

Sample Preparation Methods for Pesticides Analysis in Food Matrices and Environmental Samples by Chromatography-Based Techniques: A Review

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Abstract: Much attention has been made in pesticide analysis to improve agricultural productivity and control these compounds in food and environmental samples. Different methods have been applied in pesticide analysis, among these; methods based on chromatographic separation with mass spectrometric detection have been extremely useful methods for determination of pesticide residues. Despite employing powerful instrumental techniques, the risk of interference increases with the complexity of the matrix studied, so sample preparation prior to instrumental analysis is necessary. This article reviews the analytical characteristics of different sample preparation methods for the determination of pesticide residues in food and environmental samples and biological fluids. Furthermore this review describes the advantages, disadvantages and details of the analytical procedure that have been applied recently in different sample preparation methods and their applications in combination with chromatographic mass spectrometric analysis. This article provides selection of a reliable method which will be useful for the quantitative analysis of pesticide residues in a variety of samples based on their evaluation in recent applications.

Key words: Sample preparation • Chromatography • Solvent extraction • Pesticide residues • Sorptive extraction and mass-spectrometry

INTRODUCTION

In the past decades great advancement has been made in order to achieve efficient separation of analyte from a sample matrix with high selectivity and sensitivity. Different extraction methods are employed, consisting of solvent extraction from solids and liquid-liquid extraction from solutions. The solvents may be organic liquids, supercritical fluids or superheated liquids. Alternatively, the liquid extractant may be bonded to a support material. Selectivity can be achieved by altering the extraction temperature and pressure, by the choice of extraction solvent or liquid and the control of pH and additives such as ion-pair reagents. Poor sample treatment or roughly prepared extract will invalidate the total analysis and will make it impossible to gain a valid result even by use of the most powerful separation method. Therefore correct sample preparation can be economically valuable as well as analytically important. The purpose of sample preparation method is to convert a real matrix into a form that would be appropriate for analysis. The recent trends for sample preparation methods have been towards:

- the capability to use smaller initial sample sizes.
- better specificity or greater selectivity in extraction
- a more environmentally responsive approach by using a small consumption of solvent and small amount of organic wastes
- improved potential for automation or on-line methods

All extraction methods make use the same basic set of concepts that is to concentrate the analyte selectively in one phase, whereas an analyte will be distributed between two phases according to its distribution coefficient, temperature and the relative volumes of the phases. However, the extraction rates are based on the migration kinetics and hence are governed by temperature and diffusion rates in the two phases. A balance must often be obtained between the complete extraction of all the soluble organic components and the selective extraction of only the compound of interest. Solid samples are usually prepared by grinding, mixing, agitating, stirring, chopping, crushing, pressing and pulverizing directly or after drying followed by solvent or liquid

extraction. In most of cases, sample homogenization with an organic solvent often mixed with water is achieved by using a homogenizer, blender or sonicator [10, 11]. After the extraction steps the analytes of interest are obtained in an organic or aqueous solution, which then requires concentration or additional clean-up. The extract can then be treated similar to liquid samples. Liquid samples can be handled directly such as, quick, easy, cheap, effective, rugged and safe (QuEChERS) procedure [1], or instrumentally-based heating or agitating of sample such as, pressurized liquid extraction (PLE)[2], microwave assisted extraction (MAE) [3], ultrasonic extraction (USE)[4], supercritical fluid extraction (SFE) [5], or by solvent-solvent extraction methods or sorption methods such as, solid-phase extraction (SPE)[6], solid-phase microextraction (PME) [7], headspace-solid phase microextraction (HS-SPME) [8] and stir-bar-sorptive extraction (SBSE) [9]. The use of solid sorbent material to extract analytes from a solution was developed in the 1980s and is now widely applied to many matrices, including food. A sorbent with strong affinity towards some target analytes will retain and concentrate those compounds from the sample solution. Many sorbents are specifically suited for the extraction of different analytes with various degrees of selectivity such as (SPE), (SPME), (SBSE) and matrix solid-phase dispersion (MSPD). These methods offer both advantages and disadvantages and so the application of any one of those depends on the properties of analyte and analytical problems. Food is a complex non-homogenous mixture of a wide range of chemical substances that makes it hard to isolate and determine the analyte of interest. Therefore, analyses of pesticide residues in food samples would always suffer from interferences present in the matrix. To overcome this problem it is necessary to use appropriate extraction method and clean-up process. Many literatures in recent years have reported the works carried out to achieve this objective. This review describes the summary of previous studies on the analyses of pesticide residues with using chromatography MS.

Sample Extraction Methods: During the last decades, several modern techniques have been purposed to reduce sample handling and toxic waste, consequently to maximize recovery of the analytes and minimize the accompanying interferences by the use of appropriate extraction and clean-up procedures. Some of these methods are described in the next sections and their main parameters are summarized in Tables 1-5.

Solvent Extraction (SE): A number of solvents have been used for this purpose and the most common

include ethyl acetate (EtAc) [12-15], acetone [16, 17], acetonitrile (MeCN) [18-24], methanol (MeOH) [9, 25-27], dichloromethane (DCM) [2, 28-29], n-hexane [30, 31] and diethyl ether [32]. However, it is important to match the polarity of the solvent to the solubility of analyte and the addition of non-polar, water immiscible solvents like DCM or n-hexane to the different polarity solvents to obtain the proper viscosity and modified solvent for extraction. Roos *et al.* [33] first reported the use of EtAc and sodium sulfate in a multi-residue extraction procedure to eliminate the liquid-liquid partition (LLP) step. Whereas Holstege *et al.* [34] modified the method by the addition of acetone, methanol or ethanol in EtAc in order to increase the polarity of the solvent system. The ethyl acetate method is also named the on-line extraction method because they omit a separate LLP step. Jianhua *et al.* [35] studied the application of several organic solvents such as MeOH, chloroform, acetone-n-hexane (1:1 v/v), DCM-MeOH (9:1 v/v) and chloroform-MeOH (1:1 v/v) for extracting triazines from sheep liver, at 70°C for 10 min. According to the results of recovery obtained the use of chloroform decreased the recovery due to the emulsification procedure during extraction. However, the recoveries were highest when MeOH was used as the extracting solvent. Among these solvents, MeCN has some advantages as the extracting solvent because MeCN is polar and soluble in water. In addition, it can furnish sufficient extraction for polar and nonpolar pesticides from non-fatty foods due to its hydrophobic property. When MeCN is employed as the extracting solvent, the extracts have only a small quantity of co-extractives and facilitate direct analysis by LC-MS or LC-MS² whereas other solvents such as DCM, the extracts contain larger amounts of co-extractives. Hence it is possible to use MeCN in the analyses of pesticide residues in complex matrices with different mixture of ingredients and interferences. The special properties of MeCN make it the solvent of choice in the QuEChERS technique. Zhou *et al.* [22] compared four organic solvents such as MeCN, methanol, ethanol and acetone for the optimal selection. In their experiments, LC-grade MeCN and methanol was used directly, but analytical-grade ethanol and acetone were used after redistillation to remove the impurities. It was found that acetonitrile gave the best elution performance for the analyses of s-triazine herbicides, giving better separation and good regular peak shape. Yoshioka *et al.* [32] used the lower boiling point of diethyl ether (DEE) instead of EtAc because DEE is easier by rotary evaporator at lower temperature. DEE was employed as extracting solvent for the analysis of post harvest fungicides, phenylphenol, diphenyl (DP), thiazendazole (TBZ) and imazalil (IMZ) in citrus fruits.

However, care must be taken when using DEE because it is flammable due to its low ignition point and it tends form explosive proxides. Many extractions have also been performed using medium-polarity solvents such as acetone [16, 17] and DCM [28-29] but DCM is a carcinogenic. On-column liquid-liquid extraction method (OCLLE) (based on classical LLE principle, but assisted by inert solid support), has been tested by Pirard *et al.* [36] for the analyses of different pesticides in honey using LC-MS/MS. OCLLE combines the advantages of LLE, SPE and SPME. In LLE technique, MeCN was used as the extracting solvent whereas in OCLLE, after agitating the samples with hexane and MeCN, the solution was re-extracted with MeCN. Results proved that extraction by OCLLE can be efficient for a wide range of pesticides and nearly independent of their polarities. The recoveries were between 71% and 90%. Solvents mixture such as MeCN saturated with n-hexane [37], MeOH-water [38], acetone-n-hexane [39, 40], DCM-MeOH [41, 42] and MeCN saturated with petroleum ether [43, 44] have been also used. Because the use of low polarity solvents like EtAc and DCM increases the extracts polarity prior to LC analyses, hence some or the whole eluate is evaporated before injection to the LC or is dissolved in a high polar solvent such as MeCN [31], isooctane [45], acetone [14], mixtures of MeCN with water [43, 44] or ultra pure water [46]. SPE, dispersive SPE [47-57] and classic solvent extraction [4, 9, 20, 59], are the methods most commonly used for this purpose, although gel-permeation chromatography (GPC) [58] and SBSE (enrichment and clean-up) [9] have also been employed successfully. In the analysis of fatty samples like fish, after extraction with appropriate solvent, low temperature clean up is often performed before SPE clean up [59]. In this case, the extracted solution is collected and stored in the freezer at -24°C for 20 min to freeze lipids. After filtration to remove frozen lipids, the filtered extract is concentrated prior to SPE clean up procedure. Although SE methods have some drawbacks such as laborious, expensive and have numerous problems to evaporate large volumes of toxic eluent and consequently time-consuming, these methods are accepted and popular for sample preparation due to having advantages like simplicity, robustness and efficiency. The advent of new modified SE methods in sample treatment resulted in the decline of organic solvent consumption, more effective extraction and on-line adaptation connecting directly instruments giving high extraction yield. Some of these techniques are described in the next sections.

Super-Critical Fluid Extraction (SFE): Carbon dioxide is the most common super critical fluid used as a potential

alternative solvent. In comparison, nitrous oxide proved dangerous because of its oxidizing power and more exotic solvents like xenon were ruled out by their cost. In many ways CO₂ is an ideal solvent as it combines low viscosity and a high diffusion rate with a high volatility. The solvation strength increases with temperature and hence the extraction can be carried out at relatively low temperatures. The high volatility simply means that the pressure is reduced and thus allowing the super critical fluid to evaporate readily and concentrates the sample. The use of CO₂ reduces organic solvent consumption. It is also inexpensive and nonflammable. The incorporation of various solid-phase sorbents like alumina and octadecylsily-bonded silica at the extraction procedure for purification purpose is one of the advantages of SFE [60]. The major problem is while the relatively low polarity of CO₂ which is ideal for PAHs and halogenated pesticides or lipids and fats it is unsuitable for most pharmaceuticals and drug samples. It has been popular for solid matrices including powdered plant material, herbal medicines, some foods, but there are some problems associated with liquids like biological fluids, which require immobilizing on a solid support material. The addition of modifiers, such as methanol to the CO₂ enables more polar analytes to be extracted and increase the scope of the method. Aguilera *et al.* [5] evaluated the effects of different factors like supercritical fluid volume, pressure, temperature and static modifier additions on SFE recoveries from spiked wild rice with 6% olive oil samples with 15 ml of CO₂ at 300 atm, 50°C and 200 µL MeOH as static modifier and using alumina as the cartridge. Their studies indicated that in all cases the recoveries without modifier were less than those achieved using methanol as modifier, except for the less polar pesticides. Very polar pesticides gave poor recoveries when the modifier was less than 30%. On the other hand, when EtAc was used as modifier, recoveries were a little higher than those achieved with methanol, except again for polar pesticides that only showed high recovery with MeOH. In another report, this author and co-workers [61] evaluated the retention of fat from wild rice by various sorbent materials (Celite, Extrelut, Hydromatrix, Florisil and Aminopropyl) employing on-line SFE clean-up procedure under conditions of 15 ml CO₂ at 200 atm and 50°C. They reported that the amounts of fat extracted per 100 g wild rice using Celite, Extrelut and Hydromatrix were undesirable (1.84, 1.80 and 1.62 respectively) whereas for Florisil this amount was reduced up to 0.36 g and the best results were obtained by using 1 g layer of Aminopropyl.

Rodil *et al.* [62] employed a useful tool based on a single step extraction and clean up to determine 15

organohalogenated pollutants in aquaculture samples using aluminum oxide and acidic silica gel in the supercritical extraction cell followed by GC-MS. Factors such as, extraction temperature (60°C), pressure, static extraction time (5 min), dynamic extraction time and CO₂ flow rate (2 ml min⁻¹) were optimized. The Doehlert design, followed by a multicriteria decision-making strategy, was then carried out in order to determine the optimum conditions for the two most important factors namely; pressure (165 bar) and dynamic extraction time (27 min). After analysis with GC-MS/MS, LODs were found to be in the range of 0.01-0.2 ng g⁻¹, with excellent linearity. However, existing information about the ability of on-line clean-up method to remove fat from matrices using SFE is not comprehensive and more studies are need with sufficient number of analytes and sorbent materials in order to confirm the applicability of this technique to different group of pesticides. For example, sorbents such as alumina, Florisil and silica can be placed in the extraction cell, or used for clean-up following extraction to increase selectivity. Sorbents in the extraction cell can also be used for 'inverse' SFE extraction, in which interfering compounds are removed by a weak supercritical extraction fluid, leaving the analyte trapped on the sorbent for subsequent extraction under stronger conditions [63]. In these articles MS detection was employed just for analytical confirmation so there is no information about quantitation analysis such as linearity, precision and LODs in the Tables.

Pressurized-liquid Extraction (PLE): This method, which has been commercialized as accelerated solvent extraction (ASE) employs conventional organic solvents at elevated temperatures above the atmospheric boiling points. A restriction or backpressure valve ensures that the solvent remains as a liquid but has enhanced solvation power and lower viscosities and hence a higher diffusion rate. By employing this method, extraction procedure can be carried out in minutes on a smaller sample, considerably speeding up the sample pre-treatment and requires a small fraction of the original solvent volume. An essential feature of the success of this system is the ability to carry out multiple extractions and so the next step would be moving towards automation. The extracts are usually much more concentrated than those obtained by conventional extractions. They could be analyzed directly or the solvent could be cooled and the analyte trapped on glass beads or a cartridge and subsequently extracted

into a smaller solvent volume. The increased temperature causes the increase of extraction rate because the viscosity and the tension of the solvent is decreased therefore the rate of diffusion into the analyte is increased. The pressure holds temperature of solvent at constantly lower than its boiling point and affects solvent diffusion into the sample.

PLE method can be carried out in static or dynamic modes, or the combination of both. In the static mode, the sample is placed in a stainless steel vessel containing the extracting solvent. During extraction the solvent is wash out with N₂ into a collection vial. In the second system extracting solvent is pumped through the sample but with high solvent consumption and hence diluting the extract. Anhydrous sodium sulfate, diatomaceous earth, cellulose or sorbent material can be used in clean-up step. In order to optimize the conditions, statistical experimental design procedures are used in order to reduce the number of experiments [64].

Modifiers can be added to the extracting solvent. For instance water modified with a surfactant (sodium dodecyl sulphate) was used to extract PAHs from fish tissues [65]. Tomomi *et al.* [13] used a simple one step extraction and clean-up by PLE under optimized conditions (extraction temperature: 100°C, extraction pressure: 11 MPa, static extraction time: 10 min, extraction cycle time: once, solvent flush volume: 6.6 ml) for the determination of six insecticides, a fungicide and a herbicide in vegetables via GC-MS. Among the several drying materials, such as anhydrous sodium sulfate, alumina, silica gel, Florisil and graphitized carbon, the last one was reported to be desirable, so graphitized carbon was used to remove the co-extracted water because it produced a transparent and colorless solution with mean recovery of 95%. The extracts had a dark green color when alumina (mean recovery: 92%) was used as the clean-up agent and the result were similar to Florisil (mean recovery: 76%) and silica gel (mean recovery: 82%). By reducing the amount of graphitized carbon, with reduction of graphitized carbon from 12g to 6 g, the color of the extracts changed from colorless to dark green. The overall recovery obtained for the analysis of 8 pesticides ranged from 71-103%. By contrast, Blasco *et al.* [12] used PLE extraction after the dispersion of fruit samples with acidic alumina. They reported that anhydrous sodium sulfate instead of alumina produced an extract with a cloudy and strong color. However, they did not evaluate the cleanup effects of the extraction procedure because they used the materials as a solid

support material or a drying material. Izabela *et al.* [66] developed and validated the simultaneous extraction and in situ clean-up of polychlorinated biphenyls (PCBs, OH-PCBs, MeSO₂-PCBs) and their metabolites in small tissue samples by PLE method. A mix of fat retainer and diatomaceous earth pre-extracted in a short PLE cell of the combined extraction and in situ clean-up to prevent cell memory effects. After tissue extractions, the pre-extracted diatomaceous earth was eliminated from the PLE cell by mixing the liver from non-PCB exposed rats. After spiking, the PLE cells were extracted twice under the same conditions as pre-extraction. Separation of different fractions was carried out using different physicochemical properties of selected pesticides based on the procedure proposed by Hovander *et al.* [67] followed by optimization of PLE parameters, temperature (60-120), pressure (6.9-13.8 MPa, 1000-2000 psi). The length of static cycle (1-9 min) was investigated by using of extracting solvent consist of hexane-dichloromethane-methanol (50:45:5 v/v). Validation of PLE-based method under optimized conditions (hexane-dichloromethane-methanol; 48:43:9 v/v, temperature of 100°C, pressure of 1500 psi, 6 min heating time, 1 static cycle of 5 min and a 60% cell volume flush) was performed by comparing with the extraction method described by Jenson *et al.* [68] as well as by verifying its linearity and repeatability. The Jensen method required more labor-intensive extraction with different solvent combinations of increasing polarity and clean-up steps with additional column clean-up steps for both PCBs and MeSO₂-PCBs in comparison with the PLE method described by Izabela that required only a single, automated PLE extraction step. For lipid containing samples, further clean-up is usually required and Gomez *et al.* [69] investigated the use of several sorbents and concluded that Florisil produced the cleanest extracts for their samples. An alternative approach is to perform a preliminary PLE with a non-polar solvent to eliminate the hydrophobic compounds prior to extraction of the analytes of interest. The use of pressurized fluids in comparison with soxhlet extraction have the advantages of reducing solvent consumption and extraction time although they need to use expensive specialized equipment and clean up procedure is necessary after extraction.

Microwave Assisted Extraction (MAE): In order to achieve easier sample pre-treatment, new extraction procedures based on instrumental techniques such as MAE with smaller amounts of matrix and solvent's

consumption and rapid extraction has been investigated since 1986 [70]. The key advantages of this method are the low temperature necessity, high extraction efficiency, automation, the chance of simultaneous extraction of different samples without interference, smaller amounts of matrix and solvent and rapid extraction. In contrast to other heating methods, the extraction vessel does not need direct heating and so the extraction time required is reduced. Furthermore, MAE does not require additional clean up step and the lack of selectivity as compared to SFE. In conventional extraction techniques using higher solvent volume to solid matrix mass ratio would increase recovery. However, in MAE a higher ratio of solvent to solid matrix mass may lead to lower recoveries, probably because of inadequate stirring of the solvent by the microwaves. MAE is only employed for the extraction of compounds that are thermally stable because increase in temperature during extraction may lead to degradation, so in such circumstances the power selected during MAE must be set correctly to avoid excessive temperatures. Antioxidants and preservatives can be extracted with this technique if the matrix is low in fat. This technique can be used to extract herbicides from soil and polycyclic aromatic hydrocarbon (PAHs) from sediments. Microwave extraction has also been combined with PLE for the extraction of polymers. Alternatively, sonication can be used to enhance extraction and this has been applied for the extraction of organophosphorus pesticides [71]. MAE technique, like SFE and PLE, provides simple conditions for working at high temperatures and pressures, which intensely enhance the speed of extraction. On the contrary, traditional techniques for solid matrices, such as the well-known Soxhlet extraction, together with shaking and sonication [72], which can also provide efficient extractions with low investment, seem to get decreasing attention due to their drawbacks: long extraction times (especially for Soxhlet), relative high solvent consumption, occasional need of a clean-up step and possible repeated extractions in the case of sonication.

Extraction of triazine herbicides from environmental samples by MAE method has been studied extensively. Cheng *et al.* [35] reported a multi-residue method developed for the determination of triazine herbicides (simazine, atrazine, propazine and prometryn) in sheep liver by MAE using MeOH as the extracting solvent. This solvent has high dielectric constant to adsorb microwave energy efficiently; however non-polar solvents such as hexane and toluene, are not potential solvents for MAE,

but their extracting selectivity and efficiency can be modulated by using mixtures of solvents for example, hexane-acetone [73]. Cheng and co-workers [35] optimized the MAE operation parameters such as type and volume of solvent, time and temperature of extraction in order to increase the extraction yield. First, 10 mL MeOH was added to the extraction vessels placed in the microwave sample preparation system and the extraction was performed at 70°C for 6 min. After cooling at room temperature and filtration, the residue was washed three times with 5 mL MeOH each time. The methanol extract was then extracted three times with 10 mL petroleum ether each time. After discarding the ether layer, the extraction was repeated three more times with 1 mL of 0.1% NaCl, 9 mL water and 10 mL chloroform each time. After distilling the chloroform extract to dryness and reconstitution of the residue with 5 mL MeOH, the solution was transferred to a column containing anhydrous sodium sulfate and aluminum oxide. Using chloroform as the extracting solvent resulted in emulsification and a decreased in recoveries. The results were desirable (upper than 90%) when the extraction time was increased from 2 min to 6 min. Different clean-up procedures have been carried out after MAE extraction such as SPME [74] and disposable SPE cartridge packed with C₁₈, silica and ion exchange material [41, 75]. Among many studies that was done on different extraction method coupled with chromatographic techniques and MS to analyze and determine of pesticide residues in foods, only a few studies have been reported on using MAE coupled with both chromatographic systems and MS. The reason might be the requirement of sample filtration and clean-up steps after extraction, something that is impossible to circumvent, in comparison with SFE and PLE method, in which on line clean-up and filtration are possible. Sanusi and co-workers [74] employed focused microwave-assisted extraction (FMAE) coupled with SPME and GC-MS for the extraction and analysis of pyrethroid residues in strawberry. In order to improve the conditions of FMAE-SPME, they added co-solvent (MeOH, MeCN or EtOH) to the extraction solution instead of pure water, enabling the increase in the transfer of the analytes into the solution analyzed by SPME. The results illustrated that, the observed signal was better when co-solvent was used instead of pure water. Among the three co-solvents, MeCN was the most sensitive. The obtained LODs were in accordance with MRLs. In a second study, Iglesias *et al.* [39] developed an analytical method based on MAE with hexane-acetone (50:50 v/v) as

the extracting solvent, SPE clean up with three different sorbents (alumina/ ENVITM-Florisil, ENVITM-Carb and ENVITM-Carb II/PSA) and hexane-EtAc (80:20 v/v) as the eluent for the determination of organochlorine pesticides in animal feed. The analytes were determined by GC-ECD and quantified via GC-MS. According to the results obtained, both ENVITM-Carb and ENVITM-Carb II/ PSA furnished colorless eluates but with lower interfering peaks in ENVITM-Carb II/ PSA chromatograms, so the latter system was employed for the purification of the extracts. The recoveries (100%) were similar to those achieved with soxhlet extraction. Validation method was performed with the analysis of certified reference material (CRM-115 BCR) and the results were in accordance with certified values. The range of LODs were between 2 and 19 µg/ kg and LOQs ranged from 5 to 37 µg/ kg corresponding to the MRLs and below. Jingyan *et al.* [27] described a method using pressurized microwave-assisted extraction (PMAE) without clean-up step for the determination of triazine herbicides in infant nutrient cereal-based foods coupled with HPLC-ESI/MS. After improving the key factors of PMAE like extracting solvent, extraction temperature and extraction time, the method was validated with atmospheric pressure microwave assisted extraction (AMAE), ultrasonic extraction (UE) and soxhlet extraction (SE). The recoveries obtained (66.2-88.6%) from the proposed method were better with more efficiency, faster and without clean-up procedure. Among the different solvents used, such as MeOH, MeCN, acetone, acetone-n-hexane (1:1, v/v) and MeOH-DCM (1:1, v/v), the required microwave radiation time to reach a temperature of 85°C was less by using MeOH (241s). The ability and specific heat of solvent for absorbing microwave energy seemed to affect the temperature.

Edwar *et al.* [38, 76] worked on the determination of selected organochlorine pesticides in agricultural soil by MAE. In the first study, they used water-MeOH as a modifier for desorption and simultaneous partitioning with n-hexane (MAEP) and GC-FPD. In second study, they employed MAE coupled to SPE and GC-ECD for the determination of some pesticides in olive oil. In this study MeCN-DCM was used as the solvent for LLE, while ENVI-Carb and DCM were used as SPE cartridge and elution solvent respectively. Confirmation was performed by GC-MS/MS. In the first study, olive oil was used as matrix mimic in order to optimize GC-FPD signals and improve the extraction method. By adding KHPO₄ to the mixture of water-MeOH, the recoveries were increased (up to 73%) compared to using the mixture of water-MeOH

Table 1 Review of SFE, PLE, USE and MAE applications for the determination of pesticides in food and environmental samples

Sample	Analyte	Extraction technique	Extraction solvent	Clean-up	Analytical method	Recovery(%)	RSD(%)	Ref
Wild rice (Gazpacho)	17 Organohalogen and organophosphate	SFE	CO ₂ (50°C, 200 atm, MeOH)	no	GC-ECD/FPD/MSD	70-121	n.r*	[5]
Honey	33 Pesticides (OPPs, OCHs, Pyrethroids)	SFE	CO ₂ (60°C, 200 atm, Acetone)	Florisil	GC-EI-Q-MS	n.r	n.r	[16]
Rice	22 GC-amenable pesticides	SFE	CO ₂ (50°C, 200 atm, MeOH) CO ₂	Aminopropyl	GC-EI-IT-MS (SIM)	n.r	n.r	[68]
Aquaculture Samples	15 Organohalogen	SFE	(60°C, 210 bar, n-hexane)	Acidic silica and Aluminium basic	GC-ECD, GC-MS/MS	76-128	< 10	[69]
Green leafy vegetables	6 Insecticides, a fungicide, a herbicide	PLE	EtAc	Grafitized Carbon (GCB)	GC-MS/MS (SIM)	71-103	5.6-24	[13]
Oranges	Carbosulfan and its metabolites	PLE	DCM	no	LC-MS (MRM)	55-90	18-19	[2]
Small tissue	PCBs and their metabolites	PLE	Hexane-DCM-MeOH (48:43:9, V/V)	Florisil	GC-ECD	46-112	4-24	[66]
Frutes	10 pesticides	PLE	EtAc	MSPD (Acidic Alumina)	LC-APCI-MS (MRM)	58-97	5-19	[12]
Fine airborne particulate matter	Currently used pesticides (CUPs)	PLE	Acetone	no	LC-ESI-MS/MS	86-106	n.r	[17]
State farm soils	13 OCPs	SPLE	n-heptane-acetone (1:1 v/v)	no	GC-ECD, GC-MS	n.r	n.r	[45]
Baby food	18 Pesticides (OPPs, Pyrethroids, triazines)	USE	MeCN	SPE (NH ₂)	LC-EI/MS (SIM)	n.r	< 20	[18]
Minke whale blubber	PCBs	MAE	n-hexane	(SPD**)	GC-ECD	66-107	< 15	[30]
Strawberries	Bifenthrin, acrinathrin, Λ -cyhalothrin, deltamethrin	MAE	MeCN-Water	SPME (PDMS 100 ml)	LC-EI/MS (SIM)	n.r	1.2-14.2	[74]
Soil	Quaternary ammonium herbicides	MAE	HNO ₃ 65%, HCl 35%, HF 48%	SPE/silica cartridge	LC-MS/MS	102-109	n.r	[75]
Wheat, rice, corn, bean	OCPs	DMAE	MeCN 95%	On-line SPE	On-line-HPLC	86-105	1.2-8.7	[23]
Infant nutriel cereal - based food	Triazin herbicides	PMAE	MeOH, (10 min, 105°C)	no	HPLC-ESI/MS	66.2-88.6	≤ 12.62	[27]
Agricultural soil	6 OPPs	MAE	Water-MeOH (15:75, v/v), n-hexane	no	GC-FPD	54-77	n.r	[38]
Sesame seeds	16 OCPs	MAE	Water-MeCN	florisil	GC-MS (SIM)	> 80	< 12	[3]
A single sediment	85 OCPs	MAE	DCM-MeOH (9:1)	SPE/Florisil	GC-IT/MS	72-118	< 20	[41]
Olive oil	9 OPPs	MAE	MeCN-DCM (90:1, v/v)	SPE/ENVI TM Carb	GC-MS/MS	> 73	≤ 11	[77]
Animal feed	21 OCPs	MAE	Hexane-Acetone (50:50)	SPE/ENVI TM Carb/II/PSA	GC-ECD	100	< 10	[39]
Fish	Thiobencarb, deltamethrin, 19 OCPs	SE	MeCN-toluene (3:1)	Low temperature and SPE/ Aminopropyl(NH ₂)	GC-EI-MS (SIM)	81.3-113.7	≤ 13.5	[59]
Aquatic products	111 residues of pesticides	SE	Acetone-EtAc_n-hexane (1:1:1)	SPE(Envi-18 and PSA)	GC-EI-MS (SIM)	72-113	3.4-12.1	[4]
Aquatic products	111 residues of pesticides	USE	MeCN/water	SPE(Envi-18 and PSA)	GC-EI-MS (SIM)	51-127, 70-120	3.2-13.8	[4]
Leek	102 Multiresidue pesticides	SE	Acetone-DCM	GPC and SPE (GCB)	GC-MS (SIM)	70-113	< 13	[58]
Olive oil	8 Multiclass pesticides	SE	MeCN	SPE (ENVI-carb)	GC-NPD	72-105	< 11	[20]
Vegetables and fruits	17 Multiclass pesticides	SE	MeOH	SBSE(PDMS)	GC-EI-MS(SIM)	43-100	< 10	[9]
Vegetables	Benzoylphenylurea insecticides	SE	Dichloromethane	no	LC-ESI-MS	78.5-113.8	< 5.5	[99]

*, Not Reported; **, Fully automated Sample Preparation Device

alone where recoveries were 54-77%. However, in latter study, when MeCN was used alone as the solvent for partitioning of LLE the recoveries ranged 62-99% and adding DCM to the extracting solvent caused the increase of recoveries. Most MAE applications to date have been for the extraction of environmental samples. As for the MAE coupled with GC-MS or LC-MS, more investigations are needed in the next few years. Table 1 illustrates the operational characteristics of instrumental solvent extraction (SFE, PLE, USE and MAE extraction) methods for the determination of pesticide residues in different samples.

QuEChERS: QuEChERS is a quick and convenient replacement for LLE which offers a great quality results with less labor-intensive sample preparation steps and low consumption of solvent and glassware. QuEChERS stands for quick, easy, cheap, effective, rugged and safe and is the newest-generation method for the analysis of

pesticide residues in food matrices. These characteristics are evident in its name [77]. This method offers good features for the analysis of polar pesticides.

The main feature of this technique consists of extracting a homogenized sample by hand-shaking or vortex rotary with the same amount of acetonitrile to give a final extract adequately concentrated due to the lack of need for solvent evaporation. A mixture of 4 g anhydrous magnesium sulfate (MgSO₄) and 2 g sodium chloride (NaCl), which provides well-defined phase separation without dilution and dangerous non-polar organic solvent, are added to the sample by mixing so as to facilitate partitioning of the analytes between the aqueous residue and the solvent. After shaking and centrifugation, clean up and elimination of residual water is carried out simultaneously using a rapid technique, called dispersive solid phase extraction (DSPE), in which a primary-secondary amine (PSA) adsorbent (a weak anion-exchanger which removes fatty acids, sugars and other

matrix co-extractives that form hydrogen bonds) and extra anhydrous MgSO_4 are blended with the sample extract. DSPE is based on SPE method, but the adsorbent is added directly to the extract and the clean-up is simply carried out by shaking and centrifugation. This method takes shorter time than the traditional SPE and simultaneously enables the removal residual water and a lot of polar matrix components, such as organic acids, polar pigments and sugar. MeCN is the selected solvent to successfully extract all kinds of pesticides from various food matrices by using QuEChERS [47-57]. The use of two mixed adsorbents like C_{18} and PSA has been evaluated by Leandro and co-workers [78] in the extraction of OPPs and transformation products from baby food using QuEChERS and DSPE clean up step. The recoveries obtained were close to 100%, when 50 mg of PSA was used. Observed results were undesirable when mixed adsorbents (50 mg PSA+100 mg C_{18}) or only C_{18} were used, depending on the matrix and the class of the pesticide analyzed. So PSA was chosen as adsorbent in the analyses of these class of pesticides by HPLC-MS/MS and UPLC-MS/MS because it achieved a clean extract and peak shape with improved signal-to-noise ratio (S/N) in comparison with crude extracts. In their earlier study this research group [53] investigated the effects of different amounts of C_{18} (100-300 mg) with a constant 50 mg of PSA to the quantity of co-extractives remained after evaporation of solvent. The lack of reproducibility among the diverse range of matrices was observed when 100 mg C_{18} was used. On the other hand, non-linear calibration plots and low recoveries resulted with 300 mg C_{18} . However, cleaner extracts, improved S/N and satisfactory calibration plots

were obtained when C_{18} in the range of 100-200 mg was used as adsorbent. Recently Milagros and co workers [48] described two methods based on GC-MS (SIM) and GC-IT-MS/MS (SRM) for identification, confirmation and quantification of two insecticides in pepper samples by using QuEChERS technique. MeCN can be used as extracting solvent and clean up step was performed by dispersive solid-phase extraction using PSA as sorbent material. Average recoveries were in the range of 85-98%. In brief, no significant differences on the performance of both methods were noticed in terms of sensitivity and limit of detection, although the unambiguous confirmation capabilities provided by MS/MS cannot be achieved with a single quadrupole analyzer. The potential of the proposed methods was demonstrated by analyzing real samples with excellent selectivity and sensitivity, thus enabling the unambiguous identification of trace levels of these insecticides in pepper samples. The advantages of QuEChERS method are high recovery, high sample yield, accurate results, low solvent and glassware consumption, lower labor and bench space, less reagent costs and ruggedness. The main drawback of this method is that for 1 g sample per milliliter of final extract the concentration of obtained extracts using this method is lower than concentrated extracts achieved by the use of most conventional procedures. Hence, the final extract must be concentrated more extensively in order to provide high sensitivity and to obtain the limits of quantification (LOQ) desired. Table 2 reviews the applications of this method for the determination of pesticide residues in variety of food samples.

Table 2: Review of QuEChERS applications in the analyses of pesticides in food samples

Sample	Analyte	Extraction Solvent/ clean-up	Analytical method	Recovery%	RSD%	Ref
Grape, lemon, onion, tomatoes	105 Pesticides	MeCN/ PSA	GC-SQ-MS	70-110 and > 110	< 20	[1]
Grape, lemon, onion, Tomatoes	46 Pesticides	MeCN/ PSA	LC-IT-MS	70-110	< 20	[1]
Bananas harvested	11 pesticides	MeCN/ PSA	GC-NPD	67-118	< 16	[47]
Pepper	Isocarbophos and isofenphos-methyl	MeCN/ PSA	GC-MS/MS	85-98	< 8	[48]
Vegetables and fruits	160 Multi-class pesticides	MeCN/ PSA	LC-ESI-MS/MS	70-120	n.r*	[49]
Cabbage and radish	107 pesticides	MeCN (HAc 0.5%)/ PSA	GC-MS (SIM)	80-115	< 15	[50]
Olive oil	Multi-class pesticides	MeCN/ PSA, C_{18} , GCB**	LC-QIT-MS/MS (MRM)	n.r	< 15	[143]
Milk, eggs, avocado	32 Multi-class pesticides	MeCN/ PSA	GC-QEI-MS (SIM)	> 95	< 10	[51]
Milk, eggs, avocado	32 Multi-class pesticides	MeCN/ PSA	GC-QEI-MS (SIM)	> 27	n.r	[52]
Baby food	12 priority pesticides	MeCN/ PSA, C_{18}	GC-QEI-MS/MS (MRM)	60-113	< 28	[53]
Barley samples	43 Herbicides	MeCN/ PSA	GC-ESI-MS	62-78	1.1-9.3	[54]
Barley samples	43 Herbicides	MeCN/ PSA	LC-TQ-ESI-MS/MS (SRM)	37.4-135	1.0-19.5	[54]
Fruits and vegetables	15 Multi-class pesticide	MeCN/ PSA	LC-TOF-MS (SCAN)	n.r	0.8-11	[55]
Baby food	16 OPPs	MeCN/ PSA	LC-ESI-MS/MS	85-113	2-10	[78]
Baby food	16 OPPs	MeCN/ PSA+ C_{18}	LC-ESI-MS (MRM)	92-119	1-17	[78]
Egg, cucumber	OCs, OPPs, pyrethroids	MeCN, 1% HAc*** / PSA	GC-EI-IT-MS/MS	n.r	2-16	[56]
Egg, cucumber	OCs, OPPs, pyrethroids	MeCN, 1% HAc / PSA	GC-EI-TOF-MS/MS	n.r	1-14	[15]
Grapes	82 Multiclass pesticides	EtAc/ PSA	LC-ESI-MS/MS (MRM)	70-120	< 20	[57]

*, Not Reported

, Graphitized Carbon Black *; Acetic acid

Matrix Solid-phase Dispersion (MSPD): In order to analyze semi-solid and solid food matrices and overcome the serious restrictions of SE and SPE methods and achieve high efficiency especially in environmental analysis, in 1989 Barker and co-workers [79] described a procedure for the extraction of target analytes in solid matrices by MSPD. This technique enables disruption and dispersion of analytes simultaneously onto a solid support, thereby isolating the extracts from the matrices. Reversed phase sorbent materials such as octyl-bonded silica (C_8) and octadecyl-bonded silica (C_{18}) are the most commonly used adsorbents, because of the lipophilic characteristics of them that cause a good disruption and dispersion. In this method, the adsorbent is mixed with the sample using mortar and pestle or a related mechanical device. MSPD allows the extraction of pesticides from homogenously dispersed target samples onto a solid support, such as Florisil and silica. The homogenized mixture is then placed in a column and the analytes are selectively eluted with solvents. Thus, sample extraction and clean-up are performed in a single step. This approach can be used for screening pesticides or other chemicals in different biological matrices and could be useful in the environmental bio-monitoring programs. The application of organic solvents is minimized but not completely eliminated. Organic solvent is not used for the extraction of target analytes from matrices and this fact causes the necessity of the clean-up step. Juan *et al.* [44] reported the use of MSPD after preliminary LLE with MeCN saturated with petroleum ether for the analysis of herbicides in olive oil by LC/TOF-MS. The obtained extracts from LLE step was homogenized with aminopropyl-bonded silica as dispersant sorbent by means of a glass mortar and pestle. The mixture was then transferred into the minicolumn containing packed Florisil, that was connected to a vacuum system for clean-up procedure. After eluting with MeCN, the extracts were evaporated and dissolved in MeCN-water (1:1, v/v) prior to LC/TOF-MS. The recoveries obtained were in the range of 81-111%. Numerous adsorbents with different selectivity are available that may be selected based on the analytes of interest, type of matrix and interferences. The use of MSPD in food analysis has been reported using sorbents such as silica [80], Florisil [81-83] and C18 or C8 bonded silica [37, 84]. Inert adsorbents, for example diatomaceous earth [85, 86] and sand [87, 88], instead of reversed or normal-phase dispersant have been successfully used in the analyses of pesticides in fruit juices, fatty foods and tissues, because they enable early

elution of interferences that would not be retained by any adsorbent during elution of the target analytes. The combination of sand as dispersant with water as eluting solvent for polar analytes in any type of matrix enables almost quantitative recoveries. Recently, it has been proved that replacement of C18 by aminopropyl silica or primary and secondary amine (PSA) sorbents leads to cleaner extracts from complex fatty samples, e.g. olives [43, 44, 89-91]. It seems that the weak anion-exchange character of amino materials is responsible for this better selectivity, due to more effective retention of the fatty acids present in biological samples. Reversed-phase octadecyl silica (RP- C_{18}) [92, 93] is another commonly used dispersant because of its high reactivity that leads to the modification of its surface by chemical reaction. Another important parameter in MSPD procedure is the selection of extraction solvents that depends on the analyte polarity. Apolar solvents such as hexane, DCM, or mixture of both can be used in extraction of non-polar compounds, whereas medium or high polar substances can be recovered using polar solvents such as acetone, MeCN, EtAc, water-ethanol or methanol. Maria *et al.* [37] determined pesticides in coconut based on MSPD under optimized conditions such as type and amount of solid-phase (C_{18} , alumina, silica-gel and florisil), selection of eluent (DCM, MeCN, EtAc, acetone, n-hexane and n-hexane-water (1:1 v/v)) by GC-MS (SIM). The best result was obtained when C_{18} , Florisil and acetonitrile saturated with n-hexane were used as dispersant sorbent, clean-up sorbent and eluting solvent respectively. Average recoveries were between 70.1 and 98.7% with RSD from 2.7 to 14.7% except for two pesticides. Marina *et al.* [85] developed a rapid and sensitive LC-MS/MS method for the analysis of selected pesticides in fruit juices based on MSPD extraction process by using diatomaceous earth as dispersant and DCM as eluent. In order to avoid the use of chlorinated solvents like DCM, other extraction solvents such as EtAc and MeOH were tested for all selected pesticides. The results of recoveries were undesirable when EtAc was used. However, the use of MeOH as the extracting solvent required an additional clean-up step, so DCM was used as extracting solvent. The effects of pH were studied over the range of pH 2-8 and the highest recoveries were obtained at pH 6. The recoveries obtained were between 71 and 118% with RSD in the range of 5-15%. One paper [31], devoted an effective MSPD method for determination of cypermethrin and deltamethrin in porcine tissues with a neutral alumina-based MSPD column and HPLC-UV using reversed-phase

C₁₈ column. In order to obtain high elution efficiency, dissimilar solvents polarities (n-hexane, n-hexane-EtAc (1:1), n-hexane-DCM (1:1), EtAc and n-hexane-acetone) were tested. When EtAc, acetone and DCM were used as the extracting solvent, a greater number of interferences were extracted into the eluate. Whereas n-hexane is a nonpolar solvent, a mixture of it with other solvents has intermediate polarity and so n-hexane was used as eluent solvent. The ratio of mobile phase was optimized and acetonitrile-water (85:15 v/v) was selected. The recoveries were between 83.5 and 109%. When the traditional method is compared with the MSPD-SSEC method, the MSPD-SSEC method reduces sample contamination during the procedure and decreases the amount of organic solvent used. Fernanda *et al.* [80] compared and evaluated a variety of dispersant materials such as C₁₈, alumina, silica and Florisil with regards to the amount of solid-phase and eluent such as n-hexane, DCM, n-hexane-DCM (8:2 and 1:1 v/v), DCM-EtAc (9:1, 8:2 and 7:3 v/v) in analysis of different pesticide residues by GC-MS.

The results were excellent when 1.0 g silica and 1.0 g Florisil and DCM-EtAc (9:1 v/v) were used as dispersant, clean-up sorbent and elution solvent respectively. The main factors in the selection of elution solvent are, its capability to selectively and quantitatively recover target analytes and its compatibility with the subsequent determination technique, harmlessness, low cost, low consumption solvent and environmental friendliness are also desirable attributes. Hot water has been used for extracting polar to moderately polar contaminants from solid matrices because of the drop of its polarity with increase the temperature [94]. Extraction with high temperature water is carried out at atmospheric or elevated pressures. Low toxic solvent consumption, reducing cost and analysis time, simplifying and speeding up the sample treatment procedure, increasing reliability and in most cases integrating of extraction and clean-up in a single step are the advantages of this technique. Table 3 shows the review of MSPD applications in analysis of pesticide residues in various samples.

Table 3: Review of MSPD applications in the analyses of pesticides in food and environmental samples

Sample	Analyte	Dispersant/Clean up	Eluting solvent	Analytical method	Recovery (%)	RSD (%)	Ref
Plant matrices	Hexachlorocyclohexane isomers	Florisil/Neutral alumina	n-Hexane-EtAc (70:30, v/v)	GC-ECD	91-98	5.40-9.85	[82]
Sewage sludge	16 OCs	Deactivated alumina and activated copper powder/ Teflon frit	Dichloromethane (DCM)	GC-MS (SIM)	84.5-104.1	1.1-7.7	[28]
Fruit juices	Selected pesticides	Diatomaceous earth/Teflon frit	DCM	GC-MS/MS	71-118	5-15	[86]
Porcine tissues (liver, muscle, heart, kidney)	Cypermethrin, deltamethrin	Neutral alumina/ Diatomaceous earth	n-Hexane	HPLC-UV	87.8-105.3	< 7	[31]
Bovine samples	Five OPPs	Octadecylsilyl (C18)/ silica gel	MeCN	HPLC-DAD-UV	> 94%	15	[19]
Coconut	8 Pesticides	C18/ Florisil	MeCN saturated with n-hexane	GC-MS (SIM)	70.1-98.7	2.7-14.7	[37]
Wine	Fungicides and their metabolites	Florisil	EtAc-hexane (70:30, v/v)	GC-ECD	82.4-93.7	< 8	[82]
Propolis	4 pesticide residues	Silica/ Florisil	DCM-EtAc (9:1, v/v)	GC-MS (SIM)	67-175	5.6-12.1	[80]
Animal fats	DDT	Activated carbon fiber (KF)	Acetic acid, ethanol, Heptanes (10:20:80, v/v)	HPLC-PDA	58-93	< 7	[147]
Fruits and vegetables	Fungicides	C18-bonded silica/ glass filter paper underlay C18/Teflon frit	EtAc	LC-QIT-MS	71-102	< 13	[84]
Meat	Sulphonamide	C ₁₈ /Teflon frit/Aminopropyl/ Florisil	MeOH	LC-API-MS/MS	87-101	n.r*	[25]
Olive and olive oil	Triazines, OPPs, Ocs, prethroids	Aminopropyl/ Florisil	MeCN saturated with Petroleum ether	GC-Q-MS (SIM) LC-ESI-MS/MS	73-130	n.r	[43]
Olive oil	4 s-Triazines	Aminopropyl/ Florisil	MeCN saturated with Petroleum ether	LC-ESI-TOF-MS	81-111	< 4	[44]
Vegetables and fruits	8 Carbamate insecticides	Sand/ no	Water (50°C)	LC-ESI-MS (SIM)	88-110	< 9	[87]
Baby food	20 Multiclass pesticides	Florisil	EtAc	GC-EI-MS (SIM)	70-110	n.r	[83]
Apple juices	266 Multiclass pesticides	Diatomaceous earth	Hexane-DCM	GC-EI-MS (SIM)	64-117	2-23	[86]
Animal fats	Aldrin, dieldrin, DDTs	Acidic alumina oxide/filter disc	Heptane	HPLC-PDA	84-98	n.r	[107]
Tomato juices	Endosulfane isomers, endosulfan sulfate	Florisil	EtAc	GC-EI-MS (SIM)	81-101	< 6	[146]

*;Not Reported

Sorptive Extraction Methods

Solid-phase Extraction (SPE): Solid phase extraction is the extensively accepted alternative extraction-clean up method including a preliminary LLP step, although it can be used without this step, which involves the use of disposable cartridges to trap analyte and separate them from the bulk of the matrix. The adsorbent materials in SPE procedure play a significant role in achieving greater enrichment efficiency and lower cost of organic solvents. Many types of adsorbents such as Florisil [95], alumina, magnesium silicate, graphitized carbon and oasis HLB [96, 97], adsorbents with weak anion-exchange and polar capabilities (NH_2) [42], polystyrene-divinylbenzene supports [98] and C_{18} [15, 92, 99], SWCNTs and MWCNTs [100, 6, 14, 21, 29], mixed mode phases, bamboo charcoal [22], have been shown to be valuable adsorbents for sample enrichment and clean-up of a variety of pesticides in food matrices and environmental samples. The most commonly used material, however, is the reversed-phase octadecyl silica (RP-C18) [92, 93, 45, 101] because it is sufficiently reactive to enable its surface to be modified by chemical reaction and yet sufficiently stable to enable its use with a wide range of solutions. The introduction of the disposable pre-packed SPE cartridges had major effects on methods for the examination of the analysis in solution. The SPE cartridge introduced two critical factors namely, standardization and hence greater reproducibility and a much wider range of phases. More importantly the use of reversed-phase and ion-exchange materials enables aqueous solutions to be treated and additional trapping mechanisms to be utilized. A wide range of phases means that polarity, hydrophobicity or ionization can be used as trapping mechanisms and the sample matrix may now be non-polar or aqueous. Once trapped, the analyte can be released into a small volume of an extraction solvent by altering the polarity or pH. Although the cartridges are single use and disposable and thus present a significant consumable cost, this has been claimed to be much lower than the cost of chemicals and manpower needed for the corresponding traditional solvent extraction methods. The disposable cartridges reduced the handling of body fluids, such as urine and blood and hence the biohazard to the operator is minimized. SPE method has been widely applied for the determination of contaminants in environmental samples such as, river waters and sewage outflow, where large volumes of very dilute solutions have to be extracted [21, 22, 98, 100]. With conventional solvent extraction, large volumes of sample solution had to be manipulated to obtain sufficient analytes for assay. With SPE

cartridges, the sample is simply pumped through the SPE bed and the analytes are eluted with a small volume of organic solvent. Eluent selection is based on high performance, low consuming volume and low toxicity, non-interferences with compounds and compatibility with the chromatographic system used. Method development in SPE is usually accomplished by optimizing pH, type and solvent strength of the sample matrix, polarity and flow rate of the eluting solvent and physicochemical characteristics of the adsorbent bed. For example, sample pH can be crucial to obtaining high pesticide retention on the adsorbent. Occasionally, therefore, sample pH modification can be necessary to stabilize the pesticides and increase their absorption by the solid phase [102]. Recent use of high flow-rates through extraction cartridges has been claimed to give improved extraction [103]. Hongyun *et al.* [100] used single-walled carbon nanotubes disk as sorbent material and MeCN as eluent in SPE method for the extraction of sulfonylurea herbicides in water samples by HPLC-DAD. They demonstrated that when the selected analytes (sulfonylurea herbicides) are weak acids the solubility of them in water is increased drastically with increasing solution pH, indicating the high polarity of the analytes. Since adsorption of analytes on the adsorbent material (SWCNTs) is based on hydrophobic interaction, the sample pH is a significant factor in the enrichment of the analytes. As a result of the high adsorption of the all analytes in acidic solution, maximum recovery was obtained at pH 3.0 and it dropped clearly with the increase of pH. Flow rate was another factor to increase the enrichment efficiency of analytes and control the extraction time that was adjusted by the manifold vacuum pressure to 150 ml min^{-1} with SWCNTs as adsorbent. However, when double or triple layered disk was used, flow rate was decreased to around 50 mL min^{-1} similar to C_{18} and activated carbon. Zhou and co-workers [21] used multiwalled carbon nanotubes for pre-concentration of simazine and atrazine prior to HPLC-DAD. Under the optimal SPE procedure, the recoveries of the two analytes were in the range of 86.2-103.7%. However, Ru-Song *et al.* [22] used bamboo charcoal as SPE adsorbent in the determination of atrazine and simazine in environmental water samples by HPLC-MS. Following optimization of enrichment conditions, among three different polarity solvents (MeOH, MeCN, acetone), MeCN had a high elution performance. To obtain proper sample solution pH for increasing the extraction efficiency of the analytes, different pH ranging from 3 to 11 was studied and the recoveries at pH 5-9 were found to be appropriate.

In optimizing the flow rate of working solution for enhancement efficiency, flow rate $1.0\text{--}2.5\text{ mL min}^{-1}$ was investigated and the flow rate of 2.5 mL min^{-1} was selected. Effect of sample volume on the recoveries was investigated in the range of 100–1000 mL. Quantitative recoveries were obtained for sample volume up to 500 mL. The recoveries for simazine and atrazine slightly reduced when a volume of more than 500 mL was used, so in subsequent experiments a volume of 500 mL was selected. In this study, the recoveries ranged between 75.2% and 107.1% with RSD 8.3–8.7%. The results of different studies have revealed that the most broadly used eluents for desorption of pesticides and their degradation products from adsorbent materials are EtAc [14, 92], MeOH [95], DCM [29], MeCN [97, 100, 104], acetone [6], or mixtures of these [96, 99, 105, 106]. Most of the examples cited are multiresidue, including several groups of pesticides and so mixtures of solvents are usually used to ensure high recoveries for all the target compounds. Different mixtures have been used, including EtAc-n-hexane [26, 45], EtAc-MeOH-H₂O [40], acetone-hexane [108] and EtAc-acetone [26]. MeOH was also used as SPE eluent by Wang *et al.* [109], who developed and validated a method for the identification and quantification of trace levels of thirteen pesticides in apple-based infant food by LC-ESI-MS-MS. SPE has been successfully applied for the extraction of pesticide residues in food samples. However, the selection of proper adsorbent and eluting solvent to match the physicochemical characteristics of multiresidue analysis that is, small extracted sample volume by SPE adsorbents, high blank values are the problems that must be researched and removed. Table 4 reviews some SPE applications for the determination of pesticides residues in food matrices and environmental samples.

Solid-phase Microextraction (SPME): In solid-phase extraction, it is still necessary to extract the sample from the column, usually using of an organic solvent, prior to separation. This last step and the requirement of an organic solvent were eliminated in the ingenious SPME method, which was invented by Pawliszyn and co-workers [110, 111]. They used a fiber coated with a stationary phase as the extraction medium. After carrying out an extraction from a sample solution, the fiber could be placed in the injection port of a gas chromatograph so the analytes were thermally desorbed directly into the carrier gas stream. A number of different fiber coatings are available, which offer a range of analyte solubilities and porosities, including the non-polar polydimethylsiloxane (PDMS), semi-polar PDMS-divinylbenzene (PDMS-DVB)

and polar polyacrylate (PA) and Carbowax-divinylbenzene and the coated porous particle phase PDMS-Carboxen. Among these, PDMS fiber has been widely used in head-space (HS) extraction methods because it is the highest capacity fiber for polar compounds and enables successfully the collection of the different compounds from the sample. Recently SPME has been interfaced with HPLC and LC-MS for the analysis of compounds that are nonvolatile and thermally unstable. In this system, a SPME-HPLC interface equipped with a specific desorption chamber is used before LC separation instead of thermal desorption in the injection port of the GC. Two types of SPME techniques can be used to extract the analytes: head-space (HS-SPME) and direct immersion (DI-SPME). In (HS)-SPME, the fiber is exposed in the vapour phase above a gaseous, liquid or solid sample. In (DI)-SPME, the fiber is directly immersed in clean liquid samples. Agitation of the sample is often performed with a small stirring bar to increase the rate of equilibration. In SPME, the amount of analytes extracted depends on the partition coefficient between the sample solution and the fiber. The main advantages of this method are that no solvent is required to elute the sample from the fiber and there is a direct transfer of analytes from the sample solution to the separation method. The fiber can be reused numerous times as the thermal elution step also cleans the fiber. The disadvantages are that the fiber is fragile even though it is shielded when it is placed in the sample but it can be damaged by a build-up of involatile materials from the samples. Jingbin *et al.* [112] used polymethylphenylsiloxane-coated fiber for SPME-GC-ECD for the determination of OCs and pyrethroid pesticides (non-polar pesticides) in vegetables with recoveries of 42.9 to 105.3%. In this study, extraction efficiency of the synthesized hydroxyl-terminated polymethylphenylsiloxane (PMPS-OH) coated fiber (70 μm) was compared with commercial fibers such as PDMS (100 μm), PA (85 μm) and PDMS/DVB (65 μm). Since the mentioned pesticides are non-polar has low solubility in water, they contain one or more phenyl groups and so PMPS is one of the most common non-polar silicon oils with a chain structure. In comparison with PDMS, PMPS furnishes better thermal stability and its polarized phenyl has stronger π - π interaction with the phenyl group in aromatic compounds. The results showed that, the extraction efficiency of the PMPS coated fiber for selected pesticides with HS-SPME was higher than commercial fibers and DI-SPME mode. Among the three commercial SPME fibers tested, PDMS (100 μm) resulted in the highest overall extraction efficiency and PA (85 μm)

Table 4: Examples of SPE application for determination of pesticide residues in food and environmental samples

Sample	Analyte	Conditioning solvent	Adsorbent	Eluting solvent/ Flow rate	Analytical method	Recovery (%)	RSD (%)	Ref
Environmental water	6 Pyrethroid Pesticides And their metabolites	Acetone-water	MWCNTs**	5mL Acetone/ Eluted by gravity	HPLC-UV	70.9-117.8	1.3-5.0	[6]
Apple, orange, grape and pineapple fruit juices	8 OPPs	MeCN-water	MWCNTs	20mL DCM/ Eluted by gravity	GC-NPD	> 73	< 8.5	[29]
Water & soil samples	Atrazine and its metabolites (DIA,DAE**))	MeOH-water	MWCNTs	4mL EtAc/ 1mLmin ⁻¹	GC-EI-MS (SIM)	72.27-109.68	< 13	[14]
Soil and soil-vinasse	Durone, hexazinone, tebutiuron	MeOH	RP-C ₁₈	20mL MeOH,20mL Acetone/2mLmin ⁻¹	HPLC-UV	78-120	< 10	[101]
Royal jelly	9 multiclass pesticides	EtAc-n-hexane (1:1), MeCN, H ₂ O	RP-C ₁₈	2 mL EtAc-n-hexane/ Eluted by gravity	GC-μ-ECD	70-110	< 13	[45]
Honey	Coumaphos, carbendazim, Amitraz	MeCN-water HCl 0.1 mol L ⁻¹	Oasis HLB (waters)	3mL MeCN-MeOH-DCM (50:25:25, V/V)/ Eluted by gravity	LC-TQ-MS/MS (MRM)	n.r*	n.r	[96]
Water	Sulfonylurea herbicides	MeOH-water	SWCNTs	MeCN (0.1% acetic acid) /1mLmin ⁻¹	HPLC-PDA****	79-102	n.r	[100]
Water	Sulfonylurea herbicides and Three degradation products	MeOH-water, Hcl 10 ⁻⁴ mol L ⁻¹	Polystyrene-Divinylbenzene	5mL Water, 10mL HCl 10 ⁻⁴ mol L ⁻¹ /5mLmin ⁻¹	LC-ESI-MS/MS	n.r	< 4	[98]
Environmental water	Atrazine and simazine	MeCN-water	ENVITM-Carb	4mL MeCN/ 7mLmin ⁻¹	HPLC-DAD	82.6-103.7	n.r	[21]
Water	Multiclass pesticides	MeCN-DCM(1:1),	MWCNTs	DCM-MeCN (1:1,v/v)/ 10mLmin ⁻¹	UPLC-ESI-MS/MS	82-109	2.6-13.5	[97]
Tomatoes	5 triazine herbicides and a fungicide	DCM	Oasis HLB	3mL DCM-MeOH (99:1)/Eluted by gravity	RP-HPLC-UV	60-130	n.r	[42]
Environmental water	Atrazine and simazine	MeCN-water	Laboratory-made NH ₂ (aminopropyl)	10mL MeCN/ 2.5mLmin ⁻¹	HPLC-UV	75.2-107.1	8.3, 8.7	[22]
Water and soil	32 Multiclass pesticides	DCM-MeOH	Bamboo charcoal	5mL MeOH,DCM (1:1, v/v)/8mLmin ⁻¹	LC-ESI/MS	60-110	n.r	[104]
Bovine milk	30 herbicides and Fungicides	Water-MeOH (50:50),	Octadecylsiloxane (ODS)	1.5mL MeOH,6mL DCM-MeOH/5mLmin ⁻¹	LC-ESI-MS/MS (MRM)	78-104	< 13	[105]
Drinking water	Nicotinoid insecticides	MeOH, water	Carbograph 4TM	DI-water,3mL EtAc/MeOH (50:50)/ 10mLmin ⁻¹	LC-ESI-MS (SIM)	95-104	< 20	[106]
Surface water	12 Multi-residue pesticides	MeOH, water	LiChrolut EN	5mL Acetone-n-hexane (1:1)/3mLmin ⁻¹	GC-EI-MS (SIM)	82-103.7	3.1-15.1	[40]
Commercial juices	50 Multi-class pesticides	MeCN-water	MWCNTs	5mL Hexane-EtAc (1:1, v/v)/Eluted by gravity	GC-EI-MS (SIM)	> 91	< 9	[108]
Wine	8 Azolic fungicides	MeOH, water	Teflon frit, C ₁₈	3mL MeOH/ Eluted by gravity	LC-APCI-MS (SIM)	83-109	< 10	[26]
Citrus essential oils	12 Pesticides	Pentane	Polymeric cartridge	5mL Pentane,DCM/ 1mLmin ⁻¹	GC-ESI-MS	65-95	< 7	[95]
Citrus essential oils	12 Pesticides	Pentane	Florisil- C ₁₈	5mL Pentane,DCM/ 1mLmin ⁻¹	LC-ESI-MS	50-94	< 2	[95]
Surface water	101 Multi-class pesticides	MeOH, water	Florisil- C ₁₈	3mL EtAc/ 10mLmin ⁻¹	LC-ESI-TOF-MS	n.r	3.5-9	[15]
Honey	22 OPPs	MeOH	C ₁₈	5mL EtAc, MeOH, DCM Eluted by gravity	LC-APCI-MS (SIM)	16-102	< 17	[92]
River water	Benzoylphenylurea insecticides	MeCN, CH ₂ Cl ₂ ,	C ₁₈	5mL MeCN,CH ₂ Cl ₂ / 10mLmin ⁻¹	LC-ESI-MS	73-110	< 10	[99]
Bovine milk	Nicotinoid insecticides	MeCN water (1:1,v/v) DCM	C ₁₈	2mL MeOH,5mL DCM-MeOH/3mLmin ⁻¹	HPLC-DAD	85.1-99.7	10	[19]

*,Not Reported, **,Multiwalled Carbo Nanotube, ***,Deisopropyl-atrazine, Deethyl-atrazine, ****,Photodiode Array Detector

showed the lowest extraction efficiency, while the efficiency of the PMPS-coated fiber was much better than of PDMS (100 μm). HS-SPME is often used as a routine technique for the extraction of pesticides from liquid and solid samples. OPs and OCs are the most widely investigated compounds by this method because of their thermal stability and volatility. The extraction process of SPME method can be relatively slow because it relies

on the sufficient stirring or diffusion to bring the analytes in to the location of the fiber. In addition, good reproducibility requires that equilibrium is established. A kind of SPME extraction is the single-drop microextraction (SDME) that is a solvent-minimized sample pretreatment procedure and also has been used to analyze carbamates and organophosphorus pesticides in water samples [113-114]. However, the disadvantages of

SDME are as follows: fast stirring often break up the organic solvent drop, easy formation of air bubble [115] and the extraction procedure is time-consuming where in most cases equilibrium is not easily attained even after a long time [23]. In order to eliminate these restrictions, hollow fiber membrane-protected extraction LPME (HFM-LPME) [116-117] has been reported as an alternative. In this technique, the solvent is held and protected by a hollow fiber membrane (HFM). However, some drawbacks, such as memory effects caused by the on line configuration and poor reproducibility because of manual cutting or/and sealing of the membrane in the laboratory have been reported [118]. Lingyan *et al.* [119] applied dispersive liquid-liquid microextraction (DLLME) as sample pretreatment method coupled with HPLC-FID for the analysis of triazophos and carbaryl pesticides in water and fruit juice samples. The extraction was performed under optimized conditions including, extracting solvent; tetrachloroethane (15 μ L), dispersive solvent: MeCN (10 mL), without addition of salt and the extraction was less than 5 s. The enrichment factors obtained for carbaryl and triazophos were 87.3 and 275.6 respectively. In this technique a proper mixture of extraction and dispersive solvents was rapidly injected into an aqueous sample by a syringe, resulting in the formation of a cloudy solution. This technique (DLLME) has been employed in the analysis of trace organic contaminants and metal ions in liquid environmental samples [120]. Lidia and co-workers [121] used a combination of DI-SPME with sample stacking micellar electrokinetic chromatography (MEKC) for the analysis of 11 multiclass pesticide residues in red wine. SPME was performed by using PDMS/DVB fibers and the large sample volumes were injected into the capillary by reversed-electrode polarity stacking mode (REPSM). Apparent recovery values with REPSM-MEKC-DAD ranged between 90 and 107%. The application of SPME-MS has not been considerably established in pesticide analysis. This, along with GC-MS and LC-MS should be expected in the near future.

Stir-bar Sorptive Extraction (SBSE): The SPME fiber uses a relatively small amount of bonded stationary phase that often cause the extraction to be incomplete. Even with a favorable distribution coefficient, the phase ratio between the fiber and the sample solution is often unfavorable so that the partitioning can still leave a significant amount of the analyte in the sample phase. This problem prompted the development of the stir-bar extraction system, which uses a magnetic stirring bar or a fiber coated with a bonded adsorbent layer such as a

polymethyl diethyl siloxane. Alternatively, a magnetic stirring bar can be inserted into a short length of PDMS tubing. The surface area of the stirring bar is higher than a fiber and the volume of the adsorbent layer is much larger than in SPME and hence higher extractions yields because of the higher phase ratio. The stir-bar is simply rotated in the sample, removed and extracted thermally for GC analysis [24] or into a solvent for LC analysis [122]. The sample is typically stirred for 30-240 min and the extraction time is controlled and determined by means of sample volume, stir bar dimensions and stirring speed. In order to optimize the extraction time, the analyte recovery must be measured as a function of the extraction time. When the extraction time increases, no additional recovery is observed. However, in SPME technique, selected sampling times are often shorter than the time needed to reach full equilibrium. The non-equilibrium conditions are actually preferable in getting good sensitivity and repeatability since the extraction time is not too long. Application of sorptive extraction with PDMS for sample preparation furnishes considerable enrichment, no displacement effects, rapid thermal desorption at mild temperatures. This technique enables the absolute amount of an analyte in a sample to be determined. Bicchi *et al.* [123] studied the analysis of nine pesticide residues in heterogeneous matrices and determined the experimental recovery of these pesticides from pear pulp on the basis of their absolute amounts in the sample. In this study the amount of analyte present was evaluated in matrix and the extraction of diluted samples was performed by the stir bar technique. The main difficulty of this method is that it is hard to automate the rinsing and the extraction processes as well as the removal of the stirring-bar from the sample matrix. Liu *et al.* [124, 125] used sol-gel technology in order to achieve thin layers of PDMS on stirring rod. In another study Bicchi and co-workers [126] reported the use of a dual phase stir bar both in DI-SBSE mode and in HD-SBSE mode with PDMS coating and a carbon adsorbent material inside. This system caused the combination of both sorption and adsorption with high recovery of volatile compounds emitted from plant material. In liquid desorption technique the stir-bar is placed in a small vial and is desorbed by using non-polar solvent for GC analysis or with polar solvents for LC analysis. It should be noted that stir bar can be reused for 20-50 extractions. Leon *et al.* [127] described a multi-residue method for the analysis of PCBs and PAHs and pesticides combined with GC-MS based on ISO/EN 17025 method. In this study, thermal desorption procedure was carried out during 14 h by use of a 2 cm stir-bar coated with a 0.5 mm thick PDMS

Table 5: Examples of SPME and SBSE applications for the analysis of pesticides in foods and environmental samples

Sample	Analyte	Extraction Method	Adsorbent	Eluting solvent	Analytical method	Recovery (%)	RSD (%)	Ref
Radish	12 OCPs & their metabolites	HS-SPME	C[4]/OH-TSO**	-	GC-ECD	78-119	n.r*	[148]
Ground water	18 OCPs	SPME	DVB/CAR (50:30)	-	GC-ECD	80-120	< 8.5	[7]
Water	Organochlorine pesticides	HS-SPME	PDMS/DVB	Acetone-n-hexane	GC-EI-TOF-MS	n.r	< 20	[8]
Strawberries greenhouse	Pesticides	SPME	PDMS	-	GC-IT-MS/MS	98-124	n.r	[149]
Vegetables	OCPs, pyrethroid pesticides	SPME	PMPS-OH	-	GC-ECD	42.9-105.3	< 16.2	[112]
Black rice and ormosia	Triazines & OPPs	SPME	MAA/TRIM*** co-polymers	-	GC-FTD	79.5-102.2 & 79.8-98.7	5.1-9.0	[150]
Different fruit juices	54 pesticides	SPME	PDMS-DVB	-	GC-EI-MS/MS	71-108	< 16	[151]
Cucumber and potato	OPP	SPME	PDMS	-	GC-TSD	n.r	< 20	[133]
Water	8 Pyrethroid pesticides	SBSE	PDMS	MeCN	GC-MS(SIM)	67-100	< 11	[24]
Olive oil	9 OPPs	SBSE	PDMS	-	GC-FPD	80-106	< 10	[152]
Water	Pyrethroid pesticides	HS-SPME	PDMS	-	GC-FECD	n.r	< 16	[153]
Fruits	OPP	SPME	PA	-	GC-NPD	n.r	2.5-8	[154]
Biological samples	Four OPPs	SPME	PA	-	GC-NPD	n.r	< 9	[155]
Environmental water	Fenitrothion, its metabolit,	HS-SPME	PDMS-DVB	-	HPLC-DAD	n.r	< 12.5	[156]
Ground water	Phenylurea herbicides	SPME	PDMS-DVB	-	HPLC-PIF-FD	86-105	2-8	[157]
Fruit juices	Carbamate & phenylureas	SPME	PDMS-DVB	-	LC-ESI-MS (SIM)	25-82	1-17	[158]
Herbal and tea infusions	OCPs, OPPs, pyrethrin	SPME	PDMS	-	GC-NPD	73.5-108.3	n.r	[159]
Water	Chloroacetanilide herbicides	SPME	PDMS	-	GC-MS (SIM)	79-102	n.r	[160]
Water	46 Multi-class pesticides	SPME	PDMS/DVB	-	GC-MS (SIM)	n.r	< 20	[161]
Honey	6 OPPs	SPME	PDMS	-	LC-APCI-MS (SIM)	52-75	3-10	[12]
Honey	6 OPPs	SPME	PDMS	-	LC-APCI-MS (SIM)	75-115	5-9	[122]
Grapes	6 pesticides	SBSE	PDMS	-	LC-APCI-MS	15-100	10-19	[9]
Vegetables	Phenylurea herbicides	SPME	PA	-	GC-EI-MS	76-95	< 10	[132]
Wine & strawberries	4 Triazoles	SPME	PA	-	GC-EI-MS	n.r	7-28	[103]
Sediments	OCPs pesticides	LD-SBSE	PDMS	MeCN	GC-EI-MS (SIM)	73.9-106	0.4-5.7	[162]

*Not Reported, **SolGel Calix[4]arene/Hydroxy-Terminated Silicone Oil, ***Methacrylic Acid-Trimethylolpropanetrimethacrylate

film followed by GC-MS in scan mode. LODs were 0.1-1.0 ng L⁻¹ and the results obtained were very close to the results obtained by classical method. Stir-bar sorptive extraction, followed by liquid desorption and large-volume injection capillary gas chromatography (SBSE-LD-LVI-GC-MS) was developed by Serodio and co-workers [24] for the analysis of pyrethroid pesticides in water samples. The extraction was performed using of stirring bar coated with 47 µL PDMS under conditions of an equilibrium time of 60 min, 5% MeOH as organic modifier and MeCN as back-extraction solvent. Good accuracy (81.8-105%) and remarkable reproducibility (<11.7%) with excellent recovery were obtained. SBSE is more sensitive and accurate than SPME but the main drawback of SBSE is in the desorption step because loaded analyte on coated stir-bars cannot be desorbed directly in the injection port of a GC and so the analyte must be back extracted into a appropriate solvent which causes an additional desorption step. SPME and SBSE in combination with

LC-MS were compared by Blasco and coworkers [122] for the analysis of pesticide residues from honey. According to the results obtained both techniques are simple, cheap and can be done with low consumption of solvents without any preliminary sample preparation step. Linearity and precision obtained by the two methods were similar, while the results obtained by SBSE were more accurate and sensitive than SPME. SBSE method is applied for the analysis of halogenated solvents, volatile aromatics, PAHs, PCBs pesticides, odor compounds and organic compounds. Due to the apolar character of PDMS, it is not successful for the extraction of polar compounds except when they have been previously derivatised, hence SBSE has been applied commonly for the extraction of non-polar and weakly polar compounds. Even after derivatisation of strong polar analytes to produce more hydrophobic species, this method is not suitable and extraction of them is difficult by PDMS-coated stir bars. Table 5 reviews some recent applications

of SPME and SBSE methods in the analysis of pesticide residues in different samples.

Chromatographic Analysis: The replacement of traditional extraction such as liquid-liquid extraction (LLE) combined with high gas chromatography-mass spectrometry (GC-MS) with developed novel extraction methods, in seventies enables the effects of trace pollutants such as chlorinated pesticides, petroleum hydrocarbons and polyaromatic hydrocarbons (PHAs) in the environment to be investigated. A first step towards multi-residue method was based on thin layer chromatography (TLC), which employs on-plate detection often based on biological activity such as cholinesterase inhibition or fungi spores [128]. Prevalence of capillary columns in GC measurements was demonstrated in a survey where over 90% of GC methods were designed with capillary columns. Although capillary columns are capable of refined separations, there are some limitations in the methods of treatment during production and choice of materials. The multi-step method of column manufacture has intrinsic inefficiencies. The sol-gel method for column preparation can be considered as the most dramatic change in column technology in the past decade. Other developments such as the exploration of methods to stabilize coatings or to characterize extra thick films of stationary phases were introduced commercially in 2000. Polydimethylsiloxane or phenylmethylpolysiloxane are the most commonly used non-polar stationary phases in GC today, that were subjected to refinements with hops of improved thermal stability to 400°C and higher [129]. Addition of silphenylene unit to form tetramethyl-p-silphenylenedimethyl-diphenylsiloxane, resulted in reduced column bleed and increased the maximum allowable operating temperature [130]. Phenyl group enhances thermal stability, presumably through backbone stiffening. However, the elution temperatures of analytes need to be increased by 15-30°C against comparable polysiloxanes. Mass spectrometry was invented in 1886 when Goldstein, a German physicist discovered positive ions in a low pressure electrical discharge tube. Rapid-MS analytical column has been used in order to high speed LP-GC-IT-MS/MS analysis of multi-class pesticides [131]. In this system 14% cyanopropylphenyl and 86% dimethylpolysiloxane (BP-10) were used as a mobile phase in the analysis of phenylurea herbicides [132]. Splitless injection technique has been employed in GC analysis due to its robustness although it has some restrictions such as reduction of sample capacity (up 10-20 µL) and the lack of retention of non-volatile co-injected compounds in the

liner which subsequently influences sensitivity. It is also unable to cater for sample matrices. The advent of programmed-temperature vaporization (PTV) injectors solved these analytical difficulties as these injectors can be employed using sample volumes of up to 5 µL without matrix effects. Matrix effects can be eliminated by releasing high-boiling co-extracted compounds through split vent or by trapping them on the liner. In this field Kirchner *et al.* [133] reported the use of PTV inlet in the cold splitless mode under optimized conditions because sample vaporization and sample transformation into the column can be achieved better with good repeatability in comparison to traditional splitless GC. Many pesticides are not amenable to be analyzed by GC as a result of their thermal instability and polarity. In the past 20 years, liquid chromatography has been applied in environmental field with very few samples. Today, the instrumental detection limits are below 0.1 picogram (pg). The techniques used for the introduction and analysis of liquid samples by MS can be classified in two groups including those that introduce the sample into the ionic source of the spectrometer, namely the particle beam (PB) and those that allow 'soft ionization of the sample, namely thermospray (TSP) or interfaces of atmospheric pressure ionization (API). API includes a group of interfaces, commonly called electrospray (ESP), ionspray (ISP) and atmospheric pressure chemical ionization (APCI). ESP is the softest ionization technique available for LC-MS and has permitted large labile molecules to be studied intact. High sensitivity and capability of analysis of thermally labile and highly polar compounds are two advantages of ESP in comparison with TSP. Sveltana *et al.* [134] demonstrated that APCI in negative ion mode has bigger linearity range, lower detection limits and less sensitive to the differences in chemical structure of the analytes and nature of applied solvents than negative ion ESI in analysis of dietary tocopherols. APCI is very sensitive for the analysis of weakly basic compounds and pesticides such as triazines and phenylureas herbicides which can be simply protonated by gas-phase, mobile-phase ions, depending on their proton affinity. Thurman *et al.* [135] compared APCI and ESI for the determination of multi-class pesticides by LC-MS. When APCI was used, the sensitivities for neutral and basic pesticides was more than those when ESI was used. By contrast, ESI was more sensitive than APCI for cationic anionic herbicides. ISP interface was originally introduced by Bruins *et al* [136] to enhance the ion evaporation of the ESP. In the ISP interfaces, the electrospraying process is assisted by coaxial pneumatic nebulization of the LC column effluent.

The main advantage of the ISP interface over the ESP is the tolerance for higher flow rate. Flow rates of 40-50 $\mu\text{L min}^{-1}$, which are compatible with 1 mm inner diameter LC column, can be accommodated. The API process is a soft ionization method which typically generates only protonated molecular ions $[\text{M}+\text{H}]^+$ in positive chemical ionization (PCI) mode or deprotonated molecular ions $[\text{M}-\text{H}]^-$ in negative chemical ionization (NCI) mode, thus presents the molecular mass information which is considered the most important criterion for identification of the analyte. Structural information for identification purposes can be obtained by applying appropriate voltage difference on two regions of the sample cone and the first skimmer of the API source. Today, LC-tandem MS has been widely used with very good sensitivity and selectivity for the analysis of food and environmental pollutants. Yoshioka *et al.* [32] used atmospheric pressure photo-ionization (APPI) interface for LC-MS analysis of carbamate pesticides in fruit and vegetable to overcome the suppression difficulties encountered with APCI and ESI interfaces, but the use of APPI-MS-MS has not been reported in any literature. Chin *et al.* [137] demonstrated when APPI and APCI were used as a source in LC-MS for the analysis of phenylurea and carbamate pesticides, APPI and APCI showed lower background signals and fewer background peaks than ESI and phenylureas gave better S/N from APCI or APPI than from ESI. By contrast, the results illustrated that for carbamates the S/N is better from ESI than from APCI or APPI. Some of these pesticides exhibited protonated and sodiated dimers in the full scan ESI spectra. Triple quadrupole (QqQs), ion trap (ITs), quadrupole time of flight (Qq-TOF) and recently Q-linear traps (LITs) has been commonly employed in LC-MS/MS. Q-TOF has been introduced for the analysis of biopolymers [138]. The use of TOF instruments increased the accuracy m/z measurements and resolution of mass, which are usually within a few parts-per-million (ppm) of the extract m/z values calculated from the nuclide masses and the ionic charge z . However, in most of the published literatures, quadrupole and ion-trap instruments have been used because they provide greater ease of operation, high robustness and relatively low cost in comparison with TOF instruments. Garcia *et al.* [139] described a comprehensive method for the analysis of 100 pesticides in food based on the combined use of LC-TOF-MS and LC-MS-MS using QqLIT and compared three stages including: 1. automated pesticide screening by LC-TOF-MS; 2. identification by LC-TOF-MS accurate-mass measurements; and 3. confirmation and quantitation by LC-MS-MS. In the first

stage a set of data were obtained, including m/z accurate-mass windows (within 20 mDa width) and retention time in order to build the automated screening procedure, which was created automatically by assigning retention time and the m/z mass window for each target pesticide. After analysis and identification by LC-TOF-MS and confirmation using two MRM transition, quantitation was carried out by LC-MS/MS using a QqLIT instrument. Regarding to Figure 1 the results obtained were satisfactory. Amadeo *et al.* [140] reported that there are no pitfalls in identification and quantitation in pesticide residues analysis by LC-QqQ-MS-MS when the number of target compounds is around 100 or below. For a routine laboratory, it is very difficult to maintain a large number of methods, each with a limited number of target analytes (e.g. 300) for practical reasons and to get methods accredited. It should be noted that when LC-MS-MS techniques are employed, the scope and the capabilities of these MRMs are limited to a small number of target pesticide, hence pesticides which are not previously incorporated as targets analysis in the MRMs applied are not acquired and so not detected. Besides, as the number of target compounds in a single run increases, identification will be a problem. So the main advantage of TOF-MS analysis for large-scale screening is its ability to test a data file for a theoretically unlimited number of pesticides. However, the applications of TOF for pesticide residues analysis are restricted in comparison with other MS techniques (e.g., QqQ-MS) due to its low efficiency while achieving reliable quantitative information. Soler and co-workers [141] showed that the results obtained when LC-TQ-MS were used for quantitative analysis of pesticides in orange higher precision, linearity and robustness were obtained in comparison with the results obtained from LC-QIT-MS. Nevertheless, both systems could be employed for qualitative and quantitative analyses of traditionally treated oranges. LC-MS (QqQ) have been applied in the analysis of different classes of emerging contaminants in solid and aqueous environmental samples, using the multiple reaction monitoring mode (MRM) and obtaining LODs of typically in ng L^{-1} [142]. Among different columns in LC for the analysis of pesticides in food samples, the reversed-phase octadecyl chromatography C_{18} columns (4.6 mm i.d.) and to a lesser extent octyl C_8 are commonly used. Hernando *et al.* [143] evaluated different LC-QLIT-MS (MRM) conditions to obtain sufficient sensitivity for the detection of pesticides in olive oil by using turboionspray source in positive mode. In this work, two different

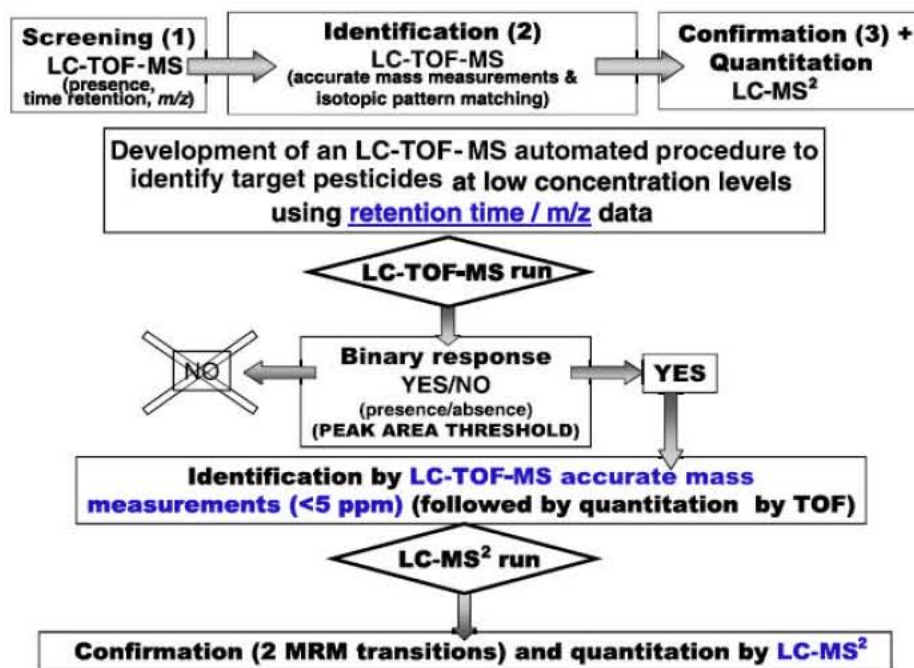


Fig. 1: Example of the combined use of LC-TOF-MS and LC-MS2 for large-scale screening of pesticides in food stuffs (for details, [139]). The proposed workflow for screening, identification, confirmation and quantitation of target pesticides in vegetable samples comprised three steps:

- (1) Screening by LC-TOF-MS with retention-time / accurate-mass m/z windows;
- (2) Identification via accurate-mass measurements (<5 ppm error); and,
- (3) Confirmation (2 MRM transitions) and quantitation by LC-MS2. (Reprinted with permission from Ref. [139])

chromatographic columns (C_{18} 100 \times 2.1 mm i.d., 1.8 μ m and C_{18} 150 \times 4.6 mm, 5 μ m), different working flows (200 and 600 μ L min^{-1}) and different injection volumes (5 and 10 μ L) were studied. The mobile phases used in both columns were HPLC water, 0.1% formic acid as mobile phase B and MeCN as mobile phase A. One approach applied to improve the sensitivity was by using small particle size (e.g., 1.8 μ m) columns, which can provide increased column efficiency with better baseline separation and narrower peaks than standard particle size columns (e.g., 3.5-5 μ m). On the other hand, the sensitivity achieved in small particle size columns is limited by the volume of sample that can be injected. In high-demand conditions, small particle size columns, such as 2.1 \times 100 mm, could even support the injection of higher volumes (e.g., 10 μ L) than the maximum volume recommended (5 μ L) without significant changes in the column pressure. But the disadvantage is a worsening of the peak shape. Another option to optimize sensitivity is the flow rate. Upon exploring two flow rates of 200 and 600 μ L/min, in term of sensitivity, a superior response was observed at 200 μ L min^{-1} and so this was judged to be more suited to the trace determination of pesticides. The benefit of using

higher flow rates is the reduction in analysis time, which is ideal for routine laboratory analysis. However, reduced sensitivity was observed at the higher flow rate explored, which could be associated with a dilution effect or a less stable spray.

Therefore, the use of C_{18} (4.6 \times 150 mm 5 μ m), at flow rate of 200 and injected sample of 10 μ L in MRM mode gave the best sensitivity with LODs = 1 μ g kg^{-1} for 84 pesticides, = 5 μ g kg^{-1} for 12 and = 10 μ g kg^{-1} for 4 pesticides. In another study Barcelo *et al.* [144] reported the application of LIT combined with orbitrap analyzer for the identification of pesticides in surface water. As can be seen in Figure 2, in the first step, extracted ion chromatogram were constructed by using a mass filter of 3 ppm for the extract molecular mass (Fig.2B). The comparison of measured spectrum and calculated spectrum of molecular $[M+H]^+$ illustrates adequate agreement of the isotopic pattern for the ^{37}Cl signal and the mass error between theoretical and measured masses of 0.3 ppm for $[M+H]^+$. Confirmation and identification was performed by comparing the data dependent MS/MS spectra of the compound and MS/MS spectra predicted by

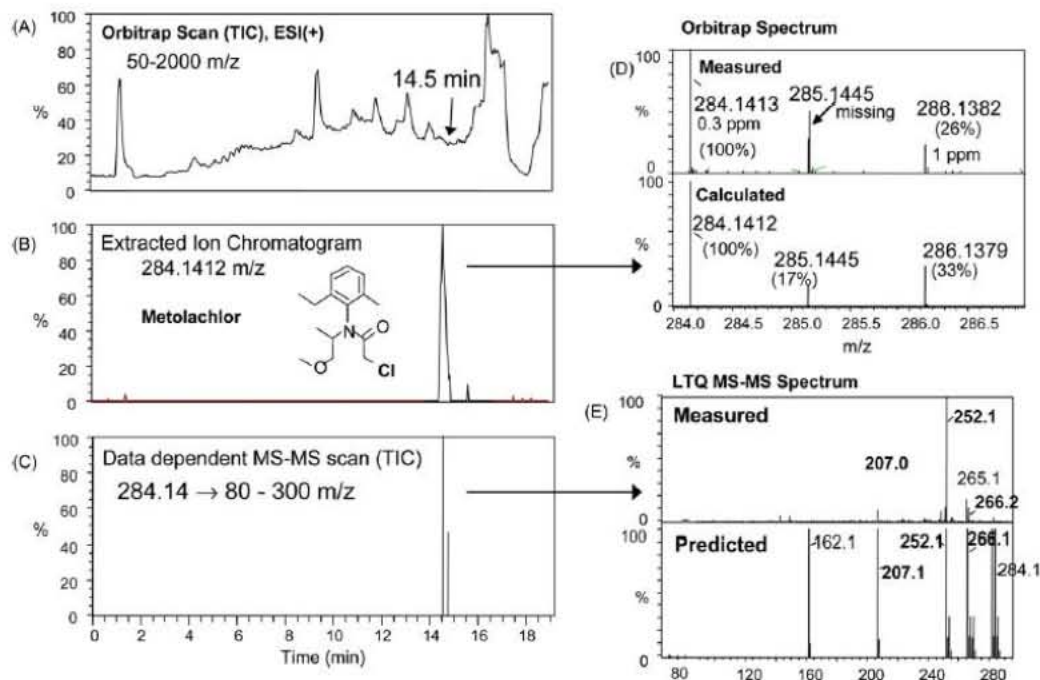


Fig. 2: Identification of metolachlor in a lake water sample using a linear ion trap combined with an orbitrap analyzer. (Adapted with permission from Ref. [144])

Massfrontier software (Fig. 2D). Fig. 2E shows the predicting fragments matched molecular with three measured product ions. To prevent matrix interferences effects, the standard additional method, labeled internal standards and external calibration plots have been recommended. The use of matrix-matched method is suggested for multi-residues analysis because of the lack of labeled standards for all analytes.

CONCLUSION

Since, pesticides belong to different groups of chemical substances with a broad range of polarity and acidic characteristics analysis of pesticide residues poses special problems for the scientists. Analysis of these compounds involves different steps, such as extraction, clean up or interference removal, determination of pesticide residues and confirmation of their identity by using different techniques. Ideally, residue isolation should involve as few steps as possible which require minimal expendable materials and low cost and also has the ability to be automated with high interferences removal. In order to analyze the pesticide residues in a variety of samples, a proper method is selected based on cost, selectivity and sensitivity which depends on the types of compounds that need varying instrumental optimization specifically the polar compounds that are

unstable heated. New sample extraction and concentration methods are evolving towards automation so as to allow on-line extraction and analysis which would increase the robustness as well as decrease the time for an analytical method. Among the extraction methods mentioned, solid-phase extraction is commonly used with often clean up step to remove interferences. In order to obtaining sensitive and selective analysis, the use of LC system is preferred rather than GC as most of the target analytes are polar, non-volatile and thermally unstable. The main advantage of the application of LC-MS/MS is the simplification of extraction methods. Between different LC techniques, LC-ESI-MS-MS provides credible results at levels of subnanogram per liter or per gram and so it can be a selective method for this aim. In spite of the high sensitivity and selectivity of LC-MS-based methods, we still need to learn more about the significance of the matrices effects in the analyses of pesticide residues in food samples like vegetables and fruits.

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