High-resolution Mass Spectrometry for the Analysis of Pesticide Residues in Food

Juan F. García-Reyes, Bienvenida Gilbert-López, David Moreno-González, Miriam Beneito-Cambra, and Antonio Molina-Díaz
Analytical Chemistry Research Group, University of Jaén, Jaén, Spain

This article addresses the use of high-resolution mass spectrometry (HRMS) in the field of pesticide testing in food. The societal interest and concerns on the presence of pesticide residues in food has triggered the interest toward the development of more comprehensive methods that enable a faster and more effective control of the chemicals. For this purpose, the introduction of HRMS in this field, first with the development of time-of-flight (TOF) instrumentation with enhanced quantitative capabilities along with the introduction of Orbitrap technology has opened new possibilities in the last decade, and nowadays constitute an attractive and versatile alternative to current targeted pesticide residue methods relying on liquid chromatography-tandem mass spectrometry (LC-MS/MS) and gas chromatography-tandem mass spectrometry (GC-MS/MS) with triple quadrupole analyzer (QQQ).

1 INTRODUCTION

The application of pesticides is one of the main practices to protect agricultural crops against weeds, pest, and diseases, and to ensure crop yields and quality in order to supply food worldwide. Although the use of agrochemicals is controlled through good agricultural practices, pesticide residues may well be present in plant-origin foodstuffs. Pesticide residue control is, thus, central, not only to secure crop quality and for official trade control purposes but also to protect human health.[1] Several regulations address this issue worldwide.[2–5] For instance, European Commission Regulation 396/2005 lists over 150 000 maximum residue levels (MRLs) for pesticides in 380 defined plant-origin commodities (http://www.pesticides-online.com/).[6–9]

Owing to the international trade of fruits and vegetables and the lack of worldwide harmonized regulations on the use of pesticides, the development of comprehensive screening methods for analyzing hundreds of pesticides and other banned chemicals in a unique assay is very convenient. From the scientific point of view, pesticide residue analysis is a relevant and challenging application of mass spectrometry. It requires the simultaneous detection of a plethora of species with a broad range of physicochemical properties. For the assessment of pesticides in food, laboratories usually rely on targeting a list of *ca*. 200–300 liquid chromatography and gas chromatography (GC)-amenable compounds, typically those more widely used or more frequently detected. The standard approach for LC-amenable compounds consists of a method using LC-MS/MS operated in the multiple reaction monitoring (MRM) mode, which remains the gold standard for the quantitative targeted analysis of a limited number of species due to its robustness, ease-of-use, extended dynamic range, and reliability. The technical progress and advances in instrumentation (e.g. software for automated MS/MS (tandem mass spectrometry) transitions optimization, reduced dwell times, enhanced separation capability using ultra high-performance liquid chromatography (UHPLC)) enable the monitoring of up to 300–400 compounds in a single run. On the other hand, the detailed prior knowledge of the method parameters (retention time, optimized MS/MS transitions, and collision energies) required in advance for each analyte sought is probably the main limitation of this approach. Method development requires studies with analyte reference standards prior to the actual sample. Therefore, LC-MS/MS (MRM) methods are blind to compounds not included (e.g. untargeted species such as pesticide metabolites,

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unauthorized agrochemicals, and/or their impurities) in the acquisition method.

The need for a comprehensive examination of hundreds of pesticides in food has recently triggered the development of the so-called *screening methods*,[10–12] which were officially introduced in the guidance document on analytical quality control and method validation procedures for pesticide residues and analysis in food and feed in 2012.[13] According to this document, screening methods provide laboratories a cost-effective approach to extend the method scope to analytes which potentially have a low probability of being present in the samples. Analytes that occur more frequently should yet be sought using carefully validated quantitative multiresidue methods. Liquid chromatography high-resolution mass spectrometry (LC-HRMS) has shown to be an effective approach to screen food samples for the presence of a higher (than QQQ) number of analytes. The use of HRMS instrumentation (Orbitrap and TOF) with either GC or LC separations allows accurate mass measurements and, thus, the effective screening and identification/confirmation of a theoretically unlimited number of compounds. This unique feature of HRMS instrumentation is remarkably convenient for food safety testing. Amongst the experiments that can be accomplished using HRMS, we should highlight the use of 'universal' accurate-mass databases for standard-free identification of pesticides and also the retrospective examination of former data for compounds not originally sought, but, that for some reason, become interesting.[14] With the recent advances of HRMS instrumentation, these attractive features are no longer associated with poor quantitative performance. Nowadays, the performance of HRMS instrumentation in terms of linearity, precision, repeatability, and ruggedness is comparable to that attainable with QQQ technology. In parallel with LC-HRMS, a growing interest has arisen in the development and application of GC-HRMS, particularly with the introduction of atmospheric pressure gas chromatography–mass spectrometry (GC-MS) sources and Orbitrap technology,[15] which provides this system the ability to cover a broader range of species, enabling both targeted and retrospective suspect screening analysis in a single GC-MS platform, overcoming most interferences usually common in GC-MS and GC-MS/MS low-resolution systems.

In this article, an overview of HRMS applications in the field of pesticide testing in food is presented. The societal interest and concerns on the presence of pesticide residues in food has triggered the interest toward the development of more comprehensive methods that enable a faster and more effective control of the chemicals. For this purpose, the introduction of HRMS has created a paradigm shift in this field. The development of TOF instrumentation with enhanced quantitative capabilities along with the introduction of Orbitrap technology has opened new possibilities in the last decade, and nowadays constitutes an attractive and versatile alternative to current targeted pesticide residue methods using LC or GC-(QQQ) MS/MS. The workflows enabled by HRMS methods do not have the boundaries related to information required and availability of standards that MS/MS (MRM) do suffer, permitting flexible acquisition schemes where both targeted and untargeted analysis are feasible.[16]

2 FUNDAMENTALS AND BASIC CONCEPTS OF MODERN HIGH-RESOLUTION MASS SPECTROMETRY

A brief summary of selected terms associated to HRMS used onward is provided in Table 1. Mass spectra can be acquired at either low or high resolution. This will depend on the instrumentation and experiment used. Typical low-resolution MS experiments, typically performed using triple quadrupole or ion trap instruments, provide information of the nominal mass of the ionized species (integer mass). In contrast, high resolution enables the measurement of ions with 3–5 decimal place accuracy. This accuracy has implications in many aspects, but perhaps, the more significant one is the ability to assign elemental compositions in organic molecules. Organic molecules are composed mainly by carbon, hydrogen, oxygen, and nitrogen atoms along with other elements in less extension such as sulfur, fluorine, or chlorine. Although the number of protons in an atom of an element is constant, atoms have different isotopes because the number of neutrons in the nucleus of the atom may vary, and thus, each of these stable isotopes has a different exact mass. For example, ^{12}C always has 6 protons and 6 neutrons, ^{16}O has 8 of each and ^{1}H only one proton. Although the number of nucleons of $^{12}CH_4$ and ^{16}O is the same, the exact mass of each species is different (16.03176 vs 15.9994 Da). This should be attributed to mass defects, the missing mass that corresponds to the energy released (*nuclear binding energy*) when the actual nucleus was formed (using Einstein's $E = mc^2$). This mass defect is unique to each individual stable isotope given its properties. Therefore, each combination of the different elements (and isotopes) that typically occurs in organic compounds (C_x,H_Y,N_Z,O_W, …) yield different and 'quantized' exact masses (monoisotopic masses, if the more abundant isotopes are used for the calculation).

Consequently, if we are able to measure with an instrument – providing high mass accuracy – the very exact mass of a molecule in the gas-phase (a previous ionization step

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Table 1 Concepts frequently used in high-resolution mass spectrometry

Term	Definition
Exact mass	Theoretically calculated mass of an ion or molecule with specified isotopic composition
Accurate mass	Experimentally determined mass of an ion of known charge. It can be used to determine elemental composition to within limits defined by both the accuracy and precision of the measurement. Note that accurate mass and exact mass are not synonymous. *Accurate mass* refers to a measured mass, and *exact mass* refers to a (theoretically) calculated mass based on the tabulated masses of the different isotopes
Mass accuracy	Difference between the mass measured by the mass analyzer (*accurate mass*) and the expected theoretical value (*exact mass*). It is usually expressed in *parts per million* (ppm)
Nominal mass	Mass of a molecular ion or molecule calculated using the mass of the most abundant isotope of each element
Parts per million (ppm)/relative mass error	It is a dimensionless unit for *mass accuracy*. It is also known as relative mass error. For a given ion measured, it is calculated as follows: *Mass accuracy* in ppm = [[accurate mass – exact mass]/exact mass] × 10^6
Monoisotopic mass	Exact mass of an ion or molecule calculated using the mass of the most abundant isotope of each element (typically the lightest)
Average mass	Mass of an ion or molecule weighted for its isotopic composition, i.e. the average of the isotopic masses of each element, weighted for isotopic abundance
Resolution or mass resolving power	Measure of the ability of a mass analyzer to distinguish two signals of slightly different m/z values. The full-width at half maximum (FWHM) definition (based on a single ion) is nowadays more widely used than the 10% valley (based on two peaks of equal height) It is expressed as $m/\Delta m$, where, m is the mass of the ion of interest, and/Δm is the ion peak m/z width at half height
Mass defect	Difference between the nominal mass and the monoisotopic mass of an atom, molecule, or ion. It can be a positive or negative value dependent upon the elemental composition
Isobar (*in mass spectrometry*) or isobaric species	Atomic or molecular species with the same nominal mass but different exact masses
Unified atomic mass unit (u)	The term atomic mass unit (amu) is deprecated. The term Thompson (*Th*) is also deprecated. Use either u symbol or Da

is required in mass spectrometry experiment), we may predict its elemental composition/molecular formula. For this purpose, the so-called isotopic signatures are also highly useful to further reduce the tentative elemental compositions and even to confirm the actual one. Once the molecules become larger and heavier with a higher number of atoms, the possible combinations of elements become larger so that the actual exact masses (if a mass accuracy of 0.0001 Da is used) are no longer quantized. Consequently, there are several element combinations that lead to the same exact mass, so that the use of high resolution and accurate mass measurements do not allow the unambiguous assignment of a unique elemental composition.

This fact is illustrated in Figure 1, where the number of possible elemental compositions is charted for different m/z values (192, 395, and 873). When HRMS is used (accuracy better than 0.001 m/z units) in relatively low molecular weight compounds (200 Da or below), there is a reduced number of fitting elemental compositions. In contrast, higher m/z values lead to larger number of possible elemental compositions. Note that this example was calculated using only isotopes from main atoms (C, H, N, and O). For a model molecule such as reserpine (Mw 608), and calculating only considering C, H, N, and O, the number of possible elemental compositions varied from above two hundred combinations using low resolution (quadrupole) (e.g. 0.1 m/z mass accuracy to only two candidates). This feature makes mass spectrometry a powerful tool for structure elucidation and for confirmatory purposes in quantitative studies, especially considering the high sensitivity featured by mass spectrometry.

2.1 Selectivity in High-resolution Mass Spectrometry: Resolution, Mass Accuracy, Accurate Mass in Qualitative Analysis

The central role mass accuracy plays in HRMS is connected to the actual resolution of the mass spectrometers. Improvements in resolving power undoubtedly lead to an improvement in mass accuracy. The greater the number of ions that are detected, in a normally distributed peak, the more precise the centroid can be assigned, and thus, the better mass accuracy.[18] The progress of TOF technology has led to an increase of the resolving power in electrospray-TOF instruments from 5 000 to 10 000 (delivering 5–10 ppm mass accuracy with internal correction) in the late 1990s instruments to current 35 000–50 000 (full-width half maximum, FWHM) for m/z values >1000, with mass accuracies

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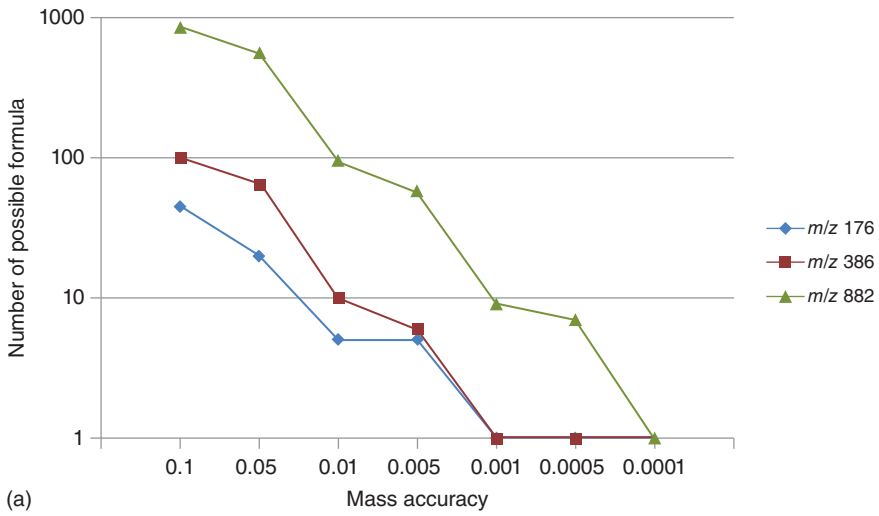

(a)

Mass accuracy, ppm	# of posible formula
165 (quad)	209
10	13
5	7
3	4
2	2

(b)

Figure 1 (a) Effect of the mass accuracy on the number of possible elemental compositions of organic molecules, limiting the type of elements to carbon, nitrogen, oxygen, and hydrogen. (b) Example of reserpine and the impact of mass accuracy on the number of possible elemental compositions.

in the 0.5–1 ppm range under optimum ion abundancies using continuous calibration systems. In the case of Q-Exactive Orbitrap (hybrid quadrupole-Orbitrap analyzer), mass accuracy is even more stable, and continuous calibration and mass correction is not required to deliver sub-2 ppm mass accuracy. If such correction is used, lower errors can be expected when the instrument is operated at resolution values above 100 000–150 000 (FWHM). All these improvements have impacted the criteria used for the application of mass spectrometry to regulatory analysis in food (e.g. pesticides, veterinary drugs) or clinical applications (e.g. sport drug testing).[19] Table 2 includes a summary of the criteria required for the confirmation of pesticide residues in incurred samples using different mass spectrometric methods including HRMS.[21] The accurate mass of a target ion is valuable information for its unambiguous identification. Modern instruments are able to provide very low mass errors, which allow a reliable confirmation. For instance, the DG SANTE establishes a tolerance in mass accuracy of 5 ppm as a reliable identification criterion, but frequently most of the modern HRMS instruments feature mass accuracies lower than 2–3 ppm.[20]

The main identification criterion is mass accuracy of precursor using a threshold of *ca*. 5 ppm and product ions from MS/MS experiments. Besides, additional information for confirmatory purposes is provided by isotopic signature of common elements with more than one stable isotope with significant abundances (e.g. Cl, Br, S, or even C). This isotopic signature represents an additional dimension of chemical information that is usually included in the qualitative analysis software of HRMS instrumentation as an isotopic fitting percentage.

Mass accuracy can be affected by different factors. Leaving aside the instrumental mass calibration aspects, which are important to deliver a stable mass accuracy performance, one of the main factors is the actual sample interrogated and the potential presence of coeluting isobaric matrix interferences, which can alter accurate mass measurements, resulting in either false-negative or false-positive results. Because of the large amount of matrix components present in food samples when using generic sample extraction procedures with limited cleanup steps such as QuEChERS or QuPPE, these coelutions are relatively frequent, especially when the number of pesticides included in the scope of the analytical method is high, as expected in HRMS methods.[22,23]

Chromatographic separation is often insufficient to overcome these interferences. Except in the case of isomers, higher mass resolutions may provide enhanced selectivity to discriminate between isobaric species (same nominal mass). In most cases, a resolution >30 000 (FWHM) is enough to distinguish the analyte from matrix interferences, although there are cases where the higher resolving power of the Orbitrap is required. The use of high-resolution acquisition (e.g. above 70 000 (FWHM)) enables the use of narrow windows to reconstruct ion chromatograms for a particular *m*/*z* value with a reduced bias of for instance ±5 ppm. This is shown in Figure 2, where the mass spectra of norfloxacin in a food matrix is shown with acquisitions at resolutions of *ca*. 10 000 and 100 000 (FWHM). The acquisition at higher resolution

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Table 2 Identification requirements for different MS techniques according to DG SANTE guidelines.[20]

MS detector/ characteristics	Typical systems (examples)	Acquisition	Requirements for identification	
			Minimum number of ions	Other
Unit mass resolution	Quadrupole, ion trap	Full-scan, limited m/z range, selected ion monitoring (SIM)	Three ions	$S/N \geq 3$[a] Analyte peaks in the extracted ion chromatograms must fully overlap. Ion ratio within ± 30% (*relative*) of average of calibration standards from the same sequence
MS/MS	Triple quadrupole, ion trap, Q-trap, Q-TOF, Q-Orbitrap	Selected or multiple reaction monitoring (MRM), mass resolution for precursor ion isolation equal to or better than unit mass resolution	Two product ions	
Accurate mass measure-ments	High-resolution MS: (Q-)TOF IT-TOF (Q-) Orbitrap FT-ICR-MS Sector MS	Full-scan, limited m/z range, SIM, fragmentation with or without precursor ion selection, or combinations thereof	Two ions with mass accuracy ≤ 5 ppm[b–d]	
		Combined single-stage MS and MS/MS with mass resolution for precursor ion isolation equal to or better than unit mass resolution	Two ions: one molecular ion, (de)protonated molecule, or adduct ion with mass accuracy ≤ 5 ppm, plus 1 MS/MS product ion[e]	

IT-TOF, hybrid ion trap-time of flight; FT-ICR, Fourier-transform ion cyclotron resonance; Q-TOF, hybrid quadrupole time-of-flight; TOF, time-of-flight.
[a]In case noise is absent, a signal should be present in at least five subsequent scans.
[b]Preferably including the molecular ion, (de)protonated molecule or adduct ion.
[c]Including at least one fragment ion.
[d]<1 mDa for $m/z < 200$.
[e]No specific requirement for mass accuracy.
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(above) revealed the presence of an interfering peak from the matrix coeluting at 6.4 min. When using a lower resolving power, the presence of this matrix component is not visible, and thus, an error is made as the integrated peak area and the quantitative data reported is higher than the true value. Therefore, the use of HRMS not only provides advantages in terms of qualitative analysis but also provides more reliable quantitative data.

3 HARDWARE: LIQUID CHROMATOGRAPHY HIGH-RESOLUTION MASS SPECTROMETRY AND GAS CHROMATOGRAPHY HIGH-RESOLUTION MASS SPECTROMETRY INSTRUMENTATION

The main HRMS available technologies so far have been TOF, Orbitrap, magnetic sector instruments (MSI), and Fourier-transform ion cyclotron resonance (FT-ICR). While the use of Orbitrap and TOF are widely extended for pesticide residue analysis, the number of FT-ICR, and MSI devoted to such application is scarce. FT-ICR is still a widely used technique as it still offers the ultimate in resolution (>1 M) for selected applications such as petroleomics and other ultra-high-resolution applications. The reason that FT-ICR is not widely used in this context is related to the relatively high acquisition time (not in the UHPLC scale) required to record spectra at resolving power above those attainable. The use of MSI has decayed because its reduced resolving power compared to FT instruments and the relatively low acquisition rate since it is a scanning instrument. For years, GC has been coupled to MSI instruments for many persistent organic pollutants (POPs) particularly dioxins such as including polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs). However, recently there has been a growing interest in GC-HRMS with TOF and Orbitrap mass analyzers partly associated with the higher resolving power and acquisition rate.

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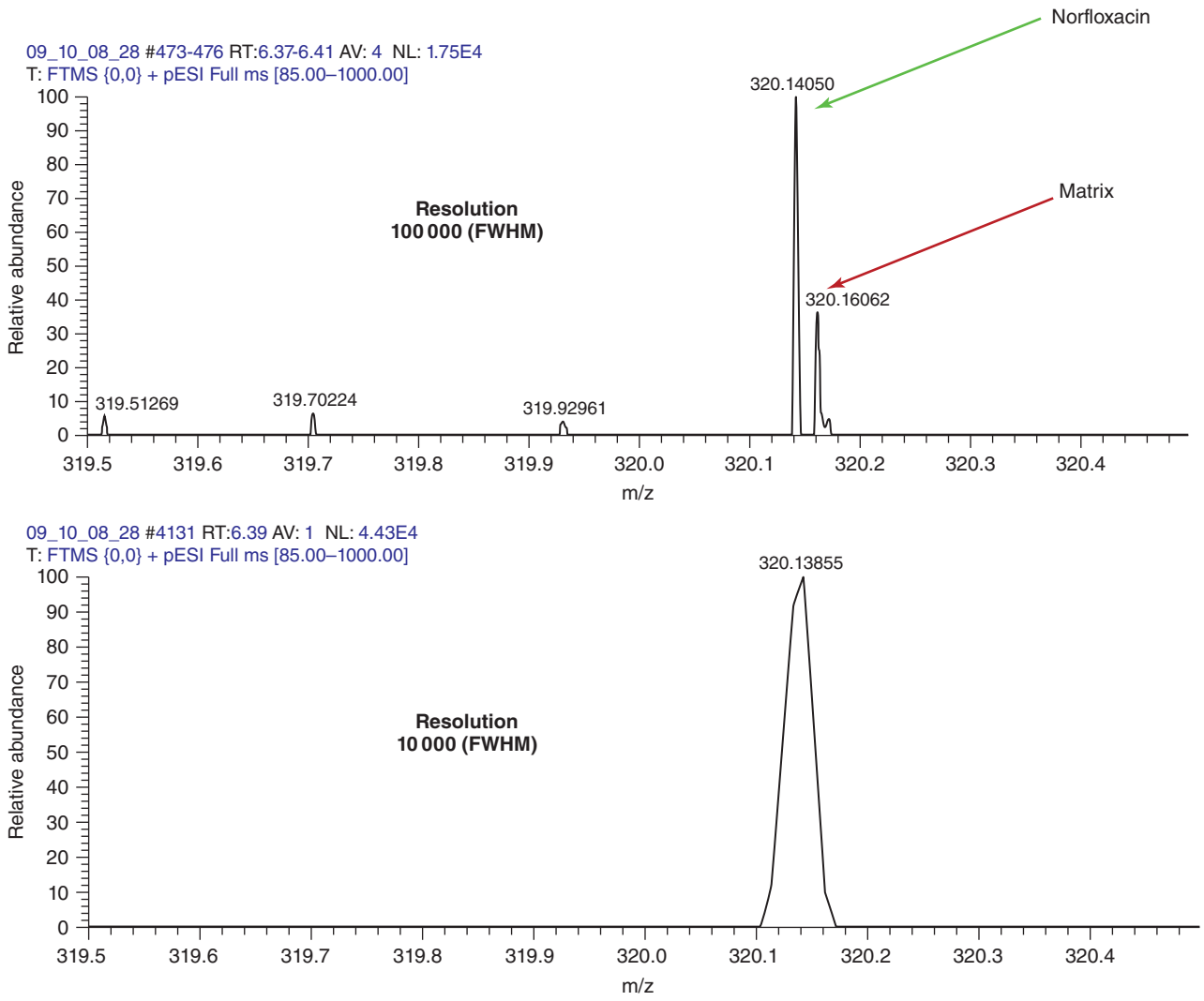

Figure 2 Illustration of the impact of HRMS acquisition on method selectivity. A case of a matrix isobaric coeluting species revealed only when using the Q-Exactive Orbitrap operated at a resolution of *ca*. 100 000 FWHM. (Reproduced with permission from Ref. 24. © Elsevier, 2012.)

Most of the HRMS instrumentation typically utilizes ionization sources operated at atmospheric pressure, mainly through electrospray ionization coupled to UHPLC as sample introduction device, although the use of GC combined with atmospheric pressure chemical ionization (APCI) ionization is also offered as an alternative. Recently, different vendors have launched dedicated electron impact GC-HRMS instruments (GC-QTOF-MS/MS and GC-Orbitrap), which is an indicator of the potential usefulness of such devices in different applications including food safety and environmental testing. Another realm that is being expanded in recent years is the combination of Q-TOF (hybrid quadrupole time-of-flight) technology with ion mobility spectrometry (IMS)[25–29] so that an additional dimension related to the shape of molecules (collisional cross section) is provided to enable the separation of the species of interest.

Besides details of electronic performance, particularly those related to the frequency at which TOF detectors operate and the ion acceleration and the pulse, the resolution of a TOF mass spectrometer depends heavily on the flight path length and the use of a reflectron. The latter reduces the spread in time of ions populations with the same m/z value.[18] In addition, it also duplicates (even multiplex) the flight path; and thus, the resolution, although sometimes at the expense of a decrease in the sensitivity. Current state-of-the-art TOF instruments deliver resolutions of up to 50 000 (FWHM) at m/z 1 000. It is important to provide the m/z value used to calculate the resolution since most of the vendors deliver resolution

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Table 3 Overview of the technical specifications and characteristic of some LC-high-resolution mass spectrometry analyzers including time-of-flight and Orbitrap

Analyzer	Manufacturer	Instrument name	Resolving power (FWHM defined at *m/z*)	*m/z* range	Mass accuracy (ppm)		Acquisition speed (Hz)	GC-HRMS available
					Internal calibration	External calibration		
Q-TOF	Bruker Daltonics	Impact II	50 000	50–20 000	<1	<3	50	Yes (through APCI)
		MaXis II	80 000	50–20 000	<0.6	<2	30 (MS), 10 (MS/MS)	Yes (through APCI)
	Waters	XEVO G2 Q-TOF	22 500 (*m/z* 956)	20–16 000	<1	–	30	Yes (through APCI)
		Synapt G2-S HDMS	50 000 (*m/z* 956)	20–100 000	<1	–	30	Yes (through APCI)
	Agilent	6550 Q-TOF	42 000 (*m/z* 2722)	50–10 000	<1	–	50	–
		7250 GC-QTOF	25 000 (*m/z* 272)	20–3000	<2	–	1–50	Yes (dedicated instrument)
	Sciex	X500R QTOF	35 000	5–40 000	<0.5	<2	100	–
		Triple TOF 5600	35 000	5–40 000	<0.5	<2	100	–
		Triple TOF 6600	40 000	5–40 000	<0.5	<2	100	–
Ion trap-TOF	Shimadzu	LC-MS-IT-TOF	10 000 (*m/z* 1000)	50–5000	3	5	10	–
Orbitrap	Thermo	Exactive	100 000	50–4000	<1	<5	12 Hz at RP 17 500 (*m/z* 200)	
Q-Orbitrap		Q-Exactive Focus	70 000 (*m/z* 200)	50–4000	<1	<5	12 Hz at RP 17 500 (*m/z* 200)	–
		Q-Exactive	140 000 (*m/z* 200)	50–4000	<1	<5	12 Hz at RP 17 500 (*m/z* 200)	–
		Q-Exactive HF	240 000 (*m/z* 200)	50–6000	<1	<3	40 Hz at RP 17 500 (*m/z* 200)	–
		Q-Exactive (GC)	100 000 (*m/z* 272)	50–3000	<1	<3	12 Hz at RP 17 500 (*m/z* 200)	Yes (dedicated instrument)
Tribrid-Orbitrap		Orbitrap Fusion Lumos tribrid	500 000 (*m/z* 200)	50–6000	<1	<3	18 Hz at RP 17 500 (*m/z* 200)	–

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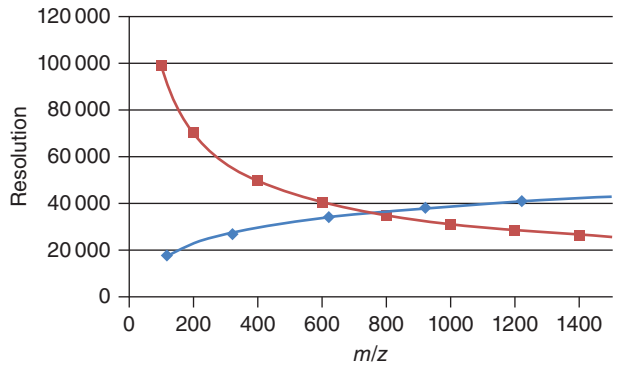

Figure 3 Dependence of the resolution of *m*/*z* for Q-Exactive Orbitrap (red line) and time-of-flight (blue line). (Reproduced with permission from Ref. 21. © Elsevier, 2016.)

values using higher *m*/*z* ratios (e.g. above 1000) than those typically found in pesticide analyses.

Resolution in Orbitrap strongly depends on the mass-to-charge ratio and the acquisition time. In this case, the resolution at which an ion is measured is inversely proportional to the square root of its *m*/*z*. Resolution is increased at higher acquisition time. To some extent, it is similar to a TOF since the harmonic oscillation of the ions trapped inside the Orbitrap originate an effective path length much longer than that from TOF instruments. The longer they are kept in the trap, the higher the resolution. Likewise, TOF are designed with a longer flight tube, which sometimes makes that the instrument cannot be designed as a benchtop unit.

TOF technology provides higher resolution at higher *m*/*z* ratios since the mass spectrum peak width did not change significantly at different *m*/*z* ratios. Therefore, considering the FWHM formula, the higher the *m*/*z* value, the higher the resolving power calculated. In contrast, Orbitrap technology performs the other way around. Higher *m*/*z* ratio leads to lower resolution. Orbitrap instruments render the highest resolution for low *m*/*z* ions (e.g. *m*/*z* 200), which are similar to those usually expected in pesticide residue analysis (Figure 3). An elegant and detailed discussion of the resolution required to match or exceed the selectivity attained with MRM mode MS/MS methods was realized by Kaufmann.[24]

With regards to the rise of interest toward GC-HRMS instruments, this is likely due to the possibility of implementing APCI offered by most manufacturers. In addition, dedicated GC-HRMS instrument with classic electron impact (EI) ionization sources are also available (Table 3). Some of these instruments offer the possibility of a cold EI ionization delivering chemical ionization-like mass spectra, which combined with HRMS features provide a powerful tool to identify unknown moderately volatile species. Another interesting feature is the ability to use exact mass electron impact libraries (e.g. National Institute of Standards and Technology (NIST) databases), which are available for selected applications such as food, environmental analysis, or forensics.

4 ACQUISITION METHODS IN HIGH-RESOLUTION MASS SPECTROMETRY: OVERLAPPING TARGETED AND NONTARGETED APPROACHES

The main features of HRMS for pesticide residue analysis include: (i) the ability to perform accurate mass measurements; (ii) increased sensitivity in *full-scan* acquisition; (iii) the inherent acquisition flexibility, since operating in full-scan mode permits the detection of a theoretically unlimited number of compounds with a minimum effort in the optimization of analytical parameters; and (iv) the possibility of retrospective analysis of data (impossible with QQQ). With these features in mind, different workflows/approaches/analytical strategies can be used in HRMS depending on the purpose of the analysis. Before getting to the description of the workflows, first we need to describe the acquisition methods available and more commonly used in HRMS.

Unlike MS/MS with QQQ instruments, HRMS can be operated with minimum *a priori* information on the analytes and their optimal conditions.[31] This represents the main strength, seamless (windowless) targeted and untargeted analysis, provided by the outstanding sensitivity available with state-of-the-art HRMS instruments, now approaching the sensitivity attained using MS/MS (MRM mode).

The acquisition methods can be classified according to the preliminary requirements of data needed to establish the method (e.g. *m*/*z* values, retention time windows, availability of standards, inclusion list).

4.1 Data-dependent Analysis

According to Mann,[17,33] DDA is a mode of data collection in MS/MS in which a fixed number of precursor ions whose known *m*/*z* values – recorded in a survey scan (full-scan) – are selected in real time using predetermined rules and are subjected to a second stage of mass selection in an MS/MS analysis (Figure 4). After acquiring the product ion mass spectra, the system returns back to the survey scan. Amongst the general term of DDA, the default and more common acquisition experiment is *product ion scan*, where a precursor ion of a particular *m*/*z* is selected and isolated, fragmentation is induced and the mass spectrum of the resulting product ions is recorded. This mode could be carried out by the different hybrid mass spectrometers

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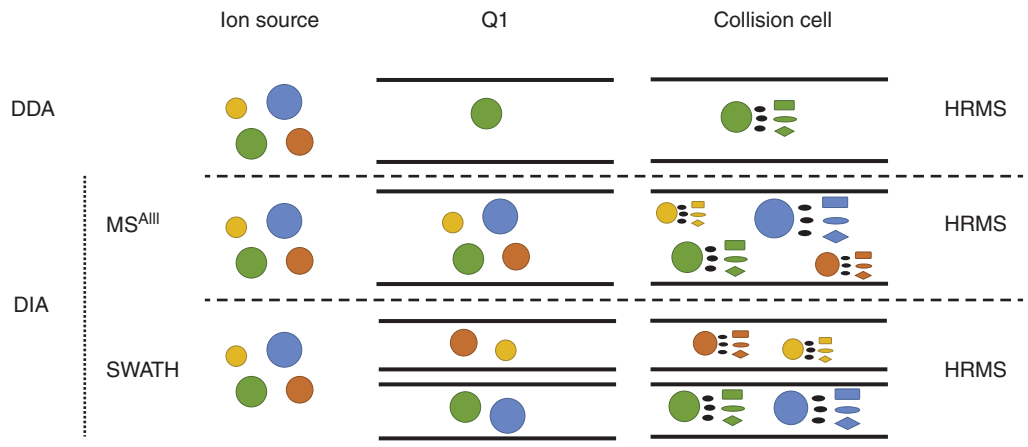

Figure 4 Scheme of strategies available for providing tandem mass spectrometry fragmentation in high-resolution mass spectrometry (HRMS). DDA, data dependent acquisition; DIA, data independent acquisition.[32] (Reprinted with permission from X. Zhu, Y. Chen, R. Subramanian. Comparison of Information-Dependent Acquisition, SWATH, and MSALL techniques in metabolite identification study employing ultrahigh-performance liquid chromatography-quadrupole time-of-flight mass spectrometry. Anal. Chem. 86 (2014) 1202–1209. Copyright 2014 American Chemical Society.)

available including Q-TOF, hybrid ion trap/time-of-flight (IT-TOF), and hybrid quadrupole-Orbitrap (Q-Exactive Orbitrap). However, the main drawback is the inherently limited MS/MS rate, the actual time required to perform each MS/MS experiment – which limits the number of species subjected to MS/MS – and the fact that these precursor species should be fixed and known in advance (inclusion lists or previous method information). A slight modification is ion intensity-dependent MS/MS acquisition (Top N-based DDA), where, only the more abundant compounds will be subjected to MS/MS experiments. In this case, there is no need for any previous knowledge of the m/z values of the precursors, as the selection is carried out after the survey scan.[34] Unfortunately, this strategy is biased toward the more abundant compounds, which are usually endogenous matrix species. Most analytes present at lower concentration levels, the usual situation in pesticide residue analysis, will not be subjected to MS/MS. Only information from endogenous species would be eventually obtained in most cases.

4.2 Data-independent Analysis Acquisition

DDA modes are the more commonly implemented in quantitative mass spectrometry. They rely on previous information collected; precursor ions should be fixed in advance to allow their isolation and subsequent MS/MS analysis. In the opposite scenario, DIA approaches have recently become a powerful alternative for identification and quantification purposes. *Full-scan* acquisition is undoubtedly the oldest and more common DIA approach and the most widely used acquisition data mode in HRMS. In full scan, the entire mass spectra are acquired across a fixed range of masses (m/z) with a typical frequency between 1 and 20 Hz, matching chromatographic requirements. All the advantages inherent to HRMS are attributed by the flexibility of full-scan acquisition. In contrast, scarce fragmentation information is usually obtained as the conditions typically used are those which provide higher intensity of (de)protonated molecules or molecular ions in the case of LC-MS or GC-MS (APCI) respectively. Full scan is neither adequate for the confirmation of targeted compounds nor to elucidate unknowns or to distinguish isomers. The more basic approach to overcome this limitation is in-source collision induced dissociation (CID), available in any mass spectrometer with ionization sources operated at atmospheric pressure,[35] where a *pseudo*-MS/MS experiment – with no precursor ion isolation – takes place in an intermediate pressure section of the mass spectrometer, between the atmospheric pressure source and the intermediate-high vacuum of the ion transportation region in the mass spectrometer. Precursor ions are generated in the ionization chamber, being directed to the vacuum region. Then, ions are accelerated under various voltage conditions, prompting gentle collisions with surrounding species (e.g. nitrogen) to yield (diagnostic) fragment ions. Thus, it would be possible to obtain *pseudo* MS/MS spectra using single-stage HRMS instruments with no dedicated devices to prompt fragmentation.

An enhanced version of in-source CID, in terms of fragmentation efficiency, is *product ion scan MS/MS acquisition without precursor ion isolation*, realized in a dedicated collision cell. This acquisition mode is referred

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by manufacturers with different brand names: MS^E (Waters), all-ion mode (Agilent), MS^{ALL} (Sciex), and all-ion fragmentation (AIF) (Thermo Scientific). Full-scan spectra are usually acquired in the same run with two different conditions: low collision energy (to yield unfragmented precursor ion species) and the other one at a higher collision energy. Therefore, all the fragment ions of each individual species eluted are acquired in a unique run. On the other hand, the interpretation of the obtained product ion spectra is a challenging task, due to the presence of fragment ions not only from the (isolated) targeted species such as in an MS/MS experiment with precursor ion isolation but also the fragmentation from all the coeluting matrix interferences. Additional data processing and peak deconvolution may be required to extract useful fragmentation information for confirmatory purposes. Yet, it is possible to find interferences and consequently, high relative mass errors in the selected ions due to these coexisting species, particularly at the expected low concentration level sought in these experiments. Anyhow, this acquisition mode has been proven very useful for qualitative purposes and retrospective analysis using full-scan HRMS acquisition.

To overcome this lack of selectivity and to approach that attained with dedicated MS/MS with precursor ion isolation, there is a relatively novel acquisition method, first introduced by Sciex, so-called SWATH (sequential window acquisition of all theoretical fragment-ion spectra). It is also used by Thermo as variable data-independent acquisition (vDIA). It consists in the use of predefined m/z windows with fixed width (e.g. 20 Da) for ion isolation, rather than the entire mass range to limit the number of potentially interfering compounds.[36,37] Thus, relatively narrow mass windows are isolated in Q1, subjected to fragmentation in the collision cell and subsequently mass analyzed. The number and width of segments are adjusted according to the nature of the samples and the molecular weight distribution expected. The use of this strategy for pesticide residue analysis was assessed by Zommer and Mol.[38] Enhanced selectivity and enhanced signal-to-noise ratio with regards to AIF approaches are the main features of this mode, while at the same time, decent MS/MS spectra are collected for each individual species detected. The main limitation is the fact that this acquisition mode is hampered by the overall cycle time, that should be within one second by LC-MS or even less in GC-MS.

4.3 Overlapping Targeted and Nontargeted Approaches

Likewise acquisition methods, typical workflows in pesticide residue analysis can be classified according to the preliminary requirements of information needed to run the method (e.g. m/z values, retention time (t_R), availability of standards, etc.). Pesticide analysis using HRMS is usually accomplished by combining full-scan mass spectra and MS/MS product ion scan (with a variable precursor ion isolation width which varies from absolutely no isolation of precursors to variable DIA/SWATH scheme or finally the more selective case of a targeted compound specific MS/MS with a m/z isolation below 3 Da[37]).

According to different authors,[37,39–41] three main data analysis workflows are used in HRMS, which includes *target screening/target analysis*, where *a priori* method information (e.g. t_R and primary standards are available); *suspect screening*, intended for the identification of suspected known substances (standards eventually available), based on previous information (databases), although no a priori information (retention time) from reference standards is available. Finally, *nontarget screening*, referring to completely or partially unknown species, when neither prior information nor reference standards are available.

According to these authors, the two first types are targeted strategies because they involve previous selection of analytes and the use of, e.g. customized information of exact masses, t_R (in target screening) or MS/MS spectra. However, there are some discrepancies in the semantics as other authors[12] classified the choice of target, nontarget, or unknown analysis, based on the availability of information from standards, the acquisition method chosen, and method information (t_R, m/z) prior to the data acquisition of the actual sample. Consequently, with the latter criterion, the retrospective inspection of a data set for compounds not specifically anticipated would be considered untargeted, despite some information (e.g. elemental composition) is already available. This is the accepted scenario in pesticide residue analysis in food.

Leaving aside semantics, the use of HRMS and the plethora of data generated require the use of tools to scrutinize raw data, desirably in an automated fashion. Much progress has been accomplished in this respect in the last years, although data mining and processing often need manual check for ultimate confirmation. Figure 5 illustrates the steps undertaken within each type of approach discussed.[37]

At this stage, the use of specific HRMS/exact masses and specific filtering algorithms/tools to discard nonrelevant or orthogonal unnecessary data is central. This is particularly important for truly unknown analysis (e.g.

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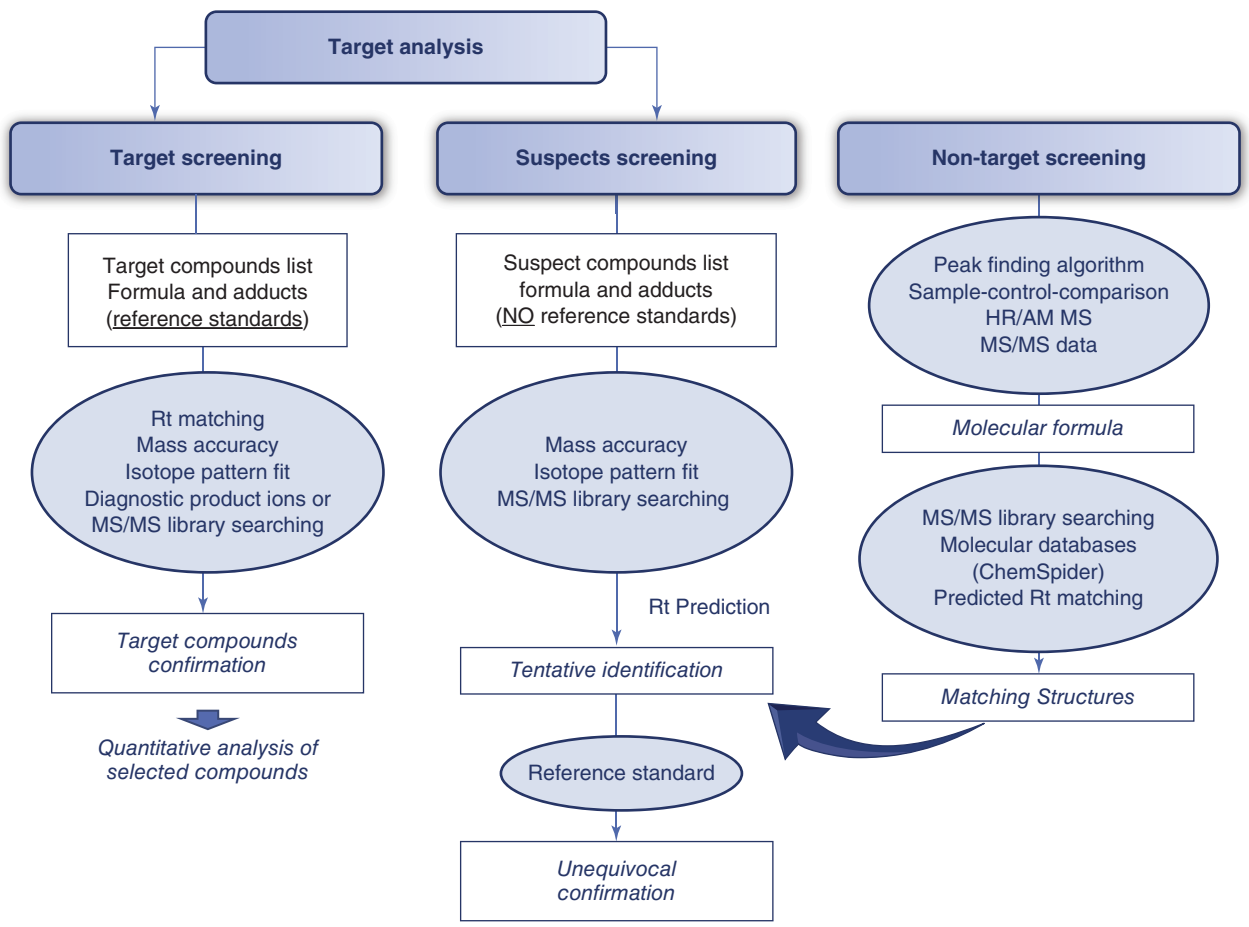

Figure 5 Main workflows used in high-resolution mass spectrometry (HRMS) methods. (Reproduced with permission from Ref. 37. © Elsevier, 2017.)

completely unknown species with no possible standards). The development of nontargeted screening strategies is challenging and requires great effort by the analysts.[42–44] Some of the different approaches used recently are as follows: (i) the application of statistical methods (e.g. PCA) to remove/discriminate peaks of interest from the endogenous matrix components[45]; (ii) the use of MS/MS fragmentation prediction tools (MetFrag, SmartMass, MIDAS, Molecular structure correlator (Agilent), MassFrontier (Thermo)); (iii) Isotope-specific filters/mass defect filters or, (iv) dedicated/custom MS/MS high-resolution libraries.

5 APPLICATIONS AND RECENT TRENDS

In the last decade, different authors have addressed the development of LC-HRMS screening methods using either time-of-flight or Orbitrap mass spectrometers.[46–71] Selected LC-HRMS applications have been summarized in Table 4. As can be observed, sample preparation based on generic procedures such as QuEChERS is commonly used for the extraction of pesticides from food, while solid-phase extraction (SPE) is employed for water analysis. LC separation is usually performed in a C_{18} column under a gradient of water–methanol or water–acetonitrile mixtures. Run time has been reduced in the last decade, from 30 to 40 min required for the separation of a hundred of pesticides in conventional columns (3–5 μm particle size)[46–48] to the analysis of more than 300 pesticides in 15 min[67] or over 600 contaminants in 10 min.[23]

Although TOF instruments are the most commonly used, interesting applications can be also found in the literature using LC-Orbitrap-MS, such as the analysis more than 350 pesticides and pharmaceuticals in meat samples[58] or in baby food,[57] requiring just 14 min run time. One approach that has gained a lot of interest is the use of accurate mass databases for both targeted and

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Table 4 Summary of LC-based HRMS multiresidue methods for pesticide testing and other contaminants in food and water[46–71]

Compounds	Samples	Extraction procedure	Method features	Method performance	Refs
			HPLC-TOF		
100 pesticides	Food and water	QuEChERS: liquid–liquid extraction with acetonitrile followed by cleanup step with PSA	HPLC-TOFMS (+) Run time: 30 min; injected volume: 50 µL; column: C_8 (150 mm × 4.6 mm, 5 µm); flow rate: 0.6 mL min^{-1}; mobile phases: A: 0.1% HCOOH in water; B: acetonitrile	LODs range: Food samples < 0.1 mg kg^{-1} Water samples < 0.3 mg L^{-1}	46
101 multiclass pesticides	Green pepper, tomato, cucumber, orange, and water	*Fruits and vegetables*: QuEChERS: liquid–liquid extraction followed by a cleanup step with PSA *Water*: SPE	LC-TOFMS (+) Run time: 40 min; injected volume: 50 µL; column: C_8 (150 mm × 4.6 mm, 5 µm); flow rate: 0.6 mL min^{-1}; mobile phases: A: 0.1% HCOOH in water; B: acetonitrile	LOQs average: 10 µg kg^{-1}	47
100 multiclass pesticides and metabolites (LC-TOFMS versus LC-QTRAP)	Vegetables and fruits	QuEChERS: solid–liquid extraction followed by a cleanup step with PSA	LC-ESI-TOFMS (+) and LC-ESI-QqLIT (QTRAP) (+) Run time: 40 min; injected volume: 50 µL; column:C_8 (150 mm × 4.6 mm, 5 µm); flow rate: 0.6 mL min^{-1}; mobile phases: A: 0.1% HCOOH in water B: acetonitrile	LOQs average: 10 µg kg^{-1}	48
300 multiclass pesticides and metabolites. Screening using automated software, including fragmentation, isotopic signature, and chromatographic data on the database	Fruits and vegetables	QuEChERS: solid–liquid extraction with acetonitrile followed by cleanup step with PSA	HPLC-ESI-TOFMS (+) Run time: 15 min; injected volume: 20 µL; column: C_8 (150 mm × 4.6 mm, 5 µm); flow rate: 0.6 mL min^{-1}; mobile phases: A: acetonitrile:water (95:5, v/v); B: acetonitrile:water (5:95, v/v), both with 0.1% HCOOH	LOQs average: 10 µg kg^{-1}	49
850 pesticides, 447 fragment ions and 99 metabolites	Fruits and vegetables	QuEChERS: solid–liquid extraction with acetonitrile followed by cleanup step with PSA	UHPLC-TOFMS (+) Run time: 31 min; injected volume: 20 µL; column: C_{18} (50 mm × 4.6 mm, 1.8 µm); flow rate: 0.5 mL min^{-1}; mobile phases: A:0.1% HCOOH in water; B: acetonitrile	–	14
300 multiclass pesticides and metabolites. Screening using automatic software, including fragmentation, isotopic signature, and chromatographic data on the database	Fruits and vegetables	QuEChERS: solid–liquid extraction with acetonitrile followed by clean up step with PSA	UHPLC-ESI-TOFMS (+) Run time: 18 min; injected volume: 20 µL; column: C_{18} (50 mm × 4.6 mm, 1.8 µm); flow rate: 0.6 mL min^{-1}; mobile phases: A: water:acetonitrile (95:5); B: acetonitrile:water (95:5), both with 0.1% HCOOH	LOQs: 20% < 5 µg kg^{-1} 40%: 5–10 µg kg^{-1} 20%: 10–50 µg kg^{-1} 20% > 50 µg kg^{-1}	10

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			HPLC-Orbitrap		
510 multiclass pesticides	Spinach	QuEChERS: solid–liquid extraction with acetonitrile followed by cleanup step with PSA	UHPLC-Orbitrap MS Run time: 14 min; injected volume: 10 µL; column: C_{18} (100 mm × 2.1 mm, 1.9 µm); flow rate: 0.3 mL min^{-1}; mobile phases: A: water; B: methanol, both with 0.1% HCOOH and 4 mM	LOQs <1 µg kg^{-1}	50
350 multiclass pesticides and veterinary drugs (including antibiotics)	Honey	QuEChERS: liquid–liquid extraction without clean up step	UHPLC-Orbitrap-MS (+ and −) Run time: 14 min; injected volume: 10 µL; column: C_{18} (100 mm × 2.1 mm, 1.7 µm); flow rate: 0.3 mL min^{-1}; mobile phases: A: water; B: methanol, both with 0.1% HCOOH and 4 mM NH_4COOH	LOQs range: 1–50 µg kg^{-1}	51
130 pesticides	Fruits and vegetables	QuEChERS: solid–liquid extraction with acetonitrile followed by clean up step with PSA	LC-ESI-Orbitrap-MS Run time: 25 min; injected volume: 5 µL; column: C_{18} (3 mm × 100 mm, 3 µm); flow rate: 0.3 mL min^{-1}; mobile phases: A: water; B: methanol:water (95:5, v/v), both with 0.002% HCOOH and 2 mM NH_4COOH	LODs range: 10–50 µg kg^{-1}	52
			UHPLC-TOF		
212 multiclass pesticides	Apple, strawberry, tomato, and spinach	QuEChERS: solid–liquid extraction with acetonitrile. No cleanup step	UHPLC-ESI-TOFMS (+ and −) Run time: 11.5 min; injected volume: 2 µL; column: C_{18} (100 mm × 2.1 mm, 1.8 µm); flow rate: 0.3–0.45–0.6 mL min^{-1}; mobile phases: A: methanol; B: 0.005 M NH_4COO in water	LOQs: <10 µg kg^{-1}	53
100 multiclass pesticides	Strawberry	Ethyl acetate partitioning	UHPLC-ESI-TOFMS (+) Run time: 6.5 min; injected volume: 3 µL; column: C_{18} (100 mm × 2.1 mm, 1.8 µm); flow rate: 0.6 mL min^{-1}; mobile phases: A: methanol:H_2O (95:5), B: methanol, both with 5 mM NH_4COOH	LOQs average: 10 µg kg^{-1}	54
60 multiclass pesticides	Fruits and vegetables	Solid–liquid extraction with acetonitrile:methanol (90:10) followed by cleanup step with PSA and GCB	UHPLC-TOFMS Run time: 5 min; injected volume: 5 µL; column: C_{18} (50 mm × 2.1 mm, 1.7 µm); flow rate: 0.5 mL min^{-1}; mobile phases: A: methanol and B: water, both with 0.1% HCOOH	LOQs range: 0.8–11.8 µg kg^{-1}	55
353 multiclass pesticides	Jams	QuEChERS: Solid–liquid extraction with acetonitrile (acetate buffer) followed by clean up-step with PSA	UHPLC-TOFMS (+) Run time: 12 min; injected volume: 20 µL; column: C_{18} (50 mm × 2.1 mm, 1.8 µm); flow rate: 0.5 mL min^{-1}; mobile phases: A: water and B: acetonitrile, both with 0.1% HCOOH	LOQs: 90% ≤ 10 µg kg^{-1}	56

(*continued overleaf*)

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Table 4 (*Continued*)

Compounds	Samples	Extraction procedure	Method features	Method performance	Refs
			UHPLC-Orbitrap		
360 multiclass pesticides and pharmaceuticals	Meat, fish, and vegetable baby foods	Extraction with water/0.1% HCOOH in acetonitrile	UHPLC-Orbitrap-MS (+ and −); Run time: 14 min; injected volume: 10 µL; column:C_{18} (100 mm × 2.1 mm, 1.7 µm); flow rate: 0.3 mL min^{-1}; mobile phases: A: water and B: methanol, both with 0.1% HCOOH and 4 mM NH_4COOH	LOQs range: 10–100 µg kg^{-1}	57
>350 multiclass pesticides, veterinary drugs, and biopesticides (fragmentation was evaluated in detail using Orbitrap and QqQ)	Pork, chicken and beef meat	Solid–liquid extraction with 1% HCOOH in acetonitrile	UHPLC-ESI-Orbitrap-MS (+ and −) Run time: 14 min; column: C_{18} (100 mm × 2.1 mm, 1.7 µm); flow rate: 0.3 mL min^{-1}; mobile phases: A:water, B: methanol, both with 0.1% HCOOH and 4 mM NH_4COOH	LOQs range: 2–16 µg kg^{-1}	58
40 pesticides (organochlorine, synthetic pyrethroid, organophosphate, and carbamate pesticides)	Grape and mango juices	Dispersive solid phase extraction (dSPE) using multiwalled carbon nanotubes (MWCNTs) and methanol/dichloromethane (40:60 v/v)	UHPLC-APPI Orbitrap-MS (+/−) Run time: 10 min; injected volume: 10 µL; column: C_{18} (2.1 mm × 50 mm, 1.9 µm); flow rate: −; mobile phases: A: methanol with 5% toluene and B: water	LODs: 0.025–0.15 µg L^{-1}	59
170 multiclass pesticides. Different resolving power tested (17 500, 35 000 and 70 000)	Tomato, pepper, orange, and green tea	QuEChERS: liquid–liquid extraction with acetonitrile followed by clean up-step with PSA and C_{18} (tomato, orange, and pepper) or PSA and calcium chloride (green tea)	UHPLC-Orbitrap-MS (+) Run time: 13 min; injected volume: 10 µL; column: C_{18} (150 mm × 2.1 mm, 2.6 µm); mobile phases: A: water:methanol (98:2, v/v); metanol:water (98:2, v/v), both with 0.1% HCOOH and 5 mM NH_4COOH	–	60

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			HPLC-Q-TOF		
317 pesticides	Fruits and vegetables	Solid–liquid extraction with acetonitrile and NaCl followed by SPE (Na_2SO_4 layer over carbon/NH_2 cartridge)	HPLC–QTOF–MS (+) and MS/MS Run time: 23 min; injected volume: 10 µL; column: C_{18} (2.1 mm × 100 mm, 3.5 µm); flow rate: 0.4 mL min^{-1}; mobile phases: A: acetonitrile and B: water with 0.1% HCOOH and 0.5 mM CH_3COONH_4	SDLs: 83.9% ≤ 10 µg kg^{-1}	61
427 pesticides	Fruits and vegetables	Solid–liquid extraction with acetonitrile and NaCl followed by SPE (Na_2SO_4 layer over carbon/NH_2 cartridge)	HPLC-QTOF-MS and MS/MS Run time: 25 min; injected volume: 5 µL; column: C_{18} (2.1 mm × 100 mm, 3.5 µm); flow rate: 0.4 mL min^{-1}; mobile phases: A: water with 0.1% HCOOH and 5 mM CH_3COONH_4 and B: acetonitrile	Screening detection limits (SDLs): 97.4 % < 50 µg kg^{-1}	62
			UHPLC-Q-TOF		
Pesticides, mycotoxins, drugs of abuse, antibiotics. (QTOF works in MS^E mode, with different collision energies. Low energy is used for identification; high energy is used for fragmentation)	Wastewater, human urine, orange, banana, and corn	*Wastewater*: SPE(OASIS HLB cartridges); *Human urine*: centrifugation; *Orange and banana*: water:methanol extraction; *Corn*: acetonitrile:water extraction	UHPLC-QTOF-MS (+ and −) Run time: 18 min; injected volume: 50 µL; column: C_{18} (150 mm × 2.1 mm, 2.6 µm); flow rate: 0.3 mL min^{-1}; mobile phases: A: in water; B; methanol, both with 0.1% HCOOH	–	41
504 pesticides commercial database; 199 spiked pesticides in samples	Fruits and vegetables	QuEChERS solid–liquid extraction with acetonitrile (citrate buffered) followed by clean up step with PSA	UPLC–QTOF–MS (+) Run time: 17 min; injected volume: −; column: C_{18} (2.1 mm × 100 mm, 1.7 µm); flow rate: 0.45 mL min^{-1}; mobile phases: A: water and B: methanol, both containing 10 mM CH_3COONH_4	Screening detection limits (SDLs): 57% comp.: 0.01 mg kg^{-1} 79%: 0.05 mg kg^{-1}	63
630 multiclass food contaminants (426 pesticides, 117 veterinary drugs, 42 food-packaging contaminants, 21 mycotoxins, 10 perfluorinated compounds, 9 nitrosamines, and 5 sweeteners)	Baby food, tomato, and orange	QuEChERS (acetate buffered procedure)	UHPLC-Q-TOFMS Run time: 10 min; injected volume: 20 µL; column: C_{18} (2.1 mm × 50 mm, 1.8 µm); flow rate: 0.5 mL min^{-1}; mobile phases: A: water and B: acetonitrile, both with 0.1% HCOOH	LOQs: 44% comp. <10 µg kg^{-1}	23

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Table 4 (*Continued*)

Compounds	Samples	Extraction procedure	Method features	Method performance	Refs
			UHPLC-Q-TOF		
50 pesticides	Minor fruits (44 star fruits and 43 Indian jujubes)	QuEChERS	UHPLC-Q-TOFMS (+) Run time: 19 min; injected volume: 5 µL; column: C_{18} (2.1 mm × 50 mm, 1.8 µm); flow rate: 0.25 mL min^{-1}; mobile phases: A: water and B: methanol, both with 1 mM CH_3COONH_4	LOQs range: 0.1–12 µg kg^{-1}	64
156 pesticides	Salmon feeds	Macromolecules precipitation by acetonitrile/water/formic acid (75:24:1, v/v/v) followed by dilution in 0.1% formic acid in water	UHPLC-TWIMS-QTOFMS Run time: 22 min; injected volume: 5 µL; column: C_{18} (2.1 mm × 100 mm, 1.7 µm); flow rate: 0.45 mL min^{-1}; mobile phases: A: water and B: methanol, both with 10 mM CH_3COONH_4 (pH 5.0)	SLDs: 82% ≤ 0.05 mg kg^{-1}	65
			UHPLC-Q-Orbitrap		
139 pesticide residues	Tomato, pepper, orange, and green tea	QuEChERS: solid–liquid extraction with acetonitrile (citrate buffered) followed by clean up step with PSA and C_{18} (tomato, orange, and pepper) or Z-Sep and Z-Sep + (green tea)	UHPLC-Q-Orbitrap-MS (+) and MS/MS Run time: 13 min; injected volume: 10 µL; column: C_{18} (150 mm × 2.1 mm, 2.6 µm); mobile phases: A: water:methanol (98:2, v/v); B: methanol:water (98:2, v/v), both with 0.1% HCOOH and 5 mM NH_4COOH	–	66
333 Pesticides and veterinary drugs	Baby food	Extraction with acetonitrile:water (84/16, v/v) with 1% acetic acid, Na_2SO_4 and sodium acetate	UHPLC-ESI Q-Orbitrap-MS Run time: 15 min; injected volume: 10 µL; column: C_{18} (2.1 mm × 100 mm, 2.6 µm); flow rate: 0.3 mL min^{-1}; mobile phases: A: water and B: methanol, both with 0.1% HCOOH and 4 mM NH_4COOH	LODs range: 0.01–5.35 µg kg^{-1}	67
539 compounds (pesticides and drug residues)	Tap water	On-line SPE (Oasis HLB column, 2.1 mm × 20 mm, 12 µm)	UHPLC-Q-Orbitrap-MS (+) and MS/MS Run time: 30 min; injected volume: 5000 µL; column: C_{18} (2.1 mm × 150 mm, 1.8 µm); flow rate: 0.5 mL min^{-1}; mobile phases: A: water and B: acetonitrile, both with 0.08% HCOOH	LODs: 0.1 ng L^{-1} to 1 µg L^{-1}	68

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166 pesticides	Tomato, lettuce, zucchini, orange, leek	QuEChERS: solid–liquid extraction with acetonitrile (citrate buffered) followed by clean up step with PSA and C_{18}	UHPLC-Q-Orbitrap-MS (+) and MS/MS Run time: 17 min; injected volume: 10 µL; column: C_8 (2.0 mm × 150 mm, 3 µm); flow rate: – 0.3 mL min^{-1}; mobile phases: A: water:methanol (98:2, v/v); B: metanol:water (98:2, v/v), both with 0.1% HCOOH and 5 mM NH_4COOH	–	69
448 pesticide residues	fruits (apple, banana, grape, orange, strawberry) and vegetables (carrot, potato, tomato, broccoli, lettuce)	QuEChERS	UHPLC-Q-Orbitrap-MS (+) and MS/MS Run time: 14 min; injected volume: 5 µL; column: Hypersil (2.0 mm × 100 mm, 1.9 µm); flow rate: 0.3 ml min^{-1}; mobile phases: A: water and B: methanol, both with 0.1% HCOOH and 4 mM NH_4COOH	Screening of: 94% pest. at 10 µg kg^{-1} 99% pest. at 100 µg kg^{-1}	70
64 pesticides	Tomato, orange, fruit-based jam, baby food, olive oil	QuEChERS: solid–liquid extraction with acetonitrile (citrate buffered) followed by clean up step with PSA, and with PSA, GCB, and C_{18} for olive oil	Nano-LC-Q-Orbitrap-MS Run time: 48 min; injected volume: 1 µL; column: C_{18} (75 µm × 150 mm, 3 µm); flow rate: 0.3 µL min^{-1}; mobile phases: A:water and B: acetonitrile, both with 0.1% HCOOH	LOQs: 80% ≤ 10 ng kg^{-1}	71

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Table 5 Summary of GC-HRMS multiresidue methods for pesticide testing and other contaminants in food and water[72–78]

Compounds	Samples	Extraction procedure	Method features	Method performance	Refs
			GC-TOFMS		
20 pesticides	Peach	Solid–liquid extraction with ethyl acetate followed by purification by gel permeation chromatography	GC-TOFMS Run time: 17 min; injected volume: 1 µL; injection temperature: 250 °C; column: 5% phenyl – 95% dimethyl polysiloxane (0.18 mm × 20 m × 0.18 µm); He flow: 1.0 mL min^{-1}	LOQs: 0.5–25 µg kg^{-1}	73
111 pesticides	Fruit-based baby food	QuEChERS (acetate buffered)	GC-TOFMS Run time: 7 min; injected volume: 2 µL; injection temperature: PTV 70–350 °C; column: 5% diphenyl – 95% dimethyl polysiloxane (0.53 mm × 10 m × 0.5 µm); He flow: 1.0 mL min^{-1}	LOQs ≤ 10 µg kg^{-1}	74
45 pesticides	tomato, spring onion, and orange	Solid–liquid extraction with ethyl acetate, NaCl, and $MgSO_4$	GC-TOFMS Run time: 40.5 min; injected volume: 2 µL; injection temperature: 280 °C; 2 columns: 5% diphenyl – 95% dimethyl polysiloxane (0.25 mm × 15 m × 0.25 µm); He flow: 1.225 and 1.4225 mL min^{-1} in first and second column, respectively	LOI ≤ 10 µg kg^{-1}	75
Nontarget screening of contaminants (pesticides included)	Honey bees and pollen	QuEChERS: solid–liquid extraction with acetonitrile (citrate buffered) followed by cleanup with PSA and Z-Sep (bees) or with PSA, C_{18}, and Z-Sep (pollen)	GC-TOFMS Run time: 40.5 min; injected volume: 2 µL; injection temperature: 280 °C; 2 columns: (5%-phenyl)-methylpolysiloxane (0.25 mm × 15 m × 0.25 µm)	–	76
			GC-Orbitrap-MS		
54 pesticides	Tomato, leek, orange	QuEChERS (acetate buffered)	GC-Orbitrap-MS Run time: 29 min; injected volume: 1 µL; injection temperature: 290 °C; column: TG-OCP I for organochlorine pesticides and herbicides (0.25 mm × 30 m × 0.25 µm); He flow: 1.2 mL min^{-1}	LODs ≤ 2.5 µg kg^{-1}	77
210 pesticides database	Fruits and vegetables	QuEChERS (citrate buffered)	GC-Orbitrap-MS Run time: 32 min; injected volume: 1 µL; injection temperature: 250 °C; column: silarylene comparable to 5% phenyl – 95% dimethyl polysiloxane (0.25 mm × 30 m × 0.25 µm); He flow: 1.2 mL min^{-1}	LOQs ≤ 10 µg kg^{-1}	15

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			GC-Q-TOFMS		
132 pesticides	Fruits and vegetables	QuEChERS	GC-(APCI)Q-TOFMS Run time: 45 min; injected volume: 1 µL; injection temperature: 280 °C; column: 5% phenyl – 95% dimethyl polysiloxane (0.25 mm × 20 m × 0.25 µm); He flow: 2.0 mL min^{-1}	SDLs: 77% comp ≤ 10 µg kg^{-1}	72
182 pesticides	Rice, mushrooms, soybeans, spinaches, tomatoes, broccoli, grapefruits, carrots, lettuces, cucumbers	QuEChERS	GC-Q-TOFMS injected volume: 1 µL; column: 5% phenyl – 95% dimethyl polysiloxane (0.25 mm × 30 m × 0.25 µm); He flow: 1.0 mL min^{-1}	LOQs range: 10–100 µg kg^{-1}	78

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suspect analysis, which allow the screening of hundreds of contaminants in few minutes.[14]

In the past, most applications were accomplished solely using full-scan acquisition and single-stage instruments. Recent developments in pesticide residue analysis have moved toward the use of tandem MS instruments. In-source CID fragmentation has been widely used in LC-HRMS to obtain additional information for compound identification in residue analysis, but this approach is clearly limited when compared to CID fragmentation obtained in a collision cell of a MS/MS instrument. Accurate-mass MS/MS analysis are typically performed in Q-TOFMS and Q-Orbitrap-MS equipment. As an example, more than 1000 contaminants were screened comparing both target and nontarget approaches by UHPLC-Q-TOFMS analysis in wastewater, urine, and food samples.[41] On the other hand, the use of UHPLC-Q-Orbitrap-MS coupled to online SPE was employed for the simultaneous semiquantitative analysis of 539 compounds (pesticides and drug residues) in tap water.[68] Other applications are summarized in Table 4, including the use of nanoflow LC separation coupled to Q-Orbitrap-MS to overcome matrix effects by the use of high dilution factors without compromising method sensitivity.[71]

In contrast to HPLC-HRMS, the number of applications in pesticide residue analysis using GC-HRMS is scarce. To a large extent, this is because of the use of electron ionization (EI) in GC. This ionization source produces extensive fragmentation of the molecule, which led to the absence of the molecular ion in most cases, thus making difficult the elucidation of unknown compounds. However, despite EI is the most extensively used ionization source in GC-MS instrumentation, equipment with soft ionization sources such as APCI is commercially available. The combination of soft ionization with high-resolution tandem MS provide additional accurate-mass information for GC-amenable compound identification. As an example, GC-(APCI)Q-TOFMS was used for the analysis of 132 pesticides in fruits and vegetables.[72]

Selected GC-HRMS applications in pesticide testing during the last decade are summarized in Table 5.[72–78] The extraction method preferentially used is QuEChERS procedure, but a solvent exchange from acetonitrile to ethyl acetate is required prior to injection of the extract in the gas chromatograph. The separation of the analytes of interest is carried out in most cases in capillary columns coated with stationary phases comparable to 5% phenyl/95% dimethylpolysiloxane, typically achieving run times between 30 and 45 min. For instance, a nontarget screening of contaminants in pollen and honeybees was performed in a 40.5 min analysis by GC-TOFMS (gas chromatography time-of-flight mass spectrometry), concluding in eight positive findings of pesticides.[76] Particularly remarkable is the separation of 111 pesticides in 7 min by low-pressure GC-TOFMS, meeting the requirements of EU regulation on MRLs of pesticides in baby food.[74] Just to cite one example on the use of the hyphenation GC-Orbitrap-MS, it has been employed for the separation of organochlorine pesticides and herbicides in tomato, leek, and orange samples.[77]

Future developments may involve the integration of IMS and the use of collision cross sections as an additional dimension for confirmatory purposes in the field of pesticide residue analysis.[25–29] Although the current selectivity achieved with resolving power above 100 000 is usually outstanding for avoiding coeluting matrix components, yet the use of IMS may provide a broader perspective enabling enhanced isomer differentiation as well as matrix background reduction. An appropriate scenario for these novel tools is also the unknown analysis, where the additional information attained can be useful for elucidation purposes including the resolution of isomers.

ABBREVIATIONS AND ACRONYMS

APCI	Atmospheric Pressure Chemical Ionization
CID	Collision Induced Dissociation
DDA	Data Dependent Acquisition
DIA	Data Independent Acquisition
EI	Electron Impact
FWHM	Full-width Half Maximum
FT-ICR	Fourier-transform Ion Cyclotron Resonance
GC	Gas Chromatography
GC-MS	Gas Chromatography–mass Spectrometry
GC-MS/MS	Gas Chromatography-tandem Mass Spectrometry
GC-TOFMS	Gas Chromatography Time-of-flight Mass Spectrometry
HRMS	High-resolution Mass Spectrometry
IMS	Ion Mobility Spectrometry
IT-TOF	Hybrid Ion Trap/Time-of-Flight
LC	Liquid Chromatography
LC-HRMS	Liquid Chromatography High-resolution Mass Spectrometry
LC-MS/MS	Liquid Chromatography-tandem Mass Spectrometry
MRLs	Maximum Residue Levels
MRM	Multiple Reaction Monitoring
MSI	Magnetic Sector Instruments
MS/MS	Tandem Mass Spectrometry

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NIST	National Institute of Standards and Technology
QQQ	Triple Quadrupole Analyzer
Q-exactive Orbitrap	Hybrid Quadrupole-Orbitrap Analyzer
Q-TOF	Hybrid Quadrupole Time-of-flight Analyzer
SWATH	Sequential Window Acquisition of all Theoretical Fragment Ion Spectra
TOF	Time-of-flight Analyzer
UHPLC	Ultra-high Performance Liquid Chromatography
vDIA	Variable Data-independent Acquisition

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