Trends in Analytical Chemistry 59 (2014) 59–72

Contents lists available at ScienceDirect

Trends in Analytical Chemistry

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

Liquid chromatography-mass spectrometry for the determination of chemical contaminants in food

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ARTICLE INFO

Keywords:
Chemical contaminant
Determination
Food
High-resolution mass spectrometry
Identification
Liquid chromatography
Mass spectrometry
Quantification
Residue
Targeted analysis

ABSTRACT

As a result of the range and the variety of toxic and undesirable substances in food, which pose a potential hazard to human health, there is an ever-increasing demand for analytical methods that can reliably detect and quantify contaminants and residues in foods. This review presents the state-of-the-art technology used in the determination of trace residues and contaminants in food by liquid chromatography-mass spectrometry (LC-MS). LC-MS instruments utilize many different types of mass analyzer to improve selectivity and also confidence in assigning the identity of the contaminants detected and to offer different approaches to analysis. We discuss current analytical approaches together with the major benefits and the limitations of these technologies with respect to screening, quantification and identification of contaminants and residues in food.

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Contents

1. Introduction

In today's global marketplace, as foods are produced and distributed throughout the world, food quality and food safety have become increasing concerns for consumers, governments and producers. To protect the health of consumers, there is a requirement for more stringent regulations and more diligent monitoring of foods for regulators, vendors and producers. Chemical contaminants in food have been defined as "any chemical not intentionally added to food but present from many potential sources" [1], including residues from the application of pesticides and veterinary medicines, those entering the food chain from the environment, those formed during the processing of food, natural toxins and accidental contamination at point sources. Contaminants can also enter the food chain through adulteration of food (intentional contamination).

To protect consumers from health risks derived from such food-borne contaminants, many countries and international bodies have introduced or adopted regulations or guidelines to limit exposure. Although thousands of chemicals are in common use, only a portion of them have undergone significant toxicological evaluation, whilst,

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http://dx.doi.org/10.1016/j.trac.2014.04.005
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Table 1
Common parameters used to compare performance of mass spectrometers used for LC-MS

Mass analyzer type[a]	Resolving power ($\times 10^3$)	Mass accuracy (ppm)	Upper limit of *m/z* range [$\times 10^3$]	Acquisition speed (Hz)	Linear dynamic range	Price
Q	3–5	Low[b]	2–3	2–10	10^5–10^6	Low
IT	4–20	Low	4–6	2–10	10^4–10^5	Moderate
ToF	10–60	1–5	10–20	10–100	10^4–10^5	Moderate
Orbitrap	100–240	1–3	4	1–5	5×10^3	High

Adapted with permission from [23].
[a] Q, ToF and Orbitrap also include common hybrid configurations with Q or LIT as the first mass analyzer providing MS/MS or MS^n capabilities.
[b] Qs with hyperbolic rods provide mass accuracies better than 5 ppm.

for many, their specific toxicological effects in humans remain unknown.

Low limits of quantification (LOQs) are required to gather surveillance data from the occurrence and background levels of both recognized and newly identified contaminants in foods in order to estimate human daily intake for risk assessment. Many regulatory limits are driven by the achievable limits of detection (LODs) or LOQs or a "minimum required performance", especially when dealing with banned substances. For example, recent analyses in European Union (EU) member states revealed the presence of phenylbutazone in horse meat fraudulently added to beef-based products [2]. Although the risk to humans from exposure was considered very low, there is no Maximum Residue Limit (MRL) set for phenylbutazone, as the use of the product on horses destined for the food chain is prohibited. A "compliant" result means that no phenylbutazone has been found in the sample above the CCα concentration (the lowest level at which a method can discriminate with statistical certainty of 1-α that phenylbutazone is present, where α is 1%). This concentration is determined during the validation of the method and, with modern instruments, calculated values are typically very low. For example, a sample of horse kidney was found to be non-compliant after detection of a residue of phenylbutazone at a concentration of 0.84 μg/kg [3].

Over the past decades, approaches to the trace-level determination of food contaminants have changed considerably, moving away from the use of gas chromatography (GC) with selective detectors to the selectivity and the sensitivity offered by mass spectrometry (MS). The application of MS in combination with chromatography [GC or liquid chromatography (LC)] has been well recognized as the "gold standard" for both quantification and semi-quantitative screening of food contaminants, such as pesticides [4]. Although GC-MS continues to be used in the analyses of volatile, moderate to non-polar small molecules (e.g. PCBs, dioxins, other halogenated aromatic compounds and many pesticides), recent developments in both LC and MS have resulted in very powerful instrumentation for sensitive and selective determination of other more polar or ionic contaminants at trace levels in food [5,6] including veterinary medicines [7,8], pesticides [9,10], toxins [11,12] and so-called "emerging contaminants" [13].

Developments in chromatography are enabling more rapid, highly efficient LC separations [14,15] and providing opportunities for the analysis of ionic or polar compounds [16–18]. Electrospray ionization (ESI) [19] remains the most common ionization technique employed for the determination of chemical contaminants in food by LC-MS. The use of atmospheric pressure chemical ionization (APCI) [20] for analysis of food contaminants [21,22] appears to have been left in the wake of the overwhelming popularity of ESI. This may be related to the increasing number and the wider range of analytes currently sought but may also reflect the improvements in source and probe design for ESI not yet paralleled in APCI.

The most important change in the past decade has been in the increase in choice of mass analyzers for LC-MS and how this has influenced the approach to monitoring chemical contaminants in food.

2. Choice of mass analyzer

Holcapek et al. recently reviewed developments in LC-MS over the past decade [23] including a helpful overview of the different mass analyzers available, many of which have been applied to the analysis of food contaminants by LC-MS [24–26]. The performance characteristics of the types and combinations of mass analyzers used for the analysis of food contaminants are summarized in Tables 1 and 2.

2.1. Tandem mass spectrometry (MS/MS)

The basic principle of MS/MS is the selection of precursor ion, fragmentation of this ion, usually by collision-induced dissociation (CID), and measurement of the *m/z* ratio of the product ions formed. There are two fundamentally different approaches to MS/MS: tandem in space and tandem in time.

Tandem-in-space instruments have separate independent mass analyzers in physically different locations of the instrument. A hybrid mass spectrometer is an instrument which combines analyzers of different types. Examples of tandem mass spectrometers include, but are not limited to, triple/tandem quadrupole (QqQ), quadrupole-time of flight (QqToF) and Orbitrap hybrid instruments.

Tandem-in-time instruments are typically ion-trapping mass spectrometers, which comprise 3-D quadrupole ion traps (QIT), linear ion traps (LIT) and Fourier transform ion cyclotron resonance (FT-ICR) instruments. The various stages of MS are conducted within the same physical trapping volume but at different times during the experiment.

Originally, LC-MS/MS for determination of food contaminants was mainly delivered on 3-D QIT instruments, as they initially provided more cost-effective access to MS/MS than QqQ instruments [27] and offered the additional capability of MS^n. As this mass analyzer suffers from some significant limitations [28], the future of ion-trap technology for analysis of contaminants in food will probably lie with LITs [29], which can be used as ion-accumulation devices in combination with quadrupole, Orbitrap, ToF and FT-ICR devices or as commercially available, stand-alone mass spectrometers with MS^n capabilities, as used for the identification of unknown transformation products. The combination of QqQ MS with LIT technology in the form of an instrument of configuration QqLIT, using axial ejection, has proved useful, because this instrument retains the selective reaction monitoring (SRM) mode but with other scan functions, such as product-ion, neutral-loss and precursor-ion scans enhanced by the use of the more sensitive ion trap. Scan combinations of QqQ and trap mode can be performed concomitantly [30].

Although tandem mass spectrometers can be operated in a variety of modes, those with a QqQ configuration are typically operated in SRM mode [also called multiple-reaction monitoring (MRM) by some suppliers]. Monitoring transitions for each analyte, typically one precursor ion to a couple of product ions, provided a significant gain in sensitivity compared with acquiring full spectral data.

Table 2
Overview of commercial mass spectrometers designed for LC-MS used to determine contaminants in food

Mass-analyzer type	Instrument name, manufacturer[a]	Resolving power (FWHM defined at *m/z*)	Resolution ($\Delta m/z$)	Mass accuracy (ppm), calibration:		*m/z* range	Acquisition speed (Hz)[b]
				Internal	External		
Q	6150, Agilent Technologies	–	1	–	–	10–1,350	10
	Flexar SQ 300 MS, Perkin Elmer	–	0.6	–	–	20–3,000	10
	LCMS-2020, Shimadzu	–	1	–	–	10–2,000	15
	LC/MS Purification System, Gilson	–	1	–	–	50–3,000	10
	MSQ Plus, Thermo Scientific	–	1	–	–	17–2,000	12
	SQ Detector 2, Waters	–	1	–	–	2–3,072	15
3D-IT	Amazon Speed ETD, Bruker Daltonics	–	0.1	–	–	50–6,000	52
	LCQ Fleet, Thermo Scientific	–	0.3	–	–	15–4,000	12
LIT	LTQ Velos Pro, Thermo Scientific	–	0.05	–	–	15–4,000	66
QqQ	6490, Agilent Technologies	–	0.4	–	–	5–1,400	10
	LC-MS 8040, Shimadzu	–	0.7	–	–	10–2,000	15
	TQ Detector, Hitachi	–	1	–	–	2–2,000	10
	API 6500, ABSciex	–	1	–	–	5–2,000	12
	TQS Vantage, Thermo Scientific	7,500 (*m/z* 508)	0.07	5	–	10–3,000	5
	EVOQ, Bruker	–	–	–	–	10–1,250	14
	Xevo TQ-S, Waters	–	1	–	–	2–2,048	10
QqLIT	API 6500 QTRAP, ABSciex	9,200 (*m/z* 922)	0.1	–	–	5–2,000	12
ToF	6230 ToF, Agilent Technologies	24,000 (*m/z* 1522)	0.06	1–2	–	25–20,000	40
	AccuToF, Jeol	6,000 (*m/z* 609)	0.1	5	–	6–10,000	10
	AxION 2 ToF MS, Perkin Elmer	12,000 (*m/z* 922)	0.08	2	–	18–12,000	70
	Citius, Leco	100,000 (*m/z* 609)	0.006	<1	–	50–2,500	200
	micrOToF II focus, Bruker Daltonics	16,500 (*m/z* 922)	0.06	<2	<5	50–20,000	40
	Xevo G2-S ToF, Waters	22,500 (*m/z* 956)	0.04	<1	–	20–16,000	30
IT-ToF	LC-MS-IT-ToF, Shimadzu	10,000 (*m/z* 1000)	0.1	3	5	50–5,000	10
QqToF	maXis 4G, Bruker Daltonics	60,000 (*m/z* 1222)	0.02	<0.6	<2	50–20,000	30 (MS), 10 (MS/MS)
	micrOToF-Q II, Bruker Daltonics	20,000 (*m/z* 922)	0.05	<2	<5	50–20,000	20
	TripleToF 4600 & 5600, ABSciex	35,000 (*m/z* 956)	0.03	0.5	2	5–40,000	100
	Xevo G2-S QToF, Waters	22,500 (*m/z* 956)	0.04	<1	–	20–16,000	30
	6550 QToF, Agilent Technologies	42,000 (*m/z* 922)	0.02	<1	–	50–10,000	50
Q-IMS-ToF	Synapt G2-S HDMS, Waters	40,000 (*m/z* 956)	0.02	<1	–	20–100,000	30
Orbitrap	Exactive Plus, Thermo Scientific	140,000 (*m/z* 200)	0.001	<1	<3	50–6,000	12 (at RP = 17,500)
Q-Orbitrap	Q-Exactive, Thermo Scientific	140,000 (*m/z* 200)	0.001	<1	<3	50–6,000	12 (at RP = 17,500)
LIT-Orbitrap	Orbitrap Elite, Thermo Scientific	240,000 (*m/z* 400)	0.0002	<1	<3	50–4,000	4 (at RP = 60,000)

Adapted with permission from [23].
[a] If manufacturers have more instruments in particular series, only the instrument with the best performance is listed here. Technical specifications are as published by the manufacturers. This list may not be comprehensive.
[b] Values for acquisition speed for low RP mass analyzers specified by manufacturers have been recalculated into Hz units for the mass range of Δm/z 1000.

Fast data-acquisition speeds and better designs of collision cell significantly shorten the minimum dwell times that can be used for each precursor/product ion pair monitored, without significantly scarifying signal-to-noise ratios (S/N) or observing crosstalk [31]. Instrument vendors have also introduced tools for automating the management of the duty cycle resulting in more data points per peak, better reproducibility and higher S/N even with a high number of SRM transitions [32]. Rapid polarity switching, moving between detection of positive and negative ions, allows a wide range of compounds to be incorporated into the one method [33]. Other operating modes using QqQ analyzers, such as product-ion, neutral-loss and precursor-ion scans, are rarely applied to the analysis of food contaminants.

2.2. High-resolution mass spectrometry (HRMS)

The use of SRM mode on QqQ instruments for the determination of chemical contaminants in food has been seen to have certain limitations:

- a limit to the number of compounds possible per analysis;
- no post-acquisition re-interrogation of data other than for those analytes pre-programmed into the method;
- reliance on the availability of reference standards; and,
- an inability to screen for unknowns.

There has been a move to an alternative approach using instruments capable of providing full spectral information with the added bonus of high mass-resolving power to provide selectivity and the capability for accurate mass measurement to aid identification with the additional advantage of retrospective analysis [34–36]. Full spectral acquisition does not rely on fragmentation, so it offers the potential to overcome some technical limitations of MS/MS, namely reliance on non-specific transitions (e.g. loss of water), difficulty fragmenting stable adducts (e.g. nivalenol), inability to generate more than a single useful product ion and the difficulty in detecting product ions of low molecular weight. High mass-resolving power that allows discrimination between isobaric interferences and ions of interest, even with a complex background, and accurate mass measurement are available using ToF and Orbitrap devices, whereas reports of coupling magnetic sector or FT-ICR instruments with API interfaces for the rapid screening of food contaminants are scarce, mainly due to the high cost [37,38].

ToF is a temporally dispersive mass analyzer using the differences in transit time through a drift region (a very low pressure tube) to separate ions of different masses. ToF analyses involve accelerating a group of ions, in a brief burst, to a detector. The ions exit the source each having received an identical high-voltage pulse. The potential of each ion accelerates it into the flight tube. Because all similarly charged ions share the same kinetic energy, those with lower masses have greater velocity and strike the detector first. Since all masses are measured for each “push”, ToF instruments can provide

full spectral acquisition with better sensitivity than scanning instruments.

Although there were plenty of examples of stand-alone early ToF instruments, more recently they were more typically combined in hybrid configurations (e.g. QqToF). Ions are typically introduced orthogonally into reflectron-based or multi-pass ToF analyzers to maximize mass-resolving power [39]. There are two basic approaches used to translate a detector signal into a digital measurement: time-to-digital detectors (TDC) and analogue-to-digital detector technology (ADC).

The Orbitrap analyzer consists of a small electrostatic device into which ion packets are injected at high energies to orbit around a central, spindle-shaped electrode. The image current of the axial motion of the ions is picked up by the detector and this signal is Fourier transformed (FT) to yield high-resolution mass spectra. The first commercial instrument involving an Orbitrap mass analyzer was a hybrid LIT Orbitrap [40,41]. Other options include a bench-top instrument with no precursor-ion selection [42] and, most recently, another hybrid instrument capable of MS/MS using a quadrupole for precursor-ion selection [43].

The primary considerations for determining whether a HRMS instrument is suitable for determination of contaminants in food are mass resolution (or mass-resolving power), mass accuracy and sensitivity. It is important to distinguish between mass resolution and mass accuracy when considering the options and use of the various HRMS instruments. The terms mass resolution and mass-resolving power are frequently confused and are often used interchangeably. The key point is that the term mass resolution should always pertain to the data, whereas the term mass-resolving power is used to describe mass-analyzer performance.

Mass resolution is defined as the mass difference, m_1- m_2, between two mass spectral peaks that can be clearly distinguished [44]. Typically this is qualified by relating the value to a specified fraction of the height of the smaller individual peak: 10% valley for sector instruments ($\Delta m_{10\%}$) and 50% valley for quadrupole analyzers ($\Delta m_{50\%}$). A different approach is applied to measuring mass resolution from ToF and subsequently Orbitrap data, where the full width at half-maximum height (FWHM) of either peak alone is used.

Mass-resolving power can be defined for an isolated peak of mass m as $m/\Delta m$ and for two peaks of equal height, $m_1$and m_2, mass resolving power is $m_2/\Delta m$ [45]. Mass-resolving power is usually a large number. For example, an instrument with a resolving power (FWHM) of 10,000 at m/z 250 could separate or resolve masses that differ by 0.025 mass units. For a given mass analyzer, it is important to specify the value of m (or m/z) at which the resolving power or resolution is reported. Despite the rapid and continuing changes to instrument specifications, ToF analyzers typically still have less mass-resolving power than instruments based upon the Orbitrap (Table 2). Orbitrap analyzers operate at a varying mass-resolving power that is proportional to acquisition time and inversely proportional to the square root of the m/z ratio. Thus, we expect values for the Orbitrap to be highest at low mass whereas resolving power is consistent across the mass range when using ToF.

When selecting mass-resolving power, one also needs to consider the trade-off between mass resolution and scan speed. With modern ToF instruments, mass-resolving power is independent of the acquisition rate [46]. High mass-resolving power with Orbitrap instruments comes at the expense of scan speed. For example, the LIT-Orbitrap achieves a mass-resolving power of 100,000 at 1 scan/s but such scan speeds cannot keep up with the increasingly narrow peaks generated by today's high-efficiency LC columns. Doubling the scan speed to 2 scans/s cuts the mass-resolving power in half, which can lead to issues with insufficient acquisition data points [47]. Insufficient data points across chromatographic peaks also results in poorly described peaks so the chromatographic resolution available cannot be fully exploited. It should be noted that whilst ToF instruments have the potential for faster acquisition rates than Orbitrap, sensitivity can be compromised if there is not enough time to accumulate enough transients to generate a spectrum with sufficient S/N. Operating with a mass-resolving power of 140,000 FWHM, the quadrupole-Orbitrap hybrid offers roughly three times the mass-resolving power of the typical QqToF, but this resolution can still be achieved only at a speed of 2 Hz. Whilst this is double that of the original Orbitrap instruments, it is significantly slower than current QqToF instruments (10–100 Hz). When acquiring at the maximum rate (12 Hz), the mass-resolving power has to be set considerably lower (17,500 FWHM at m/z 200). However, it is important to note that, in many cases, an acquisition speed of 1 Hz is sufficient to provide good data when monitoring a relatively small number of contaminants [48]. Lower mass-resolving power settings are likely to be sufficient for good mass measurement of MS/MS product ions.

When dealing with complex sample matrices, adequate mass resolution is essential. Much of the published literature is based upon measurements made with instruments with what is now considered limited resolving power (10,000–20,000 FWHM). The introduction of more advanced instruments has led to debate as to how much mass-resolving power is required when using HRMS. For example, 50,000–60,000 (FWHM) was considered adequate to ensure consistent and reliable mass assignment [49]. Whilst insufficient mass resolution may lead to inaccurate mass measurements caused by including unresolved background matrix interferences, especially when dealing with complex sample matrices, this may be less of an issue if no accurate mass measurement is required (i.e. when HRMS is used for screening only with no attempt at identification). Clearly, in such cases, enough mass resolution is required to provide sufficient selectivity to enable detection of residues or contaminants at the concentration of interest and not provide false positives in the database search. Ferrer and Thurman demonstrated a mass resolving power of 6,000–10,000 (FWHM) to be sufficient for many vegetable matrices [50]. Others have shown that higher mass-resolving power is required when faced with other food matrices, such as liver and honey [51]. Isobaric interferences can be minimized by cleaner samples (impractical for multi-residue methods), instruments with higher mass-resolving power, by use of MS/MS on hybrid tandem mass spectrometers, the use of ion mobility [52] or relying on chromatographic resolution [53]. The "one-method-fits-all" type of extraction using a simple solvent system with no sample clean-up is expected to aggravate this issue further.

Accurate mass measurement of small molecules is used to define elemental formulae and thereby to confirm the identification of target compounds or support the identification of suspects or unknowns by providing a list of possible elemental compositions [54]. Accurate mass measurement is the observed difference between the experimentally measured mass (the accurate mass) and the theoretical mass (the exact mass) of a particular ion of known charge and typically reported as a relative value (ppm). Both ToF and Orbitrap-based mass analyzers are now capable of <1 ppm mass accuracies although specifications vary (Table 2). Earlier ToF instruments exhibited poorer performance, typically 5 ppm [55]. Those instruments with time-to-digital converter (TDC) technology also produced accurate mass measurements that were detrimentally affected by the ion abundances (detector saturation), restricting the range over which measurements could be made accurately.

The best values for mass accuracies are recorded when using internal mass calibration (i.e. the sample and the calibrant solution are introduced into the ion source at the same time or background ions are employed as calibrants). Measurements of accurate mass in food extracts depend on sufficient response (without saturation of the detector) and adequate mass resolution from interferences.

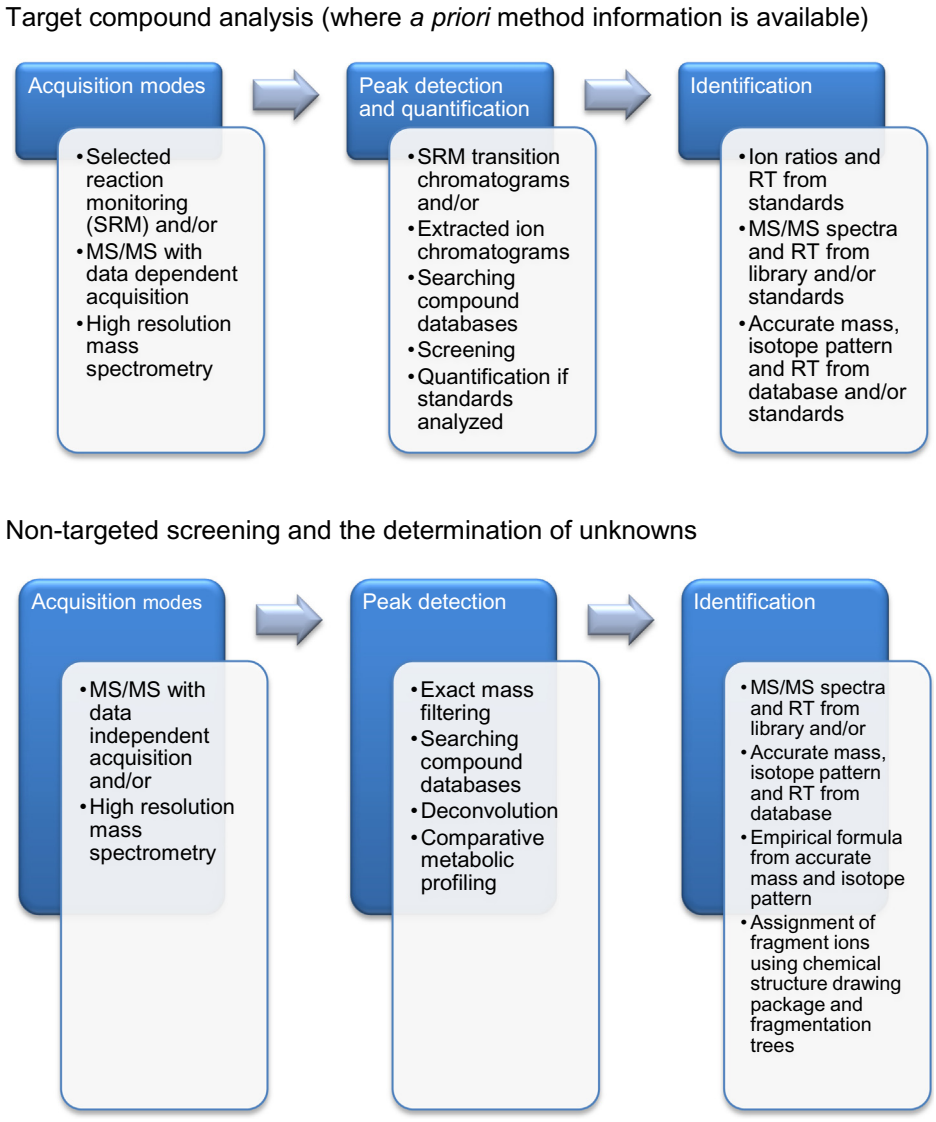


Fig. 1. Work flows for targeted and non-targeted LC-MS analysis.

3. Determination of chemical contaminants in food using LC-MS

These mass analyzers can be used in a number of different workflows, the steps of which are summarized in Fig. 1.

The use of LC-MS for initial screening is intended to offer a qualitative (yes/no) assessment of the presence of a large number of compounds in a large number of samples, although there is usually a need to relate the amount detected to some sort of action limit that triggers confirmatory analysis. The focus is on providing a rapid, cost-effective analysis that generates no false-negative results with a manageable frequency of false-positive results. Screening techniques can be targeted or untargeted.

Conventional targeted analysis is based on establishing an acquisition method to determine a list of known analytes, often using reference standards, and typically methods are validated prior to analysis of real samples. A list of selected compounds is prepared based on information, such as the likely usage of pesticides or veterinary medicines, those contaminants frequently detected in food or those included in priority lists based upon legislation. The scope of a targeted approach, although often extensive, will always be limited to the chosen list and the availability of standard reference materials. This list of compounds is continually changing and it is difficult to ensure targeted methods cover all possible compounds of interest.

To cover this gap, non-target analysis offers the possibility of detecting both unexpected compounds and true unknowns. When reference standards are not available to the user, compound-specific information, such as molecular formula and structure, can be used to construct a detection method based upon database searching. Identification in both workflows can be aided by comparison of MS/MS spectra with entries in libraries supplied by vendors. However, definitions of targeted and untargeted analysis vary, depending upon whether one considers information available related to the method or the analytes. Here, discussion of targeted analysis is applied to analyses in which compound-specific information is required before acquisition and non-target analysis refers to cases where the acquisition step has no *a priori* information (e.g. no retention time, no optimum MS conditions and no data on likely performance).

3.1. Target-compound screening

Instruments with a QqQ configuration, operated in SRM mode, deliver the selectivity and the sensitivity typically required for

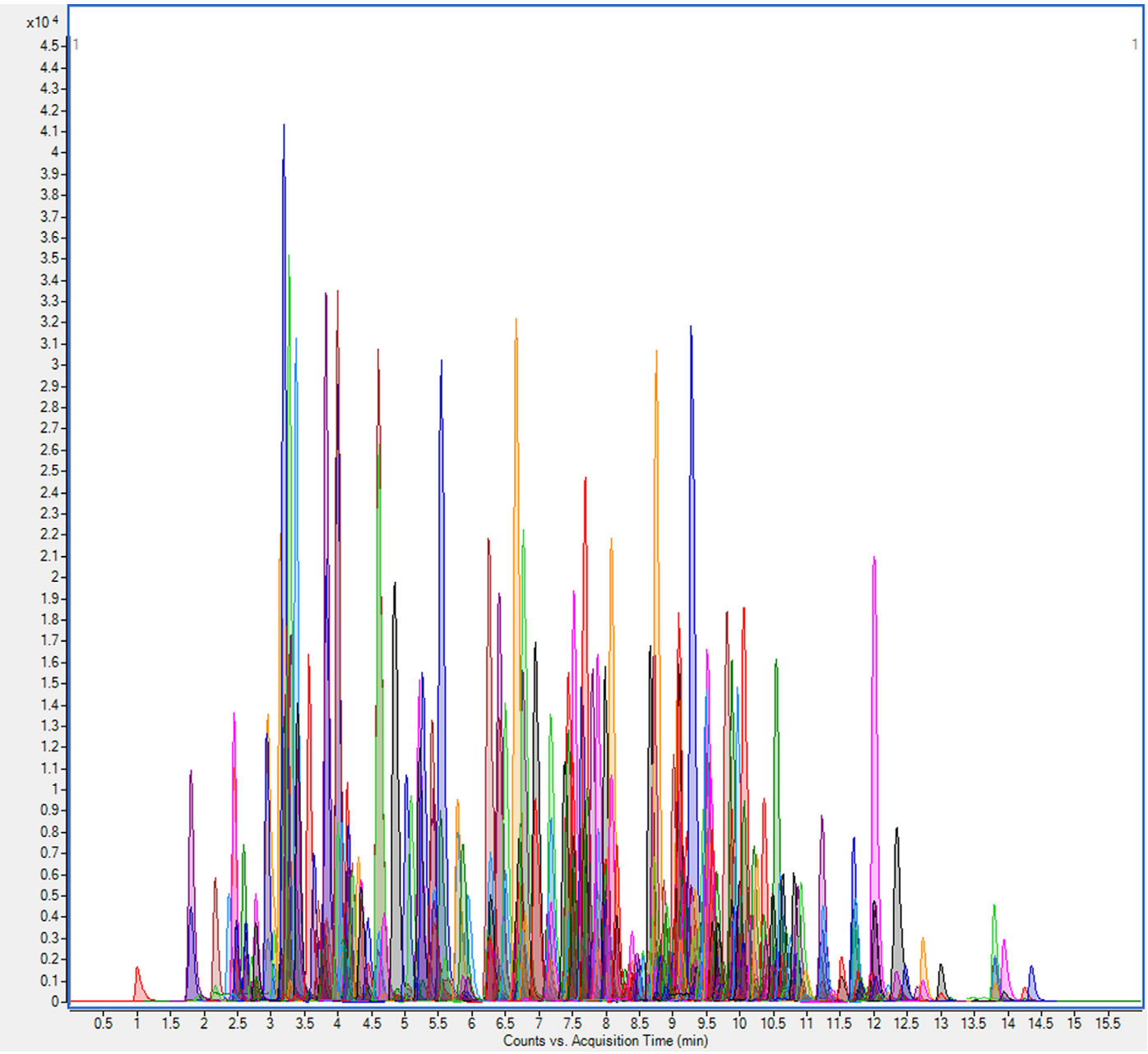


Fig. 2. Chromatograms obtained from the simultaneous analysis of a mixture of 250 pesticide residues, each at 0.01 mg/kg in grape extract, using UHPLC-MS/MS on a QqQ instrument in SRM mode with rapid polarity switching.

monitoring for compliance with legislative limits. The approach is well established for targeted multi-component determination of food contaminants. As demonstrated by the many different chromatographic peaks shown in Fig. 2, the rapid monitoring of hundreds of transitions is now achievable with good sensitivity and precision, making possible development of methods covering many more analytes than previously [56,57]. The large number of analytes that can now be monitored has been made possible by the use of retention-time window-based SRM acquisition. The user needs only to enter the masses and the retention times for each SRM and some indication of peak width and/or data points across the peak. The software sets the acquisition windows for each transition so they are centered on the time when the compound elutes. The windows are allowed to overlap and dwell time is calculated automatically so that no time is wasted acquiring other transitions for compounds that have yet to elute. This optimizes the time spent acquiring data to maximize sensitivity whilst ensuring sufficient data points across peaks to give good precision. This approach relies on not only knowledge of the retention time for each component but also retention time to be stable throughout multiple analyses. Hence, it has become essential to make regular checks on retention-time drift and to make any necessary adjustment of the acquisition method before analysis.

When coupled with multi-residue extraction techniques, LC-MS/MS on QqQ instruments in SRM mode is capable of screening a large number of target contaminants, even in difficult food matrices. For example, a method was successfully validated for screening 113 of the 127 veterinary medicines tested at or below US regulatory tolerance levels in bovine muscle. A novel aspect of this method was the post-column infusion of mobile-phase additives during the elution of anthelmintic drugs to enhance their MS-detection properties [58].

It is also possible to utilize MS/MS spectra to limit reporting of false positives through extra compound identification based upon searching against mass spectral libraries (see "Identification" below). Pre-selection of a precursor ion is required for MS/MS. For targeted analysis, this is realized by the use of information-dependent acquisition (IDA), whereby a product-ion scan takes place only after the detection of a candidate precursor ion selected using predetermined rules, such as from an inclusion list.

Kmellar et al. described the screening of 300 pesticides in fruit and vegetable samples using QuEChERS and LC-MS/MS with SRM-triggered product-ion scans, although detection parameters were reported for only those pesticides requiring confirmation [59]. No false positives were encountered from the screening analysis (only after analyst review) because all presumptive identifications were confirmed in the second analysis. One pitfall of the IDA MS/MS approach occurs when two target compounds co-elute. If only the most intense precursor ion triggers the MS/MS process, the compound with the lower intensity precursor ion may not be detected.

3.2. Non-target (or retrospective) screening

No pre-programming of multiple mass functions is required as full spectral acquisition is carried out with selectivity being provided by high mass-resolving power or MS/MS. Non-targeted analysis provides greater scope than a targeted approach. For example, one could extend monitoring to certain metabolites or other transformation products [60], for which reference standards might not be available, or to cover old or unauthorized substances no longer in use (e.g. isofenphos-methyl in peppers [61]) or, conversely, because they are very recent, so they have yet to be integrated into current monitoring plans.

Whilst all LC-MS instruments can perform full spectral acquisition, not all can maintain sufficient sensitivity in this mode for non-target analysis. HRMS instruments have been used for non-target screening of a wide range of different contaminants combined into a single analysis [62–64] and separate categories including pesticides [65,66], veterinary medicines [67,68], toxins [48,69] and other food contaminants [70,71]. Being able to carry out analysis without the need for reference standards is critical when dealing with a food-contamination crisis, especially involving previously unreported analytes [72] or food poisoning [73].

Strategies for evaluation of the data generated by non-targeted acquisition using HRMS have been developed using two different complementary processes: exact mass filtering, and searching databases relating to molecular formulae. Emphasis is focused upon detectability rather than meeting unequivocal identification criteria. To be effective, these processes must be automated and quick, but they require more computing power and data management/storage than traditionally associated with LC-MS analyses using QqQ instruments.

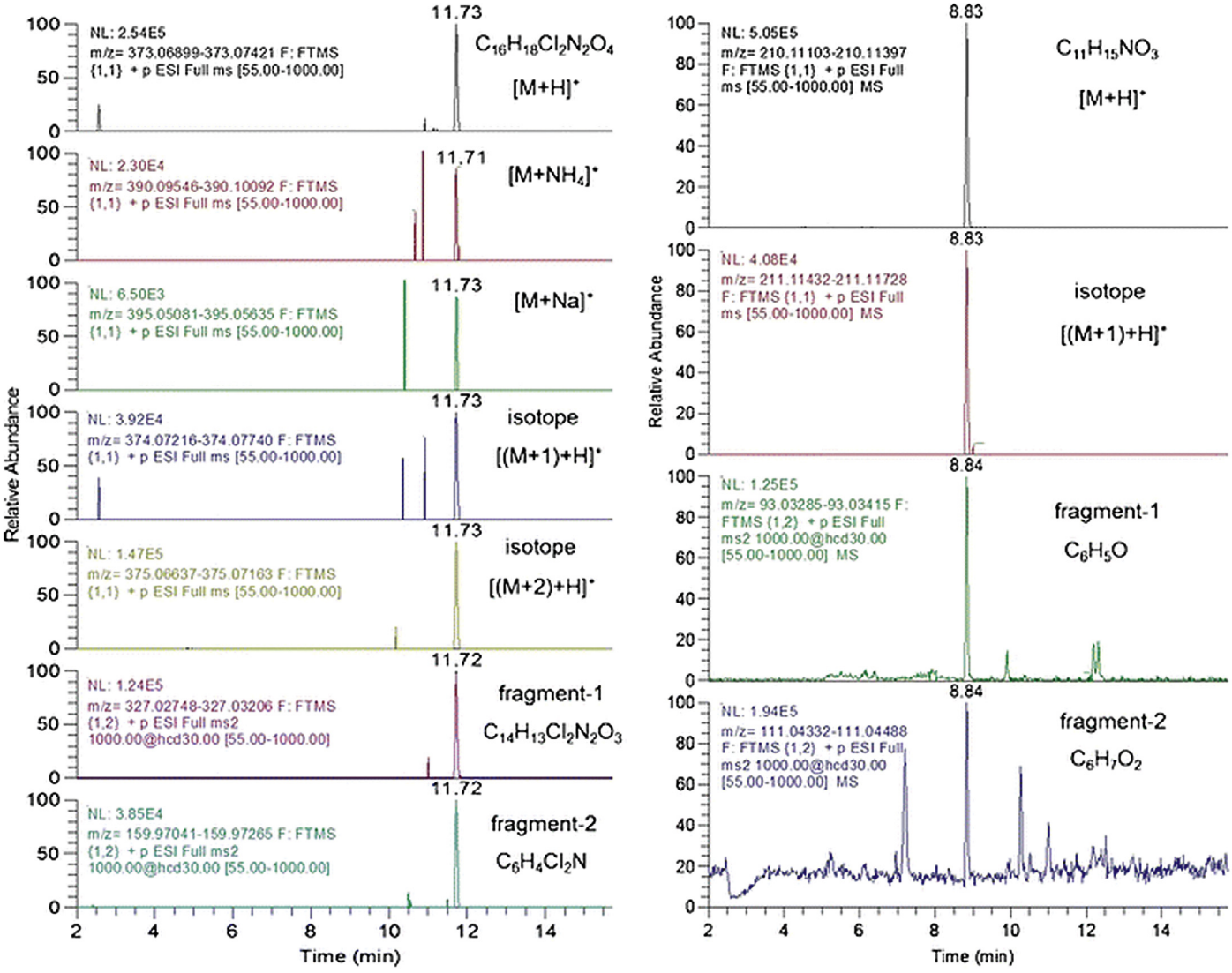
Molecular formulae databases containing information on exact mass and isotopic patterns were originally developed and customized by users in house but are now available commercially or via the Intranet. Exact analyte masses, listed in the database, are extracted from the total ion current (TIC) with a narrow mass window [74]. This can be constrained to a specific time window if information on retention time is available. Results are reported as a "hit list" with or without creating chromatographic peaks. Windows of 5 ppm have been successfully employed using an Orbitrap [75] but, when ToF analyzers are employed, more careful optimization of the accurate-mass window tolerances (typically 5–50 ppm) is required to ensure adequate selectivity as resolving power varies considerably between instrument types [76]. Applying too narrow a mass window around the exact mass can result in complete loss of the signal when the measured mass lies outside the defined tolerance, the consequence being false negatives [77].

One challenge to non-targeted analysis is the assessment of the frequency of occurrence of false negatives, as, without analytical standards, it is impossible to prove from the outset whether a compound has been recovered sufficiently during the analytical procedure or is not ionized as anticipated. Software parameters need to be optimized to find a practical balance between reported false positives and false negatives. Such filters or criteria might include tolerances on response threshold, retention time and isotopic fit and the presence of a second diagnostic ion. Mol et al. utilized adducts, isotopes and fragments to generate additional diagnostic ions [78], as illustrated in Fig. 3. With no information on retention time, the false-positive rate can be high if mass-resolving power is restricted (e.g. 10–20,000 FWHM on an older ToF instrument). The frequency of false negatives and false positives increases in complex sample matrices through ion suppression and isobaric interference, respectively. Although false positives can be rejected after confirmatory analysis, this is time-consuming and inefficient. The scope of this approach is also limited by the magnitude of the database. Screening for unexpected compounds not listed the database is facilitated by the use of some form of deconvolution algorithm. Any peak detected is then assigned a possible elemental formula based upon measured mass and isotopic fit. The most likely candidates at the top of the scored list are further scrutinized by employing additional data or extra analyses.

An automatic non-targeted screening method using LC-ToF analysis and database searching was successfully used to detect and to identify 210 pesticides in 78 positive samples of fruit and vegetable samples at concentrations greater than 0.01 mg/kg [79]. ESI in positive-ion mode on a bench-top Orbitrap was used to successfully detect 89% of the 177 pesticides spiked into spinach at 0.025 mg/kg, using an accurate mass search for $[M+H]^+$, $[M+NH_4]^+$ and $[M+Na]^+$ ions [80]. The authors concluded that improvements to instrumentation, methods, and software were needed for efficient use of non-targeted screens in parallel with QqQ platforms. In contrast, the same instrument type was successfully evaluated for the screening of at least 63 antimicrobial compounds in muscle tissue for compliance with EU MRLs [81].

It is also possible to utilize MS/MS for non-targeted analysis by comparing spectra against entries in mass spectral libraries, as used in systematic toxicological analysis [82]. For non-targeted analysis, with no prior knowledge of analytes prior to acquisition, MS/MS has to be carried out in a data-independent manner, triggering an MS/MS experiment when the TIC exceeds some specified response threshold. Selecting precursor ions from the TIC, fragmentation via CID and scanning out the product ions is very time-consuming in terms of duty cycle limiting the number of scans that can be acquired. An alternative approach is available when using some HRMS instruments, which acquire data without precursor-ion selection but rapidly alternate between low and elevated energy to give molecular species and fragment ions. The data are re-assigned using the chromatographic profile and occasionally other additional filtering criteria (e.g. neutral losses and isotopes), providing correlation of "precursor" and "product" ions within a practical time frame [83,84]. Despite these advantages, this technique is not true MS/MS, as there is no precursor-ion selection and it has yet to be widely adopted for analysis of contaminants in food [85,86], although it has been applied to the systematic screening of pesticides and other contaminants in water samples [87] and an in-house empirical spectral library was built for a large number of organic pollutants acquired in this manner using MS^E mode [88].

In another non-targeted approach, the safety of foods is not monitored directly by determination of residues and contaminants but using a metabolomics approach comparing suspected contaminated food with uncontaminated foods [89,90].



Reproduced with permission from [78].

Fig. 3. Extracted ion chromatograms illustrating need for diagnostic ions for selected pesticides in fruit. Left: 0.01 mg/kg mefenpyr-diethyl in orange. Right: 0.01 mg/kg propoxur in apple. Acquisition: alternating scan events without/with HCD fragmentation. Resolving power, 50,000. Mass extraction window +5 ppm.

3.3. Quantification

LC-MS/MS using SRM on QqQ instruments has become the standard approach for quantification, but, in the past decade, HRMS instruments were also increasingly used for this purpose [26,91,92]. In both cases, the response from peaks in sample extracts is compared to that from standard solutions, and critical issues for good quantification include avoiding carry-over and contamination, suitable quality control, an appropriate calibration strategy and good linearity.

Compared to QqQ instruments, the linear dynamic range of earlier ToF analyzers was rather narrow [55], but developments in instrument design have resulted in improved quantitative performance by extending the dynamic range, obtaining faster acquisition rates to generate sufficient data points across the peaks and providing higher sensitivity through improvements in ion-transfer devices. Acquisition rate, mass-axis stability and mass shift at high ion abundances on ToF mass analyzers can have a significant impact on precision and accuracy of measurements made using exact mass filtering. Quantification is also possible using Orbitrap analyzers but performance can be influenced by the acquisition rate, the automatic gain-control functionality, designed to avoid overfilling of the C trap collecting device. When faced with “dirty” extracts containing a lot of matrix co-extractives, the automatic gain control shortens accumulation times, reducing not only the number of matrix ions but also the number of analyte ions. Kaufmann reported that the presence of a high concentration of proteins can cause the loss of low-mass ions [93]. Once more effective cleaning was introduced, the quantitative performance of the HRMS method was comparable with that observed using QqQ in SRM mode.

The most significant issue that affects quantification using any LC-MS platform, especially when ESI is employed, is that of ion suppression or enhancement, typically known as the “matrix effect” [94,95]. The predominant cause is the presence of undesired components that co-elute in the chromatographic separation and compete for access to the surface of droplets and subsequent “ion evaporation” or changes in eluent properties, such as surface tension, viscosity, volatility – all factors known to affect the ionization process [96,97]. Matrix effects are known to depend on both compound and matrix, and vary with the choice of ionization mode [98] and the ion-source design [99]. Considerable variation in the magnitude of the matrix effects has been observed, not only among various

matrices, but from sample to sample even within the same matrix type [100].

No method validation should be accepted without a thorough evaluation of matrix effects [101,102] and possible strategies to minimize or to correct their influence should be addressed [103]. Removal or reduction of such effects can be achieved by improved sample preparation or re-optimization of LC conditions where practical. Various calibration strategies are used to compensate for matrix effects. Isotopically-labeled internal standards work very well as long as suppression is not total, but generally for the direct native analyte only. Properties, such as retention, ionization and fragmentation, are almost identical except for characteristic mass shifts caused by the number of labeled isotopes. As labeled analogues are commonly not available or prove expensive for multi-residue analyses, matrix matching tends to be the most common way to reduce matrix effects. However, there are logistical problems associated with location, preparation and storage of the many different blank matrix extracts required that make this approach time-consuming. The magnitude of the effects can be highly variable within a single food type, making it difficult to find one representative blank sample, although recent attempts have been made to use a representative matrix for quantification of pesticides in soft fruit [104]. In the absence of a suitable blank sample matrix, the method of standard addition can be used, so that replicate portions of the sample itself serve as the matrix "blank". High-sensitivity instruments allow us to dilute extracts to reduce the "matrix concentration" in the final extract and thus also the sample equivalents injected [105,106].

LC-MS/MS is often used with QuEChERS, in combination with GC-MS/MS, for quantitative pesticide-residue analysis. Recently, a method was developed and validated for quantification of 85% of the 86 pesticides sought in tea at concentrations suitable for monitoring compliance with EU MRLs, and recoveries of the majority of compounds were in the 70–120% range and were characterized by precision lower than 20% [107].

3.4. *Compound identification and the structural elucidation of unknowns*

There is no universally-accepted definition of the terms "confirmation" or "identification" [108,109]. Historically, MS tended to be employed for confirmation (a second analysis) of the result from an initial screen whilst concurrently providing structural information that met some form of acceptance criteria for identification. However, criteria are now applied to help identify suspect positives detected in a single targeted or untargeted LC-MS analysis as well as confirmation of those detected during an earlier screening experiment.

When using LC-MS/MS in SRM mode, two SRM transitions are usually acquired for each compound of interest – one for quantification and one qualifier transition. Identification is achieved through comparison of the ion ratio generated from analysis of the sample with the ion ratio from a reference. Permitted tolerances for the relative intensities of the detected ions, set for official control purposes within the EU, specify the maximum deviation between the observed and the expected ion ratios [110,111]. In some cases, however, false-positive results may be obtained by this approach [112], especially if no consideration is given to the selectivity of transitions used. One can add or selectively trigger acquisition of additional transitions or exhaustively evaluate the matrix under investigation for the presence of isobaric interferences. Whilst these approaches could prove useful, on an *ad hoc* basis, to solve particular problems as they arise, it is considered impractical to try to encompass all analytes and matrices of interest.

It is now technically possible to utilize MS/MS spectra to limit the reporting of false positives through compound identification based upon searching against mass spectral libraries supplied by the vendor [113] or prepared in house, both supported by extracting additional spectra from literature articles and Internet sites [114]. Such spectra (e.g. β-nortestosterone in Fig. 4) have the potential to contain more information and thus provide an added degree of confidence for compound identification. The prerequisite is that the analyte generates sufficient product ions with structural information and there is no isobaric interference on the precursor ion.

Historically, the low duty cycle of the QqQ arrangement limited the number of scans that could be acquired simultaneously and hence sensitivity was lacking in this mode. MS/MS spectra can now be acquired concurrently with SRM transitions typically using QqLIT instruments [115] and other means of improving the sampling duty cycle on QqQ instruments [116], although the experiment on QqQ instruments is typically limited to a couple of scans for each MS/MS spectra. There are currently only limited reports of using these enhanced acquisition modes for the confirmation of identify of food contaminants [117].

Spectral MS/MS libraries, such as MassBank or NIST, contain reference spectra for many compounds but their limited chemical coverage reduces the chance of correct, reliable identification of unknown spectra outside the database domain. Although the same product ions may be generated using the various types of MS/MS instrument, different mechanisms for ion isolation and fragmentation result in variations in abundance, so spectra are often not comparable in a library search. Unreliable results are also likely if the precursor ion and/or product ions are not sufficiently resolved from isobaric interference. Whilst the use of ion ratios is acceptable practice for confirmation of identity within the EU, there is little guidance currently on the acceptance of library searching with MS/MS product-ion scans.

Decision 2002/657/EC also introduced a system of identification points (IPs) for MS detection [118,119]. For example, a minimum of four IPs is required for identification of Group A "banned" substances. When using a QqQ instrument in SRM mode, this implies four IPs can be collected by obtaining two transitions with 1.5 identification points each and 1 point for the precursor.

HRMS has also been used for identification for official control purposes. Decision 2002/657/EC defines HRMS as MS at a mass resolution of 10,000 (according to the 10% valley definition typically used with sector instruments). This corresponds to a resolution of 20,000 using the FWHM definition [120] and so is readily achievable on the Orbitrap and more recent ToF analyzers. However, when one considers instruments without MS/MS capability, such as the Orbitrap and ToF instruments, two diagnostic ions are needed, earning 2 IPs each. This typically requires in-source fragmentation. This approach was evaluated by Blokland et al. using accurate mass measurements from analysis on LC-ToF (no MS/MS). They proposed allocation of 2 IPs to the measurement of a single ion with a mass accuracy better than 3 ppm [121].

There is some variance in the way HRMS is considered for official control purposes. Decision 2002/657/EC attaches no significance to measurements of mass accuracy. In contrast, Document No. SANCO/10684/2009 for pesticide analysis has no definition of "high resolution" but does specify the need for at least two diagnostic ions with mass accuracy of <5 ppm. False-negative results are likely when the mass resolution is insufficient to separate analyte ions from isobaric co-eluting sample matrix ions, as described earlier. The debate over the use of HRMS for identification for official control purposes has prompted proposals for additional identification criteria to be added to Decision 2002/657/EC [38,122].

No such issues with IPs are faced when using MS/MS on a hybrid HRMS instrument. MS/MS spectra can also be acquired using hybrid HRMS instruments (QqToF and Orbitrap devices) with the additional advantage of accurate mass measurements on the product ions. This facilitates the use of libraries of accurate mass CID spectra [82] or MS/MS carried out in support of a database search [123]. The

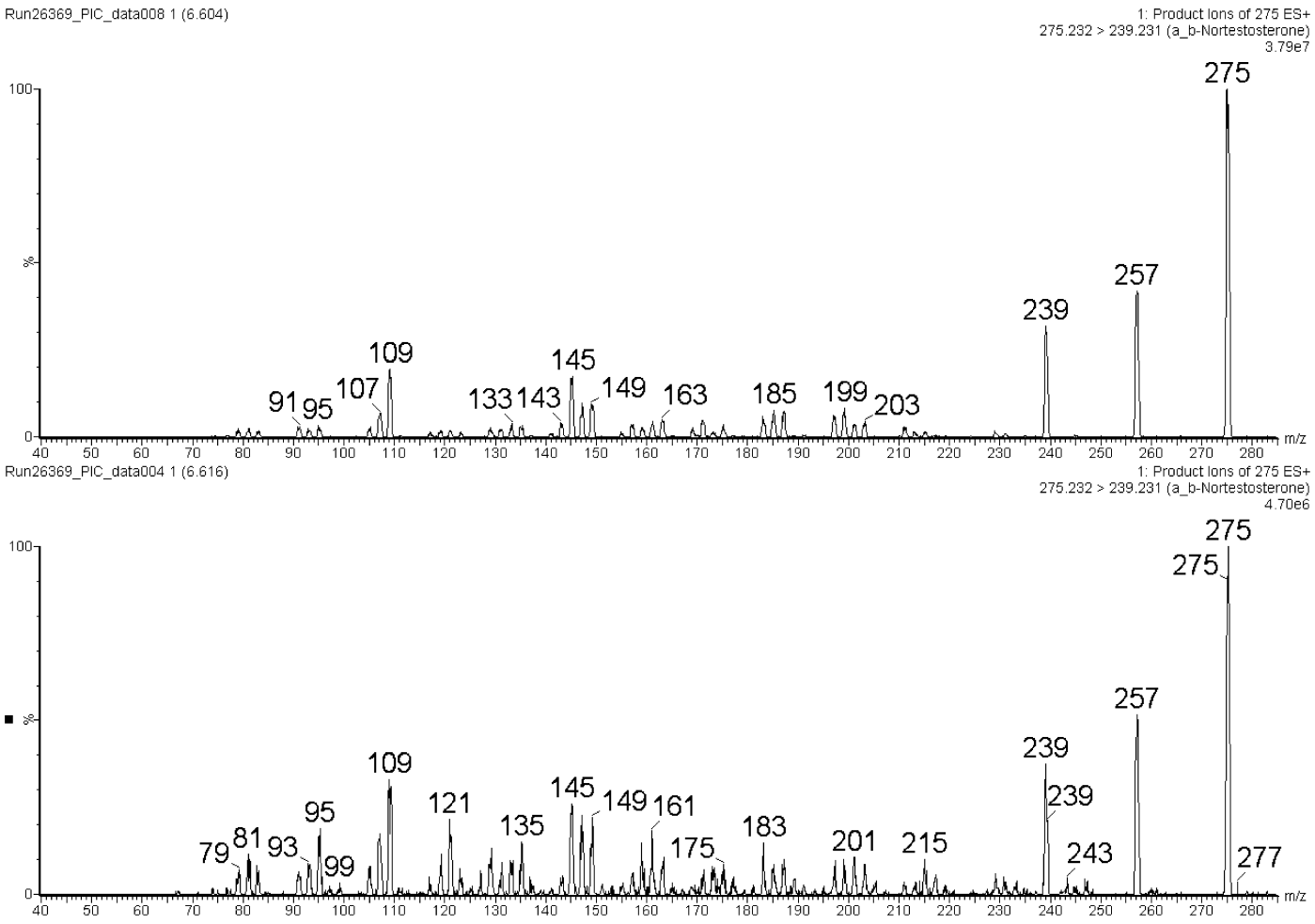


Fig. 4. Identification of nortestosterone in a non-compliant sample (A) by comparison of MSMS spectrum with that generated from a reference standard (B).

problem with using QqToF instruments for this approach is that the accuracy of the mass measurements of product ions is typically worse (>5 ppm) than that obtained in MS mode [124]. No such issues are observed when using Orbitrap hybrids, which provide good accurate mass measurements on parent and product ions alike. Mass errors of 0.3 ppm and 1.1 ppm were reported for the precursor and product ions of carbendazim using a quadrupole-Orbitrap instrument [125].

Although structure elucidation of unknown contaminants by LC-MS remains a challenge, despite the advanced stage of the hardware, progress recently reviewed could be applied to the analysis of unknown contaminants in food [126]. The development of an accurate LC-retention prediction system augments MS information, increasing the opportunity for identification [127]. Assignment of a structure for a peak detected by accurate mass alone is unlikely, unless the compound detected has a significant mass defect between the monoisotopic mass of an element and the mass of its isotopic cluster [128,129] or is known in the chemical literature, a reference database or an Internet resource [130]. Compound databases {e.g. PubChem [131] or ChemSpider [132]} have an extremely large coverage of the chemical space, but they cannot be queried with spectral information directly.

The first crucial step is to obtain correct elemental compositions. The capabilities of the vendors' tools for chemical-formula prediction are reported to be variable with others developing tools via open source [133]. The number of possible empirical formulae that can be assigned to a mass strongly depends on mass accuracy. Increased filtering or restriction of error in the measurement reduces the possible candidates for a given accurate mass measurement, but, if the ion is actually a fragment ion, unknown to the analyst, then assignment is more difficult. Data acquired even with <1 ppm mass accuracy and high mass-resolving power can still be insufficient for calculating unique elemental compositions without information about isotope pattern [134,135]. A positive result for triflumuron, reported by QqQ, proved false and was rejected due to lack of agreement with the chlorine-isotope pattern observed from analysis by ToF [36]. Very high mass-resolving power (e.g. 100,000 FWHM), capable of separating ^{15}N from ^{13}C isotopes, does provide enhanced capability for identification. In order to constrain the thousands of possible candidate structures automatically, rules have been developed to select the most likely and chemically correct molecular formulae, such as those used in metabolomics [136], but such rules have yet to be systematically applied to the identification of contaminants in food.

Fragmentation data from MS/MS or MS^n experiments, in some cases with accurate mass measurement of precursor and/or product ions, can provide a tremendous amount of information, but there is still a limited understanding of any rules associated with the fragmentation of precursor ions derived from ESI that takes place in the MS/MS collision cell (typically CID), even though the structure-fragmentation relationship and fragmentation mechanisms have been widely studied [137]. In many cases, chemical-structure drawing programs are used to try to identify fragment ions and their accurate masses [138,139]. The number of chemically meaningful

structures that can be assigned to an unknown peak detected tends to be limited to structures showing a close relationship with the parent compound [140,141]. *In-silico* fragmentation or fragmentation trees have been introduced to condense the numerous search results from a large chemical database [142] and for the automated computational identification of small molecules that cannot be found in any database [143]. Results from several resources can now be combined to improve compound identification [144]. Although the utility of hybrid analyzers for detailed assessment of certain food contaminants has been demonstrated, typically for investigating metabolism and degradation pathways for pesticides [145,146] and veterinary medicines [147], novel toxins [148,149] and other food contaminants [150,151], the elucidation of unknown compounds in food samples remains a significant challenge, which will probably only be overcome by combining the use of several analytical techniques. Two unknown red dyes isolated from a dried strawberry package were successfully identified as subsidiary colors contained in food red no. 40 (R40), which had been added to the dried strawberries, using a combination of HPLC data and UV-VIS, MS and NMR spectra [152].

4. Conclusions

With the recent advances and novel developments in chromatography and MS, it is evident that the great improvement in sensitivity and selectivity offered by the combination of these two powerful analytical techniques has made significant contributions in both screening for, and the quantitative determinations of, food contaminants. It has been well established that this is the cornerstone of analytical technique for monitoring and controlling the wholesomeness of foods.

As new techniques and instrumentation emerge, the application of LC-MS will cover a wider range of compounds and a greater variety of matrices, using a combination of targeted and non-targeted approaches. Modern instruments are also more sensitive and more selective, take up less laboratory space, are more robust, and are easier to use and to maintain than their older counterparts, whilst costing less. However, more attention is needed to implement software that can facilitate reliable acquisition by "non-specialists" and to provide more efficient solutions for the automation of time-consuming, complicated data processing. The impact of matrix effects on detection and quantification, the presence of isobaric interference and maintaining confidence in the assignment of identity remain the three major limitations for methods employing LC-MS for the determination of chemical contaminants in complex food matrices. The increasing use of hybrid mass spectrometers, incorporating mass analyzers that are capable of high mass resolution and accurate mass measurements, mitigates some of the problems associated with selectivity and identification, but further technological development of LC-MS interfaces is required to minimize matrix effects.

Acknowledgments

We thank Richard Fussell and Laurence Castle for help with proofreading this article.

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