careful optimization of several parameters such as extraction phase, desorption step, adsorption time is needed when a SPME is performed. Finally, SPME obtained similar performance compared to QuEChERS and SE [76]. Another interesting comparison between, protein precipitation, SPE and QuECh-
ERS was made by Kim et al. for the analysis of nitrosable pesticides in human serum and urine by liquid chromatog-
raphy-orbital ion trap mass spectrometry [77]. Among these sample preparation techniques, deproteinization by metha-
nol led to an excessive ion enhancement of some analytes causing the suppression of others. Solid-phase extraction was also evaluated, three types of sorbents were evaluated. Although SPE is recognized as a valid extraction technique capable of obtaining much cleaner extracts and high accu-
rracy, in this case it has achieved a significant loss for some analytes. Kin et al. in their work demonstrated that QuECh-
ERS approach is a suitable method for the extraction of nitro-
sable pesticides in human biofluids. Furthermore, QuEC-
hERS method resulted in higher recovery among the tested extraction techniques showing minimal matrix effects in both the matrices. An exhaustive comparison between soxhlet ex-
traction, microwave assisted extraction, ultrasound assisted extraction and QuEChERS has been reported by Forbes et al. in the analysis of polycyclic aromatic hydrocarbons (PAH) from lichen biomonitor [78].
Among the investigated techniques, QuEChERS and MAE performed better compared to UAE and Soxhlet extraction. Furthermore, it was found that hexane-acetone mixture (1:1, v:v) which is never reported before for the extraction of PAH achieved the highest total peak area for all the PAH of interest and a relative standard deviation equal or better of the other extraction techniques. Although the microwave extraction is uncommon for a matrix as lichens, it has widely performed to extract PAH from several matrices achieving performance comparable with QuEChERS method. Microwave assisted extraction was found to perform better than QuEChERS, Soxhlet extraction and accelerated solvent extraction of ste-
roid estrogens from sediments [79]. In Table 2, a comparison on the efficiency of different extraction approaches with the QuEChERS method is reported.
Table 1. Examples of QuEChERS application in various fields, respectively food, biological, environmental and about mycotoxins.

| Sample               | QuEChERS Method          | Analytes                        | Matrix            | Extraction solvents | Salts/buffer       | Clean-up            | Analytical method     | LOD         | Ref. |
|----------------------|--------------------------|---------------------------------|-------------------|---------------------|--------------------|---------------------|-----------------------|-------------|------|
| Food                 | Standard QuEChERS       | Multiclass pesticides           | Tobacco           | MeCN                | MgSO\(_4\) and NaCl (4:1, or 2:1) | d-SPE using MgSO\(_4\), C18, PSA and GCB | GC-MS/MS, UHPLC-MS/MS | -           | [54] |
| Modified QuEChERS    | Multiclass pesticides    | Coconuts                        | 1% Acetic acid in Acetonitrile | -                   | d-SPE using MgSO\(_4\), C18 and PSA sorbent | LC-MS/MS | 0.010 mg/kg | [55] |
| Modified QuEChERS    | Multiclass pesticides    | Brown, rice orange, spinach     | MeCN with 0.1% FA | MgSO\(_4\) and NaCl (4:1) | d-SPE using MgS, MgSO\(_4\), PSA and GCB | UHPLC-MS/MS | 10.20 µg/g | [56] |
| Modified QuEChERS    | Multiclass pesticides    | Beef meat                       | MeCN with 1% HAc:EtAc (70:30 v/v) | MgSO\(_4\) and NaOAc (4:1) | d-SPE using MgSO\(_4\), C18 and PSA sorbent | LC-MS   | 10/25 g/Kg | [39] |
| Modified QuEChERS    | Multiclass pesticides    | Whole Wheat flour               | Acidified Acetonitrile | -                   | without clean up | GC-MS   | 0.010 mg/kg | [57] |
| Modified QuEChERS    | Multiclass compounds     | Red and white wines (3-Isopropyl-3-isobutyl- and 3-sec-butyl-2-methoxy pyrazine) | Toluene           | MgSO\(_4\) and NaCl (4:1) | d-SPE using CaCl\(_2\), MgSO\(_4\) and PSA | GC-ECD   | 13.9-23.6 ng/L | [34] |
| Modified QuEChERS    | Multiclass pesticides    | Fish tissue                     | Acetone:HEX (1.1 v/v) | MgSO\(_4\), NaCl and Na\(_2\)SO\(_4\) (4:1:2) | d-SPE using MgSO\(_4\), C18 and PSA sorbent | LC-MS/MS | 0.8-9.6 g/kg | [58] |
| Modified QuEChERS    | Multiclass pesticides    | Sweet green pepper              | MeCN with 5% FA   | MgSO\(_4\), NaCl, SCTD, SCDS (4:1:1:0.5) | d-SPE using MgSO\(_4\) and PSA | UHPLC-MS/MS | 1-200 g/kg | [64] |
| Modified QuEChERS    | Multiclass pesticides    | Wheat, soil (Afidopyropen and its metabolite) | H\(_2\)O:MeCN (3:10 v/v) | MgSO\(_4\) and NaCl (2:1) | d-SPE using MgSO\(_4\), C18 and GBC sorbent | UHPLC-MS/MS | 1 ng/g     | [37] |
| Sample       | QuEChERS Method         | Analytes                                      | Matrix                      | Extraction solvents                                        | Salts/buffer                                   | Clean-up                                      | Analytical method                                         | LOD          | Ref.       |
|--------------|-------------------------|-----------------------------------------------|-----------------------------|------------------------------------------------------------|------------------------------------------------|------------------------------------------------|----------------------------------------------------------|--------------|------------|
| **Food**     | Modified QuEChERS      | Multiclass pesticides                         | Honey                       | 1% acetic acid in 10 mL of Acetonitrile: Ethyl Acetate (70:30 v/v) | MgSO₄ and NaOAc (4:1) | d-SPE using MgSO₄, Florisil and PSA sorbent | -                                                        | 0.005 mg/kg   | [59]       |
|              | Standard QuEChERS      | Drugs (Zolpidem zolpidem phenyl-4-carboxylic) | Body fluid, tissues         | MeCN Captiva ND Lipids cartridges                          | MgSO₄ and K₂CO₃ | d-SPE using MgSO₄ and C18 sorbent         | LC-MS/MS                                               | -            | [60]       |
|              | Standard QuEChERS      | Drugs: 15 Psychotropic drugs                  | Post-mortem blood, serum    | MeCN MorfSpe ND Lipids cartridges                           | MgSO₄ and NaCl (4:1) | d-SPE using MgSO₄ and C18 sorbent         | LC-MS/MS                                               | 1-50 ng/mL    | [46]       |
|              | Standard QuEChERS      | Drugs: Valproate                              | Whole Blood                 | MeCN MgSO₄ and NaCl (4:1)                                  | d-SPE using MgSO₄ and C18 sorbent         | GC-MS/MS                                               | 10 ng/mL                                               | [47]         |            |
|              | Modified QuEChERS      | Drugs: 7 agonists                             | Muscle, viscera             | MeCN with 1% EtAc MgSO₄ and NaOAc (4:1)                     | d-SPE using MgSO₄ and C18 sorbent         | LC-MS                                                  | 1 ng/g                                                 | [35]         |            |
| **Biological** | Modified QuEChERS     | Bisphenol A                                  | Human Urine                 | MeCN with 1% EtAc MgSO₄ and NaOAc (4:1)                     | d-SPE using MgSO₄ and C18 sorbent         | GC-MS                                                  | 0.43 g/L                                               | [61]         |            |
|              | Modified QuEChERS      | Pesticides                                   | Human hair                  | MeCN:H₂O (1:1 v/v) MgSO₄ and NaOAc (4:1)                    | d-SPE using Z-Sep                          | UHPLC-MS/MS, GC-MS                                    | 0.6-288.5 pg/mg                                        | [45]         |            |
|              | Modified QuEChERS      | Drugs: Zearalenone and its 4 metabolites     | Human tissue                | EtAc MgSO₄ and NaOAc (4:1)                                  | d-SPE using Z-Sep                          | HPLC-FLD, UHPLC-QTOF                                   | 232 ng/g                                               | [62]         |            |
|              | Modified QuEChERS      | Drugs: Avermectins, benzimidazoles and         | Bovine muscle tissue        | MeCN with 2% HAc MgSO₄ and NaCl (1:2)                       | d-SPE using Z-Sep                          | UHPLC-MS/MS                                            | 0.011-113.674 g/kg                                    | [63]         |            |

**Table 1.** Cont’d.
| Sample       | QuEChERS METHOD | Analytes                                  | Matrix          | Extraction solvents                     | Salts/buffer               | Clean-up                  | Analytical method | LOD          | Ref. |
|--------------|-----------------|-------------------------------------------|-----------------|-----------------------------------------|---------------------------|---------------------------|-------------------|--------------|------|
| Biological   | Modified QuEChERS | Drugs: 26 Veterinary Drugs                 | Swine manure    | MeOH, MeCN, 0.1 EDTA-McIlvaine buffer (12.5:37.5:50 v/v) | MgSO₄ and NaCl (4:1)      | d-SPE using PSA and C18 | LC-MS/MS         | 0.05-5.91 g/kg | [64] |
|              | Modified QuEChERS | 7 PBDEs, 8 MeO-PBDEs                      | Fish tissue, feed, blood | d-SPE using EMR-lipid, MgSO₄ and Z-Sep | MeCN: Toluene (4:1)      | MgSO₄ and NaCl (4:1) | GC-MS/MS         | < 265 pg/g     | [65] |
| Environmental| Standards QuEChERS | Imazethapyr, Imazapic                    | Soil            | MeCN                                    | MgSO₄ and NaCl (4:3)      | d-SPE using MgSO₄        | LC-MS/MS         | 6.1-6.6 g/kg   | [66] |
|              | Standards QuEChERS | Cyazofamid                               | Soil            | MeCN                                    | MgSO₄ and NaCl (4:1)      | d-SPE using MgSO₄, C18 and PSA sorbent | LC-MS/MS         | 0.33-3.8 g/kg   | [67] |
|              | Standards QuEChERS | Indaziflam                                | Soil, water, fruits | MeCN with 1% NH₄OH                      | MgSO₄ and NaCl (3:2)      | d-SPE using MgSO₄ and C18 | UHPLC-MS/MS     | 0.01-1.01 g/kg | [68] |
|              | Modified QuEChERS | Indaziflam and its five metabolites      | Sediments       | EtAc                                    | MgSO₄ and NaCl (4:1)      | d-SPE using MgSO₄, Florisil and PSA sorbent | GC-MS/MS         | 0.01-0.08 ng/mL | [69] |
|              | Modified QuEChERS | Pesticides                               | Soil            | MeCN with 1% HAc and SCTD, SCDS (4:1:1:0.5) | MgSO₄, NaCl and SCTD, SCDS (4:1:1:0.5) | d-SPE using Al₂O₃ | LC-MS/MS         | 10 g/kg        | [70] |
| Sample                        | Analytes                                                                 | Extraction solvent | Matrix            | Clean-up       | Analytical method | LOD       | Ref.    |
|------------------------------|---------------------------------------------------------------------------|--------------------|-------------------|----------------|-------------------|-----------|---------|
| Mycotoxins                   | 12 Mycotoxins and their related metabolites                              | MeCN               | Breakfast cereals | d-SPE using MgSO₄ and PSA | LC-MS/MS | 0.004-19.4 g/kg | [51]    |
| Mycotoxins                   | 27 Mycotoxins and their related metabolites                              | MeCN               | Ready-to-eat food | d-SPE using MgSO₄ and PSA | LC-MS/MS | -        | [71]    |
| Mycotoxins                   | 16 Mycotoxins and their related metabolites                              | MeCN               | Vegetables oils   | d-SPE using C18 | LC-MS/MS | 0.13-10 ng/g   | [72]    |
| Mycotoxins                   | 15 Mycotoxins and their related metabolites                              | MeCN with 5% FA    | liquorice         | d-SPE using MgSO₄ and PSA | LC-MS/MS | -        | [52]    |
| Mycotoxins                   | 16 Mycotoxins and their related metabolites                              | MeCN with 10 mMol/L citric acid | nuts, dried fruit | d-SPE using C18 | UHPLC-MS/MS | 0.1-2.5 ng/g | [53]    |
| Ochratoxin A                 | 15 Mycotoxins                                                           | MeCN or MeCN with 5% HAc | grape, animal-derived products | d-SPE using MgSO₄ and PSA | UHPLC-MS/MS | -        | [73]    |
5.0 Conclusions

The QuEChERS approach is presented as a rapid, economical, and very advantageous sample preparation technique in terms of environmental safety. From the initial limited use of pesticide research in fruit and vegetables, it has been possible to extend its application in various other fields, from food to pharmaceutical, environmental and forensic, thanks above all to its versatility. The ease in preparing the sample thanks to only two steps, extraction and clean up, is the main advantage of the method which guarantees quality, safety, authenticity and traceability of the analytes in the various matrices. Through the control of various factors, such as the extraction solvent, the sample quantity, the sample/solvent ratio, the pH, the salts and the sorbent phases, the QuEChERS protocol guarantees a high recovery rate and a better analytical performance compared to other conventional extraction techniques. Reliability and reproducibility make QuEChERS the procedure of excellence in the pretreatment phase of samples destined for analysis by chromatography or spectrometry. The future perspectives are aimed at reducing the manual steps turning their attention to the automation and miniaturization of the method, to speed up the analysis time, and to increase the efficiency and the selectivity through the coupling to other preconcentration methods.

Table 2. Comparison of QuEChERS method with other extraction methods.

| Analytes              | Matrix               | Instrumentation | Extraction method       | Comments                                                                                   | Ref.  |
|-----------------------|----------------------|-----------------|-------------------------|-------------------------------------------------------------------------------------------|-------|
| Fipronil              | Honey                | HPLC-DAD        | DLLME, QuEChERS         | Although DLLME achieved higher enrichment factor, smaller LOQ and used lower extraction solvents, QuEChERS demonstrated to be more robust. | [80]  |
| 56 pesticides         | Hop samples          | LC-MS/MS        | Hengel’s method, Biendl’s method, QuEChERS | The three methods provided the same analytical performance in the analysis of pesticide residue in hop samples. However, the QuEChERS approach seems to be the easiest to perform | [81]  |
| Difeconazole          | Cowpea               | LC-MS/MS        | ME-IL-VALLME, QuEChERS  | In this case, ME-IL-VALLME seems to be the more performant in terms of enrichment factor compared to ME-IL-VALLME | [75]  |
| 12 pesticides         | Soil                 | GC-MS           | Soxhlet, SLE, QuEChERS  | QuEChERS showed much better results in terms of accuracy and confidence.                  | [74]  |
| 100 veterinary drugs  | Chicken, Beef        | LC-MS/MS        | SPME, QuEChERS          | Both methods ensured high accuracy and similar analytical performance. However, SPME used fewer organic solvents and, when automated, a high-throughput extraction. | [76]  |
| PAHs                  | Lichens              | GC-MS           | USAE, MAE, Soxhlet, QuEChERS | MAE and QuEChERS methods had better analytical performance compared to USAE and Soxhlet extraction. | [78]  |
| Steroid oestrogens    | Sediments            | LC-MS/MS        | Soxhlet, MAE, ASE, QuEChERS | MAE and QuEChERS methods demonstrated to achieve best recoveries and repeatability compared to ASE and Soxhlet extraction. | [79]  |
| Nitrosable pesticides | Human plasma and urine | LC-MS/MS      | Protein precipitation, SPE, QuEChERS | QuEChERS achieved best recovery and accuracy compared to other methods. Furthermore, QuEChERS method ensured minimal matrix effect in both biomatrices. | [77]  |
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