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Determination of Pesticide Residues in Food of Animal Origin

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Introduction

Organic pollutants present in food of animal origin can be classified in two main categories: *contaminants* and *residues*. *Contaminants* (e.g. dioxins, polychlorinated biphenyls - PCBs) are substances that are not deliberately added to the food and that can enter in food during its production process, transformation, storage, packed, transport, or because of fraudulent practices. *Residues* are compounds that can occur in foodstuffs because of intentional usage of phytosanitary or veterinary products during plant or animal production. Pesticides (found incorporated or onto the surface of food) can thus be included in the latter category.

Pesticides are a group of chemicals used either to directly control pest populations or to prevent or reduce pest damage on crops, landscape or animals. Consequently, they may be present in fresh or processed animal foodstuffs, if animals have been fed with contaminated feed or water, or if practices involving pesticides are performed in food-processing factories and/or where animals eat and live (e.g. stables, roosts, meadows and pastures, grazing lands, beehives, etc.). Pesticides can be classified by the target organisms they are designed to control. The main classes are represented by *insecticides* and *acaricides* (to control insects, acari and mites), *fungicides* (to control fungi and oomycetes), *herbicides* and *algicides* (to control weeds and algae) and *rodenticides* (to control rodents). In food of animal origin, pesticide residues can be grouped into main chemical families of public and regulatory concern, such as *organochlorines* (OCs), *organophosphates* (OPs), *carbamates* (CBs), *pyrethroids* (Py) and *neonicotinoids*.

Knowledge of the physicochemical properties of pesticides is very important in environmental risk assessment, because they influence the distribution, persistence and fate of parent compounds and their metabolites into the environment. The most important physicochemical properties are vapour pressure, water solubility, and octanol-water partition coefficient (K_{ow}), which dictates how a pesticide will distribute among animal (fatty) tissues.

Chronologically, OCs have been the first class of chemicals used to control pests in agriculture and public health. They are persistent, lipophilic (Log K_{ow} values of approximately 6), they can bioaccumulate and biomagnify through the food chain and present potential for adverse effects in humans and the environment. Because of worldwide restrictions in their usage and production since the 1970s and 1980s (with exceptions for malaria control in some developing countries), other classes of pesticides, such as OPs, CBs and Py, have been used as alternatives to OCs on a large scale. Despite their lower environmental persistence compared to OCs and their wider range of lipophilicity (Log K_{ow} ranging between -1 and 6), OPs and CBs can also accumulate in fatty matrices of animal origin. However, unlike most OCs, OPs and CBs are stored in animal fatty tissues for a shorter period of time (e.g. days). Nevertheless, these compounds present high acute toxicity. For these reasons, OPs and CBs have been gradually replaced by Py pesticides, known as non-persistent lipophilic compounds (Log K_{ow} ranging between 4.2 and 7) with low water solubility and lower toxicity to mammals and birds. Lastly, neonicotinoids are a more recent class of insecticides, currently among the most popular and widely used insecticides. They are much more toxic to invertebrates, like insects, than to mammals, birds and other higher organisms. What has made neonicotinoid insecticides popular in pest control is their systemic nature and high-water solubility, which allows them to be applied to soil and be taken up by plants. However, in recent years, serious concerns raised about the impact neonicotinoids may have on non-target organisms (e.g. honeybees).

Pesticides can also be classified according to their mode of action¹. The most common mechanisms are listed below:

Enzymatic inhibition: This is, by far, the most important mechanism of toxicity. The toxicant reacts with an enzyme or a transport protein and inhibits its normal function. Typical pesticides included in this group are OPs and CBs which affect the nervous system by disrupting

acetylcholinesterase (AChE) activity. However, some enzymatic inhibitors have little specificity and, therefore, different enzymes may be targeted.

Disturbance of the chemical signal transmission: The toxicant imitates the true chemical signal substances, by transmitting a signal too strongly, too long lasting, or at a wrong time. Typical examples are neonicotinoids, acting as agonists on AChE inducing continuous excitation of the neuronal membranes, producing discharges leading to paralyses and cell energy exhaustion.

Generation of reactive molecules: The toxicant forms reactive radicals or intermediates which are very aggressive and can attack biomolecules non-selectively. The classical example of a free radical producing poison is the herbicide paraquat, which delivers an electron to molecular oxygen, further producing a reactive hydroxyl radical.

Disturbance of the chemical properties of cell membranes: For Py, the insecticidal action depends on the ability to bind to and disrupt voltage-gated sodium channels of insect nerves.

Despite undeniable benefits of pesticides in controlling pests and plant disease vectors and controlling nuisance organisms that harm human activities and structures, pesticide residues on foodstuffs, resulting from the use of plant protection products, may pose a risk to public health². For this reason, a comprehensive legislative framework has been established in the European Union (EU) which defines maximum residue levels (MRLs) of pesticides in or on food and feed of plant and animal origin (Regulation EC 396/2005)³. These MRLs, derived after a comprehensive assessment of the properties of the active substance and the intended use of the pesticide, are based on good agricultural practice and the lowest consumer exposure necessary to protect vulnerable consumers.

This chapter critically reviews the most recent analytical methods (2010-2018) for pesticide analysis (including practical aspects on sample preparation, analytical techniques and quality

control) in food of animal origin (e.g. milk and dairy products, meat, fish and seafood, honey and eggs). As such, it updates the previous version edited in 2008⁴. Current issues and future perspectives regarding pesticide analysis are also largely discussed.

Sample Preparation

Despite the tremendous growth during recent years in the number of papers dealing with the determination of pesticide residues in various food of animal origin, no standard analytical procedures have been set yet for these compounds. This has resulted in a variety of analytical approaches for both sample preparation and instrumental analysis. Because of the low levels at which these compounds may be present in complex animal matrices, sample treatments often include several steps for exhaustive extraction and pre-concentration of the target compounds, usually followed by purification before final chromatographic separation, detection and quantification. In most cases, the need for additional fractionation depends on the selected chromatographic approach, detection systems, and/or on the specific study goal. Tables 1 and 2 summarise relevant data on selected analytical procedures used for the determination of pesticide residues in a wide variety of food samples of animal origin. Furthermore, due to the specific physicochemical properties of various classes of pesticides, their determination may require specific analytical approaches, as it has been presented below.

Sample pre-treatment

Only freeze-drying and homogenization are usually carried out before extraction of biological samples. Alternatively, (semi)liquid (e.g. eggs or milk) samples may be freeze-dried and then treated as any other solid biological sample. Losses of volatile compounds might occur during freeze-drying. The samples should be stored in an inert material (e.g. glass containers) to avoid possible sorption of the pesticides into the storage medium or to prevent contamination of the

sample from the storage medium (e.g. with phthalates). Most commonly, samples are kept in glass or Teflon containers. Screw caps should be lined with solvent-rinsed aluminium foil or with Teflon inserts. Polyethylene or other plastics should be avoided, unless a thorough validation has been previously carried out and contamination has been ruled out. Alternatively, solid samples can be wrapped in aluminium foil and then inserted into plastic bags. Preferably, samples should be frozen (-20 or -80 °C) as soon as possible after sampling. Freezing and storage of multiple small samples suitable for analysis, rather than larger masses, is recommended to avoid multiple freezing/thawing of tissue and to reduce sample handling, which, in turn, reduces the potential for contamination.

In general, for pesticide residue analysis, maintaining sample tissues in their original wet state is regarded as the most appropriate approach for preparing samples. Instead, homogenized samples should be mixed with a desiccant such as sodium sulphate, Celite or Hydromatrix to bind water. The desiccant must be free of analytes, e.g. by heating at high temperature in the case of sodium sulphate or by pre-extraction (Celite or Hydromatrix).

Extraction techniques

For food samples of animal origin, the selection of the most suitable extraction technique mostly depends on the nature of the matrix investigated; different procedures are used for solid and liquid samples. The amount of sample to analyse largely depends on the anticipated sample contamination level and on the sensitivity provided by the detection technique.

Solid samples can be extracted by different techniques (Tables 1 and 2). The key-points are the use of adequate solvent mixtures (e.g. low boiling point to facilitate concentration), adequate exposure time between solvents and the sample matrix, and limitation of sample handling steps, i.e. avoid filtration steps by using semi-automated extraction systems (e.g., pressurized liquid extraction, PLE). Contamination by carry-over (e.g. high pesticide residues in the previous

analysed sample) should be avoided by thoroughly cleaning any lab equipment from batch to batch. Purity of extraction solvents should also be guaranteed by only using pesticide-grade or high-purity glass-distilled solvents, to avoid the presence of contaminant residues in the solvent volume concentration step.

Different extraction methods have been applied for the determination of pesticides extraction in food from animal origin. The conventional solid-liquid extraction (SLE) technique is still widely used, performed by homogenizing the solid sample with a variety of solvents, e.g. acetonitrile (ACN) 1% formic acid, v/v^{5,6} or McIlvain solution⁷, partitioning of analytes from the matrix to the solvent. Such techniques allow quantitative extraction of pesticides directly from dry matrices or after drying the original fresh sample with anhydrous Na₂SO₄⁸. Alternatively, the use of matrix solid-phase dispersion (MSPD) in different variants is a suitable choice, which results in an intimate contact between the sample components and the sorbent particles and in a more efficient retention of impurities⁹. For liquid or viscous samples, solid phase extraction (SPE) can be employed for the extraction of pesticide residues from milk¹⁰ and honey¹¹. SPE is based on the elution of analytes with appropriate solvents, such as methanol (MeOH), which were previously retained in the cartridge¹². However, high solvent consumption and laborious sample-handling can be expected by using these methodologies. Therefore, an automated extraction technique, as PLE, has been applied for the extraction of milk, egg and meat^{13,14}, liver and fish^{15,16}, and honey¹⁷. The use of elevated temperatures and pressure increases diffusion and desorption rates. Although PLE is an extraction technique that provides good recoveries and reduces the use of solvents, it has high costs and the preparation of the extraction cells is tedious and time-consuming. Moreover, the preparation of a homogeneous dry sample from wet tissue for PLE can be challenging due to the limited volume of PLE extraction vials.

Miniaturized techniques have also been applied for the extraction of pesticide residues from honey samples by dispersive liquid-liquid microextraction (DLLME)^{18–20}, microextraction in

packed sorbent (MEPS)²¹ and solid-phase microextraction (SPME)²². Moreover, Campillo et al. (2013) have combined SPE extraction with DLLME for the extraction of neonicotinoids from honey²³. DLLME is a simple and rapid extraction technique that consumes low volume of organic solvent. On the other hand, MEPS can be considered a green extraction method because the sorbent can be reused for more than 40 times with minimum loss of extraction efficiency²¹. However, due to the complexity of the honey-matrix, is often necessary to perform a previous step, such as liquid-liquid extraction (LLE). Another environmentally friendly method has been developed by Campillo et al. (2012) for the determination of organotin compounds in honey samples using headspace-SPME (HS-SPME)²². Although conventional SPME does not require solvent or multi-stepped cleanup/concentration procedures, adsorption efficiency can be affected by complex matrices, especially when the fibre is directly immersed in the sample. Other non-classical techniques have been employed for the analysis of pesticides, such as purge and trap²⁴ and coacervation microextraction ultrasound-assisted back-extraction technique (CME-UABE)²⁵, in honey and animal tissues.

Despite the advantages of these extraction techniques, none of them have overcome critical flaws and practical limitations to enable their widespread implementation. For example, PLE requires time-consuming manual steps and specialized items that necessitate thorough cleaning after use, the sample throughput is not always optimal, and instruments and maintenance are often expensive. Other techniques, such as MSPD and SPME, do not provide a wide enough analytical scope within a single procedure, or enough selectivity. In 2003, Anastassiades et al. developed a method for the extraction of multi-class pesticide residues from fruits and vegetables, naming it QuEChERS (Quick, Easy, Cheap, Effective, Rugged and Safe)²⁶. The optimized original method consisted of the extraction of the homogenized food sample with ACN, followed by the addition of salts (e.g. anhydrous MgSO₄, NaCl). The extract was then cleaned up by dispersive solid phase extraction (d-SPE) with primary secondary amine (PSA), C18 and/or graphitized carbon black

(GCB) sorbents, with the aim of eliminating possible interfering compounds from the food extract (e.g., organic acids, certain polar pigments, sugars, etc.). After centrifugation, the supernatant was finally ready for analysis in the GC-MS system²⁷. Although the original QuEChERS method is not likely to be applicable for the extraction of more lipophilic pesticides from high fatty samples, it is considered optimal for their extraction from low fatty foods and for the extraction of polar and semi polar pesticides from a wide variety of fatty foods²⁸. Subsequent adjustments/modifications to the original method were then developed to improve its performance for some more complex analytes and foodstuffs (e.g. foods of animal origin which contain proteins, lipids, and saturated and monounsaturated fatty acids), to avoid pesticide degradation and to diminish the matrix effects^{29–33}. For these reasons, the QuEChERS method and its following modifications, with its unique combination of extraction and clean-up procedures, solvents, salts and sorbents, is currently considered the standard sample-preparation procedure for pesticides analysis in foodstuffs²⁷.

Another approach for the determination of multiple classes of pesticides in different food matrices (such as honey⁵, meat^{6,34}, baby food³⁵ and liver³⁶) is the “dilute and shoot” method, by using ACN (1% formic acid, v/v) as extraction solvent. A critical factor is the extraction time for properly mixing the target compounds with the solvent, and 1 h is usually enough to allow an exhaustive extraction of the target compounds. Considering that more than 10 samples could be simultaneously analysed in the “dilute and shoot” extraction, the sample throughput can be considered suitable to apply this approach in routine analysis³⁷.

Clean-up and fractionation

The non-selective nature of the exhaustive extraction procedures and the complexity of sample matrices result in complex extracts that often require further purification. SPE and d-SPE are currently the most commonly used purification steps³⁸. Several sorbents have been used

depending on the type of matrix, such as C_{18} ³⁹⁻⁴¹ in egg, meat, honey and milk samples, PSA^{36,42,43} in honey, liver, milk and meat samples, GCB⁴⁴⁻⁴⁶ in fish, honey, milk, cream and meat matrices, alumina^{8,47} in several matrices as meat, fish, egg, milk and liver matrices, Florisil^{35,48,49} in honey and baby food samples and anhydrous $MgSO_4$ ⁵⁰⁻⁵², mostly in honey matrices. In some cases, depending on the type of matrix and the determination technique, there is no need to use these clean-up stages^{53,54}. Nowadays, prepacked column for the SPE and sorbents for d-SPE extraction are commercially available, being OASIS HLB one of the most used cartridge⁵⁵. Typical purification and fractionation procedures have been summarized in Tables 1 and 2. For biological samples, including food of animal origin, lipid elimination should be accomplished by non-destructive methods, before chromatographic analysis. Traditionally, *n*-hexane saturated with ACN is used for the extraction of fat content. However, it is not effective during the extraction of weak and non-polar compounds. To overcome this problem, the low-temperature clean-up could be an alternative extraction to remove most of lipids co-extracted in ACN⁵⁵. Because the fatty substances have lower melting points than the solvent, freezing centrifugation is a simple approach to remove the fatty co-extracted interferents³⁸. Gel permeation chromatography (GPC) is a non-destructive treatment applied for lipid elimination. GPC is mainly performed either in automated systems^{14,16} or by gravity flow columns⁹. The current use of pre-packed polystyrene-divinyl benzene based high performance GPC columns has resulted in higher separation efficiencies, improved reproducibility and lower solvent consumption as compared to manually packed columns. Satisfactory isolation of the target compounds from the co-extracted organic material after single GPC analysis has been achieved for some samples that contain limited amounts of lipids like fish and meat (approx. 2% of lipid). However, for more complex matrices, such as milk, cream and egg (with more than 40 % of lipid), GPC followed by a further clean-up step by SPE may be required to remove remaining low molecular weight lipids, waxes and pigments^{9,44}.

Analytical Techniques

The choice of the best analytical technique for the detection and quantification of pesticide residues strongly depends on the analyte's polarity. Compounds with high log K_{ow} (e.g. OCs, Py and most OPs) are non-polar and are preferably analysed by gas chromatography (GC), while polar compounds, such as CBs, neonicotinoids and some OPs, are amenable by liquid chromatography (LC). GC and LC can be coupled to several detectors such as electron capture detector (ECD)^{56–62}, nitrogen-phosphorus detector (NPD)^{24,49,63,64}, photodiode array detector (PAD)^{65–68}, diode array detector (DAD)^{23,69–71} and variable wavelength detector (VWD)⁷², depending on the targeted compounds. However, EU requirements indicate that all confirmatory methods for pesticide residues in food must use mass spectrometry (MS) detection⁷³. Nowadays, LC and GC coupled to MS²⁰ or to tandem mass spectrometry (MS/MS)¹⁸ are the most widely used analytical techniques for the determination of pesticide residues in food of animal origin. Low-resolution mass spectrometry (LRMS) usually provides better robustness and lower limits than high-resolution mass spectrometry (HRMS). However, the number of pesticides analysed by HRMS is commonly higher than those analysed by LRMS. For instance, Gómez-Pérez et al. (2014) determined more than 350 compounds in meat by LC coupled to an Exactive-Orbitrap detector (HRMS)⁶, meanwhile García-Chao et al. (2010) quantified 7 pesticides in honey and pollen by LC coupled to a triple quadrupole (QqQ) analyser (LRMS)¹¹. Moreover, retrospective analysis can be performed when HRMS is applied.

Gas Chromatography coupled to mass spectrometry

GC-MS is the most commonly applied technique for the determination of volatile and semi-volatile analytes of low-medium polarity⁷⁴. Furthermore, it has become a powerful technique for

the quantitative determination at low levels of contaminants in complex matrices, such as honey and meat¹².

Low resolution mass spectrometry applications

There are three modes of GC-MS available, electron impact (EI), positive chemical ionization (PCI) and negative chemical ionization (NCI), with the first one being the most widely used. Due to its adequate sensitivity and selectivity, GC-MS in selected ion monitoring (SIM) is commonly used in the determination of different classes of pesticides in animal tissues^{8,16,62}, milk^{8,57}, fish^{8,16} and honey^{20–22,24,49,60,75}.

GC-MS/MS commonly provides higher sensitivity and selectivity, as well as higher degree of certainty than GC-MS in SIM mode, because it involves at least two stages of mass analysis, separated by a fragmentation step. The most common tandem mass spectrometers for GC, namely ion trap (IT)^{17,25,48,75} and QqQ^{9,40,47} are important tools in food analysis. GC-IT-MS/MS has been employed in honey samples for the analysis of OPs²⁵, OCs^{17,75} (Figure 1), or for the determination of multiclass pesticide as OCs and OPs⁴⁸. However, GC-QqQ-MS/MS has been less frequently used to determine pesticide residues in meat^{40,47}, fish, egg^{9,40,47} and milk samples⁴⁷.

In the above mentioned GC-MS applications, fused capillary columns with bonded phases of different polarities (non-polar NST-05MS; low polar HP-5, DB-5MS, ZB-5, VF-5MS, DB-5MS, ZB-5MS, HP-5MS, RTX-5MS, AT-5MS and low/mid polarity (DB-1701)) have been used at various lengths (15 - 30 m), internal diameters (0.25 - 0.32 mm) and film thickness (0.10 - 0.50 μm) (Table 1).

Insert Fig. 7.1 here.

Insert Table 7.1 here.

Insert Table 7.2 here.

High resolution mass spectrometry applications

Even though LRMS has been used for the determination of pesticide residues in food of animal origin, it is sometimes not selective enough and only unit mass resolution is provided. Besides, in one single run, a “limited” number of compounds can be simultaneously determined³⁷. Therefore, HRMS has been applied to improve the requirements mentioned above. This technique provides some advantages, such as non-target approach, post-target analysis, and the (theoretically) unlimited determination of compounds. A great variety of pesticides could be detected in food of animal origin. Therefore, HRMS is a powerful technique to cover a wide range of pesticides, reducing the cost of the analysis and improving the cost-effectiveness of the developed method³⁷. The time-of-flight detector (TOF) has been applied in different matrices like fish¹⁴ and honey, honeybee and pollen⁷⁶ for the determination of multiple classes of pesticides. Both of them operated in the EI mode and employed a BPX-50 column¹⁴ and a DB-XLB column⁷⁶. On the other hand, to improve the drawbacks of the TOF detector, a hybrid system, consisted on a quadrupole/TOF (Q-TOF), has been applied for the determination of 50 pesticides in meat samples³⁴. In this study, atmospheric pressure chemical ionization (APCI) has been used as an alternative to conventional ion sources applied in GC (EI or CI), minimizing the matrix effect observed applying other ionization techniques. An overview of the recent literature for the application of GC coupled to TOF and Q-TOF in the determination of pesticides residues have been performed by Elbashir and Aboul-Enein (2017)⁷⁴.

Other GC applications

Two-dimensional or comprehensive GC (GCxGC) involves the separation of target analytes by two orthogonal capillary columns in which the first column has normally larger diameter and longer length than the second column. Hayward et al. (2010) determined 34 compounds in milk and cream by GCxGC coupled to a TOF detector, being the first column a HP5-MS (30 m x 0.25 mm i.d, 0.25 μ m film thickness) and the second one a BPX-50 (1.5 m x 0.15 mm i.d, 0.15 μ m film thickness)⁴⁴. The observed peaks were higher and sharper peaks (smaller peak width) than those obtained by conventional GC approaches, offering sensitivity enhancement. Besides, the second column could separate the co-eluting peaks from the first column⁷⁷.

Several pesticides have optically active or chiral isomers (e.g., cis/trans-imiprothrin, resmethrin or tetramethrin)⁴⁷. As a consequence, biotransformation reactions in biological samples can result in non-racemic patterns in environmental samples. Dallegrave et al. (2016) analysed the isomeric composition of some Py, cyfluthrin and cypermethrin in chicken, fish, eggs, milk and beef by GC coupled to a QqQ⁴⁷. Crucial for chiral analysis is the availability of chiral capillary GC columns such as those with various cyclodextrins chemically bonded to a polysiloxane. While use of chiral GC separations is not part of routine pesticide analysis, it is a well-developed technology that is relatively easy to implement in existing GC-MS instruments.

Liquid chromatography coupled to mass spectrometry

LC is the preferred method when dealing with thermally labile, ionic and polar compounds (such as CBs, neonicotinoids, urea and phenoxy herbicides or benzimidazoles). Some reviews focused on the applications of LC-MS (LRMS and HRMS) for the determination of pesticide residues in environmental and food analysis⁷⁸ or in food⁷⁹ have recently been published. This technique meets the EU legislation requirements^{73,80} to ensure appropriate selectivity and sensitivity.

Low resolution mass spectrometry applications

LC has been coupled with different types of MS detector for the monitoring of pesticide residues in food of animal origin and QqQ is the most common analyser^{6,9–11,15,18,19,35,39,50,51,55,70,76,81–91}. Besides, other detectors have been employed in the quantification of pesticides such as single quadrupole (Q)⁹², IT^{13,23,42,93} and QTRAP^{40,41,52,94,95}. Of the different LC-MS methodologies, electrospray ionization (ESI) and APCI are the most used. Both techniques allow the detection of pesticides in food of animal origin in positive ionization mode^{23,90,94} or both ionization modes, negative and positive^{11,42,91}. García-Chao et al. (2010) and Kasiotis et al. (2014) determined fipronil and its metabolites by LC coupled to a QqQ in negative ionization mode in honey^{11,87}. In addition, Lichtmanegger et al. (2015) quantified 80 multiclass pesticides in egg and meat by LC coupled to QTRAP⁴⁰. Most of these applications involve the use of the C₁₈ reversed phase column at different sizes, e.g. (100 x 2.1 mm i.d, 1.7 µm particle size)¹⁰ or (50 x 2.0 mm i.d, 4.0 µm particle size), although other reversed phase columns have been employed like C8 (Table 2)⁹³. The elution most widely used is a gradient of methanol-water, methanol-aqueous solution of formic acid or methanol-aqueous solution of ammonium formate. Danezis et al. (2016) applied a QqQ analyser coupled with a hydrophilic interaction liquid chromatography (HILIC) column using a gradient acetonitrile/water-aqueous ammonium formate for the analysis of cyromazine, amitrole and the metabolite of propylenethiourea simultaneously with plant hormones, veterinary drugs and mycotoxins in milk, baby food and meat⁸³.

High resolution mass spectrometry applications

The Orbitrap mass analyser has been applied for the determination of several types of contaminants or residues, including pesticides. For instance, 118 alkaloids, CBs, OPs and veterinary drugs have been analysed in several matrices, such as milk, liver and muscle tissue⁴³; 36 pesticides, mycotoxins, antibiotics and veterinary drugs in milk, and bakery products^{7,97};

pesticides, antibiotics and veterinary drugs in honey^{5,53}, meat⁶, baby food³⁵, meat⁴⁶; rodenticides and transformation products in liver³⁶.

Most of the literature reports the use of ESI in both ionization modes (positive and negative)^{5-7,35,36,46,54} or acquired the data employing only the positive mode^{38,45,53,97}.

However, comparing to the LRMS analysers, Orbitrap provides lower sensitivity, but better selectivity. Hybrid analysers can even improve this last characteristic, bearing in mind that precursor ions can be selected. They are based on a hybrid system that couples two analysers such as a quadrupole with an Orbitrap (Q-Exactive) or TOF^{53,54}. Farré, Picó, and Barceló (2014) used a combination of linear ion trap with an Orbitrap analyser (LTQ Orbitrap) for the determination of 54 pesticide residues in fish and honey matrices⁴⁵. Moreover, Náchter-Mestre et al. (2013) analysed 82 compounds in fish by a hybrid system consisted on a Q-TOF³⁸.

On the other hand, HRMS allows post-target analysis to search for additional compounds, avoiding additional analyses. In that sense, Náchter-Mestre et al. (2013) performed a retrospective approach in order to detect and tentative identify other compounds³⁸. In addition, the need to analyse transformation products has increased in the last few years because, sometimes, they are also toxic compounds. HRMS is a powerful tool for the determination of target and non-target compounds at low concentration levels in complex matrices. For instance, a retrospective analysis was applied to identify transformation products of chlorpyrifos (one of the most widely used OP insecticides) in different food matrices, such as honey and meat (United States, EPA, 2013)⁴⁶. Furthermore, Cotton et al. (2014) detect a metabolite of dichlobenil (banned in France since 2010) in lavender honey samples, 2,6-dichlorobenzamide (Figure 2)⁵³.

Insert Fig. 7.2 here.

Internal Quality Control

Quality control is a part of quality management focused on individual measures used to fulfil the quality requirements⁹⁸, including internal and external activities.

Internal quality control (IQC) is a set of procedures undertaken by laboratory staff for the continuous monitoring of an operation and the measurements to evaluate whether results are reliable enough to be released⁹⁹. On the other hand, *external quality control* (EQC), also known as proficiency testing (PT), evaluates lab's performance against both its own requirements and similar laboratories. However, both activities are strictly related, because laboratories that receive poor PT scores often encounter analytical problems and show a lack of attention to their internal quality control. In the framework of using validated analytical methods by internationally accepted criteria⁸⁰, IQC activities must be suitable to ensure the performance of the analytical method in routine practice. This goal is achieved when the quality level of the results allows detecting whether unexpected or unwanted modifications of the method capabilities have occurred during sample analysis.

Basic activities of IQC in pesticide residue analysis

1. The laboratory must be divided in well-defined working areas to avoid contamination of standards, samples and extracts.
2. All equipment (measurement instruments, balances, flasks, pipets, etc.) must be regularly cleaned and calibrated.
3. Personnel must be qualified, motivated, and continuously trained.
4. Sampling procedures require well-trained staff. Samples must be transported to the laboratory and processed as soon as possible. If not possible, they must be stored in adequate conditions to assure their stability.

5. The quality of reagents must be appropriate for the performed test. Individual primary calibration solutions, generally 100–1000 mg/L, should be prepared by weighing not less than 10 mg of the pesticide using a 5-decimal place balance.
6. The method validation process should include the estimation of uncertainty, essential in establishing the comparability of the measurements.

IQC measures

IQC measures¹⁰⁰ must be included in each analytical batch to evaluate whether or not the processed batch satisfies the pre-set quality criteria and its results can be accepted.

1. *Solvent blanks* eliminate false positives by cross contamination or carry-over in the extraction process, used instruments, or chemicals. *Procedural blanks* should be analysed to detect interferences of sample matrix and the laboratory background contamination.
2. *Certified Reference Materials* (CRMs) or *home-made reference materials* (checked for stability and homogeneity), prepared by spiking a blank sample with 5–10 % of the targeted pesticides, are used to evaluate the accuracy of the performed analysis and to investigate possible variation between batches of samples. CRMs should be analysed in every batch of samples by applying the analytical method and providing additional information about instrument performance (instrument sensitivity, column performance, etc.). The variation in the data obtained from the analysis of the quality control sample is normally monitored on a quality control chart. However, CRMs related to pesticide determination in food from animal origin are still scarce, and they show limitations, such as a limited number of certified pesticides, wide uncertainty ranges, higher concentrations than the current range of interest or a physical state not matching routine samples.
3. A *calibration curve* must be carried out for every batch of samples, although single-level calibration can be performed if the response in the sample is close to the response of the standard.

A minimum of three standard concentrations, prepared in solvent or in extract of blank matrix, should be used for each pesticide⁸⁰, although more levels are desirable (usually five to eight points). The lowest calibration point should be equal to or lower than the limit of quantification (LOQ). The fit of the calibration function (linear, quadratic, etc.) must be checked to ensure that it is satisfactory. Individual points of the calibration curve should not differ more than $\pm 20\%$ ($\pm 10\%$ if the MRL is exceeded or approached).

4. *Recoveries and accuracy* of spiked matrices or blanks (by adding all analytes to a matrix/blank at a concentration equal to the LOQ) should be used to check the extraction efficiency of each batch of samples. Acceptable recovery ranges have been set in function of the amount of the analyte(s) added to the blank matrix. For instance, if a CRM is used at 10 $\mu\text{g/kg}$, a range from -20 to +10 % has been set as acceptable by the Commission Decision 2002/657⁷³, whereas, when spiked samples are evaluated, acceptable recoveries within the range 70-120 % has been accepted by current SANTE guidelines⁸⁰.

5. *Replicated samples* provide a less-formal approach than quality control samples to check for drifts. The results obtained from the analysis of these samples must be comparable, considering the uncertainty of the method. They are in the batch every certain number of samples (e.g. each 10 samples) and their presence is known by the analyst.

6. *Blind samples* are replicate samples placed in the analytical batch without being known by the analyst. They are complementary to replicated samples, providing information about the analyst's proficiency.

Application to Real Samples

Multi-residue analysis of pesticides

Despite their numerous merits, pesticides are considered as one of the most dangerous environmental contaminants. These chemicals can be transferred from plants to animals via the

food chain, leading to their bioaccumulation in food of animal origin, such as meat, fish, eggs, milk and honey². Since diet is the main source of chronic exposure to low doses of pesticides, humans are mainly exposed to these chemicals through diet². Consequently, there is an increasing demand worldwide for reliable and sensitive analytical methods for multi-residue surveillance of pesticides¹⁰¹. Fast, simple, efficient, and cost-effective analytical methods for pesticides are thus needed in food safety monitoring programs to provide high sample throughput and accurate results³².

In the next paragraphs, the most recent analytical methods for the determination of pesticides in products of animal origin are reported for five main groups of pesticides, namely OC pesticides, OP pesticides, CBs, Py and neonicotinoids.

Organochlorine pesticides

The determination of OC residues in biological matrices (including food of animal origin) has been a major subject because of their potential risk for human health, persistence and tendency to bioaccumulate¹⁰². OC pesticides have been heavily used in the past, but they are now outdated and, with few exceptions, are banned in most industrialized countries. Since the environmental levels of various OCs are on a decreasing trend, the studies focusing on the determination of OCs in food matrices often deal with low analyte levels and many interfering substances. The extraction of OCs is usually performed by SPME, stir bar sorptive extraction (SBSE) and MSPD^{102,103}. In addition, due to their good thermal stability, GC coupled to ECD or to MS or MS/MS is considered as the preferred method for the analysis of OC pesticides residue in food of animal origin.

Organophosphorus pesticides

OPs represent a group of compounds with a wide range of physicochemical properties, but all having the same mode of action, which has enabled to develop compounds against ecto- and endoparasites, active in the vapour phase or in the soil, and used against a wide range of crop and public health pests. Although most of OPs are insecticides, some of them have also fungicidal or herbicidal activities. Many OPs present high acute toxicity and are suspected of carcinogenic, mutagenic and endocrine disruptive effects. In the past decade, most of published studies based their analysis on the use of GC coupled to various detectors. GC-ECD or GC-atomic emission detector (AED) have been applied to the determination of OPs in honey, GC-NPD and GC-flame photometric detector (FPD) were applied to the analysis of OPs in dairy products, meat and honey⁴.

More recently, analytical methods for multi-class analysis of selected pesticides, including OPs, based on QuEChERS extraction and d-SPE clean-up and on analysis using low pressure (LP)-GC-MS/MS and LC-MS/MS were developed and applied for several foods of animal origin (e.g. fish, seafood, eggs, dairy products, meat, poultry)^{30,32,104}.

Carbamates

CB insecticides are commonly used as surface sprays or baits in the control of household pests. Their mode of action is similar to that of the OP insecticides, but their inhibitory effect on cholinesterase is shorter. CBs can vary in their spectrum of activity, mammalian toxicity and persistence, but they are generally unstable compounds that break down in the environment within weeks or months. The presence of CB residues in food of animal origin, as mainly attributed to the contamination of feedstuff, is a matter of concern because of their possible adverse effects in humans. Since, in some cases, CB residues appear in the samples at trace levels, an efficient sample preparation is a key-aspect in the development of appropriate analytical methods. In addition, foodstuffs of animal origin are generally considered as complex

matrices, where lipid, carbohydrate and protein components could often interfere in CB analytical determination^{105,106}. For this reason, sample pre-treatments to remove the high molecular-mass lipid from the sample are often required.

A modified QuEChERS procedure using SupelTM QuE Z-Sep+ as sorbent, followed by ultra-high-performance liquid chromatography with MS/MS (UHPLC-MS/MS), has been used for the determination of CB residues in dairy products (i.e. high-fat cheese)¹⁰⁶. This approach has also been successfully used in the determination of residues of 7 CB pesticides in milk¹⁰⁷, where different d-SPE sorbents (e.g. PSA and C18) were tested. A modified version of the QuEChERS approach was used by Holmes et al. (2015) to quantify 185 pesticide residues, including CBs, in samples of fresh salmon. Their validated QuEChERS method used ethyl acetate (EtAc) as extraction solvent and involved two freezing steps and a C18 d-SPE for lipid removal. The quantification was performed using a combination of LC-MS/MS and GC-MS/MS. With their approach, 708 salmon samples collected as part of the U.S. Department of Agriculture's Pesticide Data Program were analysed over 12 months³¹. A sample analysis method based on QuEChERS and liquid chromatography–tandem mass spectrometry was validated by Chung and Chan (2010) in the analysis of ultra-trace levels of 24 CB residues in a total diet study involving diversified food types (including, eggs, dairy products, meat, poultry, and seafood)³⁰.

Pyrethroids

Py are a class of synthetic organic insecticides derived from pyrethrins. They have been used worldwide since the 1980s because of their high level of effectiveness and low toxicity compared to other insecticides, such as OPs and CBs. They are currently among the major kinds of pesticides used worldwide and constitute the majority of commercial household insecticides. Py are hydrophobic molecules which tend to deposit in the lipid fraction of food and, because fatty food of animal origin (e.g. eggs, milk, meat, fish) is an essential component of the human diet,

the possibility of bioaccumulation of these pesticides in fatty food can present a hazard to humans⁴⁷.

The complexity of these samples requires efficient extraction and clean-up procedure prior to analysis, in order to isolate the targeted pesticides and allow reproducible results. For this purpose, in the past decade, different sample extraction procedures have been used based on techniques such as LLE, supercritical fluid extraction (SFE), PLE, SPME, MSPD, etc^{4,108}. Py residues in different food matrices have mainly been analysed either by gas chromatography with GC-ECD or GC-MS and GC-MS/MS and by LC-UV or LC-MS, and LC-MS/MS.

More recently, extraction of Py pesticide residues in fatty food samples of animal origin (including chicken, beef, fish, eggs, and milk) has been performed using DLLME¹⁰¹, ultrasound solvent-assisted extraction followed by SPE cleanup⁴⁷, LLE with purification at low temperature (LLE-LTP)¹⁰⁸, and QuEChERS¹⁰⁹. For the analysis of Py residues in food of animal origin, GC-MS and LC-MS or GC-MS/MS and LC-MS/MS are still among the most common quantification techniques. These combinations of extraction procedures and analytical methods claim to provide good precisions, wide linear ranges, and sensitive limits of detection for the analysis of Py pesticides in such samples.

Neonicotinoids

Neonicotinoids are a class of neuro-active insecticides chemically similar to nicotine. They are mostly applied against soil pests, seed and animal pests, as well as foliar treatments. Compared to organophosphate and CB insecticides, neonicotinoids cause less toxicity in birds and mammals than insects. It has been estimated that neonicotinoids are currently among the most widely used insecticides in the worldwide market. Analytical methods for the determination of neonicotinoid residues in food mainly include HPLC and LC-MS. More recently, for the detection of pesticides, chromatographic columns with sub 2 μm particle size at elevated pressure up to 15,000 psi

(UHPLC) have been introduced coupled to mass spectrometry. This technique has been used for the quantification of neonicotinoid residues in food of animal origin (including eggs, chicken and pork meat) by SPE and UHPLC-ESI-MS/MS¹¹⁰.

When first introduced, neonicotinoids were thought to have low toxicity to many insects, but recent research has suggested a potential toxicity to honey bees and other beneficial insects even with low levels of contact. The honey bee exposition to neonicotinoids can lead to contamination of apiarian products, especially honey, which is the most commonly consumed bee product.

Because of the potential threat to human health, the European Union established maximum residue limits (MRLs) for acetamiprid, clothianidin, imidacloprid, thiacloprid and thiamethoxam in the range of 50–200 µg/kg⁸⁵. In addition, in response to the European Food Safety Authority (EFSA) study on the safety of 3 neonicotinoids (namely clothianidin, imidacloprid and thiamethoxam)¹¹¹, the European Commission recommended a restriction of their use across the European Union in crops attractive to pollinators, emphasizing the awareness of the potential harmful impact of the neonicotinoids on honeybees and their products (EU Regulation 485/2013)^{112,113}. Therefore, monitoring and determination of trace levels of neonicotinoids in honey are necessary and demand highly efficient, selective and sensitive analytical techniques. Several sample preparation techniques, including LLE, SPE, QuEChERS and combinations of them, DLLME, diatomaceous earth material (Chem Elut cartridges) were reported for the sample preparation in honey (and in other food of animal origin)^{69,85,114}. Neonicotinoids are usually determined by LC-DAD, ultraviolet, fluorescence, mass spectrometric (MS or MS/MS), and electrochemical detectors⁶⁹. GC analysis is more complex due to neonicotinoids' low volatility and relatively high polarity⁶⁹.

New trends and emerging issues in analytical methods

Although pesticide analysis is a mature area within environmental and food analytical chemistry, analytical methods are constantly evolving and improving and, undoubtedly, new technologies will emerge in the future. While in the 1990s GC-MS was mainly used to confirm identification of analytes after quantification by means of specific detection methods (like ECD, FPD and NDP), in the 2000s, GC-MS/MS became widely used for identification and quantification of pesticide residues in food of animal origin². Nowadays, LC techniques coupled to (tandem) mass spectrometry (LC-MS and LC-MS/MS) are considered the “golden standard” in routine laboratories to perform pesticide residue analyses, providing the sensitivity, selectivity, and specificity needed to meet EU legislation requirements for the analysis of pesticides in food samples⁷⁸. They are generally preferred over GC because several currently used pesticides are quite polar, thermally labile or not easily vaporized, and thus, having an unsatisfactory performance by GC. MS/MS detectors are also enough sensitive to quantify ultra-traces that are “blind” to “non-targeted” approaches or to identify unknown compounds not included in pre-target lists.

With these regards, the recent introduction of HRMS analysers (e.g. Orbitrap and time of flight - TOF) for screening pesticide residues is a powerful tool for the detection of target/non-target pesticides in food, confirming the identification of contaminants and elucidating the structure of their metabolites. This technique works in full-scan mode (possibly identifying an “unlimited” number of compounds in the samples), it gives accurate masses for both parent and fragment ions and enables the measurement of the elemental formula of a compound achieving compound identification. Thus, in addition to target pesticide residue analysis, other related contaminants (i.e. other pesticides or their metabolites) could be detected and identified, increasing considerably the scope of the analyses and the analytical capabilities of the performing laboratories. However, several important limitations should be considered for the implementation of these HRMS detectors in routine laboratories, such as their higher price and lower sensitivity

compared to target MS/MS techniques, although, in the last few years, the sensitivity provided by HRMS analysers allows for the quantification of pesticide residues at concentrations below 10 µg/kg. In addition, systematic approaches for the detection of untargeted pesticides and their metabolites by HRMS analysers are still scarce and, since the compound identification is a labour-intensive activity, automated strategies are needed.

To detect a wide range of compounds by HRMS analysers, generic extraction methods, such as “dilute and shoot” and QuEChERS, are currently performed to ensure their identification during analysis. In addition, an interesting trend in sample pre-treatment is the miniaturization of this step, reducing the organic solvents consumption and achieving “greener” analytical performances. Also semiautomatic procedures can improve the sample throughput and the accuracy of the extraction method, avoiding the unwanted co-extraction of interferences.

For GC amenable pesticides, comprehensive GCxGC has recently gained interest in the analysis of food of animal origin¹¹⁵. The applications of GCxGC in food analysis are both untargeted, when coupled to TOF-MS, and targeted, when coupled to MS. However, it is in the field of untargeted analysis (both qualitative profiling and fingerprinting of foodstuffs) that GCxGC shows its superiority over conventional GC¹¹⁵.

Together with the recent miniaturized extraction and pre-concentration techniques (e.g. SDME, SBSE, DLLME, MSPE, etc.), there is currently a tendency to reduce GC separation times^{116,117}. In this respect, the rapid GC separation of pesticides by “fast GC” is performed on short micro-bore (≤ 0.18 mm i.d.) or narrow-bore (≤ 0.25 mm i.d.) columns, which reduce peak widths and shortened total run times to few minutes¹¹⁷. Another recently applied technology is the low-pressure vacuum outlet gas chromatography (LPGC), which speeds the analyte separation by applying a vacuum to the column in GC to generate a greater pressure drop than possible with the outlet at atmospheric pressure¹¹⁶.

In conclusion, by combining suitable extraction methods to efficient chromatographic procedures and mass analysers, wider scope analytical methods can be developed, allowing the most reliable determination of pesticide residues and identifying non-targeted compounds (e.g. contaminants and their metabolites) potentially present in the food samples.

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Table 7.1. Overview of typical analytical procedures used for the determination of pesticides by GC-MS techniques in food of animal origin

Pesticide	Sample type (g, mL)	Extraction procedure	Clean-up	Analytical column	Instrumental analysis	Recovery (%)	Ref.
22 OCs	Fish (5)	PLE	GPC	BPX-50 (30 m × 0.25 mm, 0.25 µm)	GC-EI-TOF-MS	71-113	14
11 OCs	Honey (0.5)	DLLME	-	Zebtron ZB 5-MS (30 m x 0.25 mm, 0.25 µm)	GC-MS	35-83	20
18 OCs	Honey (20)	PLE	SPE aluminum/silica (methylene chloride/n-hex 1:1)	DB-5MS (30 m x 0.25 mm, 0.25 µm)	GC-IT-MS	60-85	17
15 OCs	Honey (5)	DLLME	-	Heliflex AT TM -5MS (30 m × 0.25 mm, 0.25 µm)	GC-EI-IT-MS/MS (SIM)	81-117	75
OPs	Honey (10)	CME-UABE	-	VF-5MS (25 m × 0.25 mm, 0.25 µm)	GC-EI-IT-MS	90-107	25
OPs + Py	Beef, chicken, eggs, milk, fish (0.1-0.3)	SLE (n-Hex:DCM 2:1)	SPE basic Al + C18	DB-5ms (15 m x 0.25 mm x 0.1 µm)	GC-ECNI-MS/MS	27-128	47
Py	Bovine Milk (5)	LLE-LTP (ACN)	-	OV-5 (15.0 m × 0.25 mm × 0.1 µm) DB-5ms (30 m x 0.25 mm x 0.25 µm)	GC-ECD GC-MS/MS	87-100	108
50 Multiclass	Meat (2.5)	“dilute and shoot” (EtAc)	Florisil	DB-5 MS (30 m × 0.25 mm, 0.25 µm)	GC-APCI-QTOF-MS	70-120	6
34 Multiclass	Milk and cream (4)	GPC	SPE PSA+GCB (acetone/toluene)	HP5 ms (30 m x 0.25 mm, 0.25 µm) coupled to BPX-50 (1.5 m x 0.15 mm, 0.15 µm)	GCxGC-TOF-MS	66-84	44
174 Multiclass	Egg (5)	MSPD (Cyclohexane/EtAc)	GPC + SPE C18 and PSA (ACN)	HP5 ms (30 m x 0.25 mm, 0.25 µm)	GC-EI-QqQ-MS/MS	70-120	9
14 Multiclass	Milk (15)	QuEChERS	d-SPE MgSO ₄ , C18 and PSA	Rtx-5MS (30 m x 0.25 mm, 0.25 µm)	GC-MS	72-99	57
25 Multiclass	Beef, cattle liver, chicken, fish and milk (5)	SLE (NaCl)	SPE AL ₂ O ₃ (acetone-n-hex 1:1) n-Hex +	DB-1701 MS (30 m × 0.25 mm, 0.25 µm)	GC-EI-MS (SIM)	68-111	8
80 Multiclass	Egg and meat (5)	QuEChERS	d-SPE C18 (ACN)	HP-5MS UI (15 m × 0.25 mm, 0.25 µm) coupled to HP-5MS UI (15 m × 0.25 mm, 0.25 µm)	GC-QqQ-MS/MS	70-120	40
28 Multiclass	Honey (10)	SLE (Water)	SPE Florisil (methylene chloride/n-hex (80:20, v/v) and n-hex/acetone (60:40, v/v))	RT-5MS (30 m × 0.25 mm, 0.1 µm)	GC-IT-MS/MS	75-102	48
4 Multiclass	Honey (22)	LLE-LTP	Florisil	HP-5 (30 m × 0.25 mm, 0.1 µm)	GC-EI-MS (SIM)	93-101	60
53 Multiclass	Honey (1)	SLE (MeOH+citrate)	Florisil (EtAc:hexane 1:1.25)	HP5 ms (30 m x 0.25 mm, 0.25 µm)	GC-MS	30-128	49
22 Multiclass	Honey (3)	MEPS	-	NST-05MS (30 m × 0.25 mm, 0.25 µm)	GC-EI-MS	82-114	21

80 Multiclass	Honey (5), honeybees (10) and pollen (2)	QuEChERS	d-SPE PSA and C18	DB-XLB (30 m x 0.25 mm, 0.25 µm)	GC-EI-TOF-MS	60-120	76
109 Multiclass	Meat and fish (10)	PLE	GPC	DB-5MS (30 m x 0.25mm, 0.25 µm)	GC-EI-MS (SIM)	63-108	16
9 Multiclass	Eggs (0.25)	MSPD with Florisil (ACN)	SPE-C18	DB-5ms (30 m x 0.25 mm x 0.25 µm)	GC-EI-MS	62-95	118
192 Multiclass	Meat of beef, pig, poultry (5)	QuEChERS	d-SPE	DB-5ms (15 m x 0.53 mm x 1 µm)	LPGC-MS/MS	70-120	32
Multiclass	Milk (20), Honey (20)	SPE-C18 + DLLME	-	CP-Sil 8 CB (50 m x 0.25 mm x 0.25 µm)	GC-MS	66-99	101

Table 7.2. Overview of typical analytical procedures used for the determination of pesticides by LC-MS techniques in food of animal origin

Pesticide	Sample type (g, mL)	Extraction procedure	Clean-up	Analytical column	Instrumental analysis	Recovery (%)	Ref.
14 OPs	Honey, pollen and honey bee (3)	QuEChERS	d-SPE C18 (ACN 1% acetic acid)	Kinetex C18 (100 x 4.6 mm, 5.0 µm)	HPLC-ESI-QqQ-MS/MS	-	39
6 OPs	Fish tissue (5)	“Dilute and shoot” (ACN)	SPE NH ₂ cartridge	Atlantis T3 C18 (2.1 x 150 mm, 3.0 µm)	HPLC-ESI-QqQ-MS/MS	80-99	84
CBs + OPs	Meat, eggs, cheese, seafood (10)	QuEChERS	d-SPE	Synergi MAX-RP-80A (50 mm x 2 mm x 4 µm)	HPLC-MS/MS	81-111	30
CBs	High fat cheese (3)	QuEChERS	d-SPE	ZORBAX ECLYPSE plus RRHD (50 mm x 2.1 mm x 1.8 µm)	UHPLC-MS/MS	70-115	119
5 Neonicotinoids	Honey (2)	SPE-DLLME	-	Spherisorb ODS2 C18 (150 x 4 mm, 5.0 µm)	LC-APCI-IT-MS/MS	90-103	23
13 Neonicotinoids	Honey and honey bee (2)	Incubate (30 min) + SLE (ACN:EtAc (8:2, v/v)) (for honey bee) Incubate (30 min) + SLE (ACN:EtAc (8:2, v/v))+ACN 20% of TEA) (for honey)	SPE Sep-Pak Alumina N Plus Long (for honey bee) SPE Strata X-CW (for honey)	Luna C18 (100 x 2.0 mm, 3.0 µm)	HPLC-ESI-QqQ-MS/MS	85-112	85
7 Neonicotinoids	Honey (5)	DLLME	-	Zorbax Eclipse XDB-C18 (50 x 4.6 mm, 1.8 µm)	LC-multimode interface-QqQ-MS/MS	74-114	18
7 Neonicotinoids	Honey (5-15)	DLLME (Sample: 5 g) QuEChERS (Sample: 15 g)	- d-SPE PSA and MgSO ₄	Zorbax Eclipse XDB-C18 (50 x 4.6 mm, 1.8 µm)	LC-multimode interface-QqQ-MS/MS	69-113 72-95	19
13 Neonicotinoids	Honey bees and bee products (15)	QuEChERS (ACN (2% triethylamine))	d-SPE PSA and MgSO ₄ + SPE C18 (ACN (2% triethylamine))	Acquity HSS T3 column (10 cm x 2.1 mm, 1.8 µm)	UHPLC-ESI-QqQ-MS/MS	35-145	86
6 Neonicotinoids	Honey (5)	QuEChERS	d-SPE PSA and MgSO ₄	Hypersilgold C18 (50 x 2.1 mm, 1.9 µm)	UHPLC-HESI-QqQ-MS/MS	75-114	90
4 Neonicotinoids	Honey (1)	QuEChERS	d-SPE PSA and MgSO ₄	Zorbax Eclipse XDB-C18 (250 x 4.6 mm, 5.0 µm)	LC-ESI-QTRAP-MS/MS	-	52
10 Neonicotinoids	Honey (5)	QuEChERS	d-SPE PSA and MgSO ₄	Synergi Fusion RP C18 (50 x 2 mm, 4.0 µm)	HPLC-ESI-QqQ-MS/MS	60-114	51
7 Neonicotinoids, 6 metabolites	Honey (2)	SLE (ACN:EtAc 4:1 + TEA)	SPE - Strata X-CW	LUNA C18 100A (100 mm x 2 mm x 3 µm)	LC-MS/MS	85-112	85
7 Neonicotinoids	Honey (15)	QuEChERS (ACN)	d-SPE	ZORBAX ECLYPSE XDB-C18 (50 mm x 4.6 mm x 1.8 µm)	HPLC-DAD	70-120	69
	Honey (0.5)	DLLME (ACN:DCM 1:4)	—				

7 Neonicotinoids	Muscle and liver (2.5)	PLE	SPE Oasis HLB (MeOH)	Symmetry Shield™ RP C18 (150 × 2.1 mm, 3 μm)	HPLC-ESI-QqQ-MS/MS	83-102	15
7 Neonicotinoids	Eggs, chicken, pork (1)	SLE (ACN)	SPE-HLB	HSS T3 (100 mm x 2.1 mm x 1.8 μm)	UHPLC-ESI-MS/MS	80-103	110
4 Neonicotinoids	Bovine milk (5)	SPE (DCM)	Diatomaceous earth - Chem Elute	Synergi Hydro-RP-C18 (250 mm x 4.6 mm x 4 μm)	HPLC-DAD	85-100	114
>350 Multiclass	Honey (2.5)	“Dilute and shoot” (ACN 1 % formic acid, v/v)	-	Hypersil GOLD aQ C18 column (100 × 2.1 mm, 1.7 μm)	UHPLC-ESI-Exactive-Orbitrap-MS	60-120	5
83 Multiclass	Honey (5)	QuEChERS	-	Xterra C18 (150 × 2.1 mm, 5.0 μm)	HPLC-ESI-Q-Exactive-MS/MS LC-Exactive-MS	53-114	53
115 Multiclass	Honeybees, honey and bee pollen (1)	QuEChERS	d-SPE PSA and MgSO ₄ + SPE Extra Bond C18 (ACN)	Zorbax Eclipse XDB-C18 (2.1 × 150 mm, 3.5 μm)	LC-ESI-QqQ-MS/MS	59-117	87
13 Multiclass	Honey (1)	LLE	-	Atlantis™ dC18 (100 x 2.1 mm, 3.0 μm)	HPLC-ESI-QTRAP-MS/MS	63-117	94
30 Multiclass	Honey (5)	QuEChERS	n-Hex	Kinetex C18 (50 x 2.1 mm, 1.7 μm)	UHPLC-ESI-QqQ-MS/MS	34-86	88
80 Multiclass	Honey (5), honeybees (10) and pollen (2)	QuEChERS	d-SPE PSA and C18	Nucleodur Sphinx RP-C18 (50 x 2 mm, 1.8 μm)	HPLC-ESI-QqQ-MS/MS	60-120	76
3 Multiclass	Honey (10)	QuEChERS	d-SPE PSA and MgSO ₄	XTerra C18 (50 × 3 mm, 3.5 μm)	LC-ESI-QqQ-MS/MS	90-120	70
9 Multiclass	Honey (10)	QuEChERS	d-SPE PSA and MgSO ₄	XTerra (50×3 mm, 3.5 μm)	LC-APCI-QqQ-MS/MS	70-112	50
30 Multiclass	Honey (1)	QuEChERS	d-SPE	Poroshell 120 EC-C18 (3 x 100 mm, 2.7 μm)	LC-ESI-QqQ-MS/MS	80-110	33
12 Multiclass	Honey (1.5)	QuEChERS	d-SPE PSA and MgSO ₄	Luna C18 (250 x 4.60 mm, 5.0 μm)	LC-APCI-IT-MS/MS	87-98	42
7 Multiclass	Honey and pollen (1)	SPE Florisil (MeOH)	-	Symmetry Shield (150 × 2.1 mm, 3.5 μm)	HPLC- HESI-QqQ-MS/MS	90-102	11
54 Multiclass	Fish and honey (1)	QuEChERS	d-SPE PSA, anhydrous MgSO ₄ and GCB	Kinetex XB-C18 (5 × 2.10 mm, 1.7 μm)	UHPLC-HESI-LTQ-Orbitrap-MS/MS	70-100	45
13 Multiclass	Fish muscle (3)	QuEChERS	n-Hex	Zorbax Eclipse C18 (50 × 2.1 mm, 1.8 μm)	LC-ESI-QTRAP-MS/MS	6-110	95
82 Multiclass	Fish (5)	SLE (ACN/water (80:20, v/v) 0.1% formic acid)	-	Acquity UHPLC BEH C18 (2.1 × 100 mm, 1.7 μm)	UHPLC-ESI-QTOF-MS/MS	-	38
228 Multiclass	Fish (20)	QuEChERS	d-SPE	HSS T3 (50 mm x 2.1 mm x 1.8 μm)	UHPLC-MS/MS	70-120	31
18 Multiclass	Egg (5) and egg products (2.5)	QuEChERS	d-SPE PSA, C18, GCB and MgSO ₄	Kinetex C18 (100 x 3 mm, 2.6 μm)	HPLC-ESI-QqQ-MS/MS	71-95	82

174 Multiclass	Egg (5)	MSPD (cyclohexane/EtAc)	GPC + SPE C18 (MeOH 0.5 % acetic acid)	Zorbax Eclipse plus-C18 (2.1 × 100 mm, 3.5 µm)	HPLC-ESI-QqQ-MS/MS	70-120	9
80 Multiclass	Eggs and meat (5)	QuEChERS	n-Hex + d-SPE C18 (ACN)	Acquity UPLC BEH C18 (2.1 × 100 mm, 1.7 µm)	LC-Turbo spray-QTRAP-MS/MS	74-121	40
>350 Multiclass	Meat (2.5)	“dilute and shoot” (ACN 1 % formic acid, v/v)	-	Hypersil GOLD aQ C18 column (100 × 2.1 mm, 1.7 µm)	UHPLC-ESI-Exactive-Orbitrap-MS	70-120	6
128 Multiclass	Meat (2)	QuEChERS	d-SPE ODS and MgSO ₄	Zorbax Eclipse Plus C18 (100 × 2.1mm, 1.8 µm)	UHPLC-ESI-QqQ-MS/MS	70-120	91
192 Multiclass	Beef, pig, poultry meat (5)	QuEChERS	d-SPE	Hypersil C18 (150 x 2.1 mm, 5.0 µm)	LC-ESI-QqQ-MS/MS	70-100	32
118 Multiclass	Milk (10), liver (1) and muscle tissue (5)	QuEChERS	d-SPE PSA and C18 (only for liver)	BEH C18 (100 mm x 2.1 mm x 1.7 µm)	UHPLC-MS/MS	70-120	43
48 Multiclass	Milk (10)	SPE C18 (MeOH)	-	Hypersil Gold AQ C18 (2.1 x 50 mm, 1.9 µm)	UHPLC-HESI-Exactive-Orbitrap-MS	-	10
28 Multiclass	Milk, baby food and meat (1)	“dilute and shoot” (MeOH 1% formic acid, v/v)	-	Acquity UPLC™ BEH C18 (100 × 2.1 mm, 1.7 µm)	UHPLC-ESI-QqQ-MS/MS	<30-129	83
31 Multiclass	Milk (15)	LLE (ACN)	SPE C18 (ACN)	ZIC-pHILIC (150 mm x 4.6 mm, 5 µm)	LC-ESI-QqQ-MS/MS	70-120	41
40 Multiclass	Milk, yogurt and cheese (5)	SLE (ACN:EtAc:acetic acid (49.5:49.5:1, v/v/v))	Low temperature + SPE Oasis HLB (MeOH:ACN:ammonium hydroxide (47.5:47.5:5, v/v/v))	SB-C18 (2.1 x 150mm, 5.0 µm)	HPLC-ESI-QTRAP-MS/MS	62-107	55
36 Multiclass	Milk and other matrices (2-10)	QuEChERS	d-SPE PSA and C18	ZORBAX SB-C18 (100 × 2.1 mm, 3.5 µm)	LC-ESI-QqQ-MS/MS	67-107	97
333 Multiclass	Baby food (meat-based food and milk-based formulae) (5)	QuEChERS (ACN:water (84:16, v/v))	-	Accucore C-18 aQ (100 × 2.1 mm, 2.6 µm)	UHPLC-HESI-Q-Orbitrap-MS/MS	80-111	54
Transformation products	Honey and meat (2.5)	“dilute and shoot” (ACN 1 % formic acid, v/v) or QuEChERS	d-SPE PSA and GCB	AccuCore C-18 aQ (100 × 2.1 mm, 2.6 µm)	UHPLC-HESI-Q-Orbitrap-MS/MS	80-111	54
				Hypersil GOLD aQ C18 column (100 × 2.1 mm, 1.7 µm)	UHPLC-ESI-Exactive-Orbitrap-MS	-	46

Figure 7.1. GC-IT/MS (SIM) chromatogram of organochlorine pesticides spiked at 1 µg/L (corresponding to 20 ng/g) in pooled honey sample after DLLME. Peak identification: (1) etridiazole; (2) chloroneb; (3) propachlor; (4) trifluralin; (5) hexachlorobenzene; (6) chlorothalonil; (7) chlorpyrifos; (8) cyanazine; (9) DCPA; (10) trans-chlordane; (11) cis-chlordane; (12) trans-nonachlor; (13) chlorobenzilate; (14) cis-permethrin; (15) trans-permethrin.

(Reprinted with permission from Zacharis, C. K. et al. Dispersive liquid-liquid microextraction for the determination of organochlorine pesticides residues in honey by gas chromatography-electron capture and ion trap mass spectrometric detection. Food Chem. 2012, 134 (3), 1665–1672)

Figure 7.2. Identification of 2,6-dichlorobenzamide in honey ($[M + H]^+ = 189.9821$, $m/z \pm 8$ ppm).

(Reprinted from Cotton, J. et al. High-resolution mass spectrometry associated with data mining tools for the detection of pollutants and chemical characterization of honey samples. *J. Agric. Food Chem.* 2014, 62 (46), 11335–11345)

List of Abbreviations

AChE	Acetylcholinesterase
ACN	Acetonitrile
APCI	Atmospheric pressure chemical ionization
CBs	Carbamates
CME-UABE	Coacervation microextraction ultrasound-assisted back-extraction technique
CRMs	Certified Reference Materials
DAD	Diode array detector
DCPA	Dimethyl 2,3,5,6-tetrachloro-1,4-benzenedicarboxylate
DLLME	Dispersive liquid-liquid microextraction
d-SPE	Dispersive solid phase extraction
ECD	Electron capture detector
EFSA	European Food Safety Authority
EI	Electron impact
EQC	External quality control
ESI	Electrospray ionisation
EtAc	Ethyl acetate
EU	European Union
GC	Gas chromatography
GCB	Graphitized carbon black
GCxGC	Two-dimensional or comprehensive GC
GPC	Gel permeation chromatography
HILIC	Hydrophilic interaction liquid chromatography
HRMS	High-resolution mass spectrometry
HS-SPME	Headspace-SPME
IQC	Internal quality control
IT	Ion trap
K_{ow}	Octanol-water partition coefficient
LC	Liquid chromatography
LLE	Liquid-liquid extraction
LLE-LTP	Liquid-liquid extraction with purification at low temperature
LOQ	Limit of quantification
LPGC	Low pressure gas chromatography
LRMS	Low-resolution mass spectrometry
MeOH	Methanol
MEPS	Microextraction in packed sorbent
MgSO ₄	Magnesium sulfate
MRLs	Maximum residue levels
MS	Mass spectrometry
MS/MS	Tandem mass spectrometry
MSPD	Matrix solid-phase dispersion
Na ₂ SO ₄	Sodium sulfate
NaCl	Sodium chloride
NCI	Negative chemical ionization

<i>n</i> -Hex	<i>n</i> -hexane
NPD	Nitrogen-phosphorus detector
OCs	Organochlorines
OPs	Organophosphates
PAD	Photodiode array detector
PCBs	Polychlorinated biphenyls
PCI	Positive chemical ionization
PLE	Pressurized liquid extraction
PSA	Primary secondary amine
PT	Proficiency testing
Py	Pyrethroids
QqQ	Triple quadrupole
Q-TOF	Quadrupole/TOF
QuEChERS	Quick, Easy, Cheap, Effective, Rugged and Safe
SBSE	Stir bar sorptive extraction
SFE	Supercritical fluid extraction
SIM	Selected ion monitoring
SLE	Solid-liquid extraction
SPE	Solid phase extraction
SPME	Solid-phase microextraction
TOF	Time-of-flight
UHPLC	Ultra-high-performance liquid chromatography
VWD	Variable wavelength detector