Chapter 3
Mass Spectrometry Methods for Food Safety/Detection of Toxins in Food

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Abstract In this chapter, a brief overview of fundamentals in mass spectrometry (MS) and on methods for food safety and detection of toxins in food is described. It is focused on ionization techniques, analyzers, high resolution MS, tandem MS and on different methodologies and approaches that modern mass spectrometry offers in this field.

3.1 Mass Spectrometry: An Overview

Mass spectrometry (MS) is an important and very powerful methodology for structurally characterizing, identifying, and for quantifying wide classes of unknowns, ranging from apolar low molecular weight (MW) analytes to polar big molecules with MW of millions of Daltons [1–3].

MS finds applications in many fields, such as food, biomedicine, environment, archaeology, forensics, *omics* sciences, etc. Its most important features are high specificity and selectivity, high sensitivity and high speed. Its coupling with separative techniques, such as gas chromatography (GC) and high performance liquid chromatography (HPLC), lets possible to carry out analysis of very complex mixtures with high sensitivity and specificity. The scheme of a mass spectrometer is reported in Fig. 3.1.

Mass spectrometry studies ions in the gas phase. As we are generally dealing with molecules, the first event which must occur in a mass spectrometer, and in particular in the ion source, is the ionization, *i.e.* transformation of a molecule into an ion. Once formed, ions are driven towards the analyzer, which separates them according to their mass-to-charge (*m/z*) ratios, and finally to the detector.

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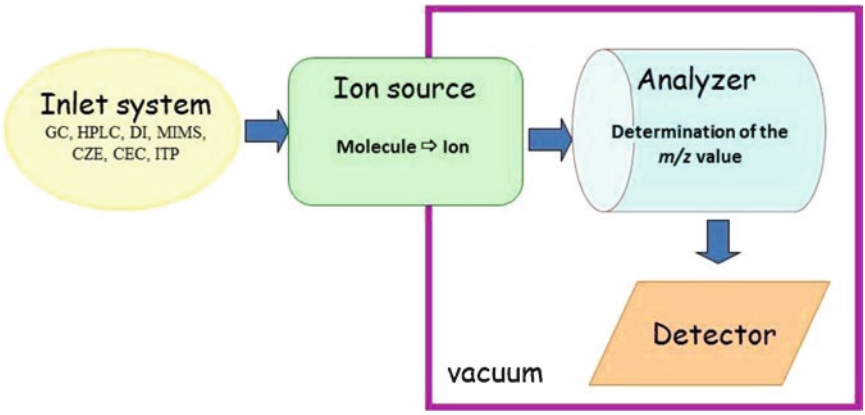

Fig. 3.1 The diagram of a mass spectrometer

3.2 Ionization Techniques

Ionization is the crucial event in every MS experiment: if ions are not formed, no any datum will be obtained.

Mass spectrometry can study wide classes of molecules with different chemico-physical properties. Having different properties, they cannot be ionized with the same ionization technique. So there are ionization techniques for volatile molecules and many others for ionizing polar analytes. All of them can be used for ionizing different toxins [4].

3.2.1 Volatile Molecules

Ionization techniques for ionizing volatile molecules are mostly limited to electron ionization and chemical ionization. The former is the first ionization technique used in MS more than one century ago and it is based on gas phase interactions between a molecule with an energetic electron beam. Chemical ionization has been introduced around the middle of the previous century and it is based on gas-phase ion-molecule reactions between the neutral analyte and a gas introduced in the ion source.

Both these ionization techniques can be coupled to gas chromatography (GC-MS) for the analysis of complex mixtures.

As an example, volatile toxins, such as polychlorinated dibenzo-*p*-dioxins (PCDDs), poly-chlorinated dibenzofurans (PCDFs), polychlorinated biphenyls (PCBs) [5] and mycotoxins [6] can be ionized by electron ionization and chemical ionization.

3.2.2 Polar Analytes

The real revolution in ionization methods for polar compounds is represented by Fast Atom Bombardment (FAB) introduced in 1981 by Barber and Bordoli [7]. FAB overcame the previous methods as it was easy, sensitive, reproducible, fast and able to ionize relatively big molecules.

But few years after its introduction, other ionization techniques, and in particular electrospray (ESI) and matrix-assisted laser desorption (MALDI), owing to their higher versatility, replaced FAB. Soon other atmospheric pressure ionizations were introduced, *i.e.* atmospheric pressure chemical ionization (APCI), atmospheric pressure photo ionization (APPI). More recently an increasing plethora of ambient mass spectrometry methods [8], such as desorption electrospray ionization (DESI) [9], direct analysis in real time (DART) [10], low temperature plasma (LTP) [11], rapid evaporative ionization mass spectrometry (REIMS) [12], paper spray ionization (PSI) [13], electrospray laser desorption ionization (ELDI) [14] and many others, which ionize analytes in their ambient, reducing or eliminating extraction and purification steps, have been introduced. As an example, ambient conditions using DART ionization coupled to high resolution mass spectrometry have been used in the analysis of multiple mycotoxins in cereals [15], while ELDI has been used for a rapid identification of herbal toxins emergency care [16].

3.3 Analyzers

Once the ions are formed in the ion source, they are accelerated towards the mass analyzer where their separation occurs according to their *m/z* ratios.

Analyzers can be divided into two main groups: those based on ion separation *in space* (or ion-beam analyzers: sectors, quadrupole, time of flight) and those separating ions *in time* (ion traps, Orbitrap, FT-ICR) (Table 3.1).

For ion separation, analyzers can use a magnetic field (B), an electric field (E) and a radiofrequency. As an example, quadrupoles use an electric field and a radiofrequency while with Orbitrap only an electric field is used.

Analyzers differ each other for some features, such as coverage of *m/z* range and resolving power. While time-of-flight has not restriction on *m/z* range, routinely all the others can analyze ions up to *m/z* 4000÷6000.

Actually, analyzers with high resolving power are: sectors (EB, BE), time of flight, FT-ICR and Orbitrap. A high resolving power allows to obtain some advantages, such as an increase of selectivity due to isobaric ion differentiation, elimination of interfering species and measurement of accurate mass from which the elemental composition of an ion can be obtained. On the other hand, an increase of resolving power implies a decrease of sensitivity and an increase of scan time.

Analyzers are involved not only in obtaining a full scan mass spectrum but also in tandem mass spectrometry experiments. Briefly, tandem mass spectrometry uses

Table 3.1 Analyzers and their main features

Analyzer	Force	Separation based on	*m/z* range	Resolving power	Mass accuracy
Ion separation *in space*					
Sectors (EB, BE, ….)	Magnetic and electrostatic fields	Ion momentum and kinetic energy	10,000	10,000	1–3 ppm
Quadrupole (Q)	Electric field and radiofrequency	Stability/ instability	4000	Unit	No
Time of flight (ToF)	Electric field	Speed	>100,000	>30,000	1–3 ppm
Ion separation *in time*					
3D and 2D ion trap (IT)	Electric field and radiofrequency	Frequency of the orbits	4000	<500	No
Fourier transform ion cyclotron resonance (FT-ICR)	Electric field, radiofrequency, magnetic field	Frequency of the orbits	10,000	>1,000,000	<1 ppm
Orbitrap	Electric field	Frequency of the harmonic oscillations	<6000	>300,000	1–3 ppm

two (MS/MS or MS^2) or more (MS^n) sequential stages of mass analysis (which can be spatially or temporally separated) in order to examine selectively the dissociations of given ions in a mixture of ions. For small molecules, ion dissociation can be induced by collision with a gas, such as nitrogen, argon, helium, occurring in a collision cell (q) located after the first analyzer, or inside an ion trap.

Different instrumental setup can be used in tandem mass spectrometry, such as sectors (B,E; E,B), triple quadrupoles (QqQ), ion traps, QqToF, Q-Orbitrap, FT-ICR, ToF/ToF.

3.4 Study of Complex Mixtures by MS

In the study of complex mixtures by MS, the classical approach consists in an extraction, a preliminary purification of the sample and a coupling of MS with gas chromatography (GC) for volatile compounds or with high performance liquid chromatography (HPLC) for polar compounds. Thus GC-MS(/MS) and HPLC-MS(/MS) couplings are extensively used when complex mixtures have to be analyzed. This approach increases specificity and selectivity of the analysis, because, for each compound, in addition to its mass spectrum, its retention time is also obtained. So, even if different compounds might yield the same mass spectrum, they will have different retention times.

A new tendency is to reduce at minimum or remove at all the extraction and purification steps and to introduce the entire sample inside the ion source. This can

be done in classical atmospheric pressure ionizations, such as ESI, by direct infusion, or by using ambient mass spectrometry techniques, such as DESI, DART, LTP, REIMS, PSI, etc.

The simultaneous introduction of many analytes in the ion source gives a molecular fingerprint of the sample and it is very effective for rapid screening analyses. On the other hand, it can have some drawbacks, such as ion suppression phenomena, presence of isobaric species, need of a high dynamic range, difficulty to detect trace molecules.

3.5 Identification, Confirmation and Quantitation of Analytes by Mass Spectrometry

Depending on the information we are interested in, different mass spectrometry approaches and strategies, using MS, high resolution mass spectrometry and tandem mass spectrometry, can be followed for identification, confirmation and quantitation of different compounds in complex matrices.

3.5.1 Structural Characterization and Identification of Unknowns: Untarget Analysis

In a discovery phase of a study in many fields, such as metabolomics [17], proteomics [18], toxicology [19], and many others, for structurally characterize and identifying unknowns without any preliminary information, an untarget analysis has to be performed.

An untargeted profiling shows the presence of all ionizable and detectable analytes and it can be advantageous for novel marker and toxin discovering. Further, this approach permits retrospective analysis of data based on a-posteriori hypothesis.

On the other hand, low abundance compounds might be likely missed because ion suppression or obscuration by background signals from the matrix.

In mass spectrometry untarget analysis, two main methods can be used: Data Dependent Acquisition or Data Independent Acquisition methods.

3.5.1.1 Data Dependent Acquisition (DDA)

In Data Dependent Acquisition a full MS scan is performed and ions are ranked by their intensities and/or charges. Then, according to user defined criteria, software applies automated real-time decisions for subsequent HRMS/MS^n analysis (Fig. 3.2).

A user-defined criterion might be: for ions exceeding a signal threshold, a high-resolution mass spectrum in a narrow *m/z* range followed by MS^2 or MS^n product ion scans have to be performed. To avoid repeating the same experiment for the

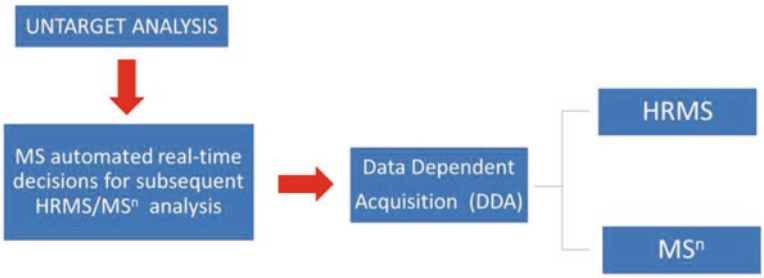

Fig. 3.2 Scheme of untarget and data dependent acquisition analysis

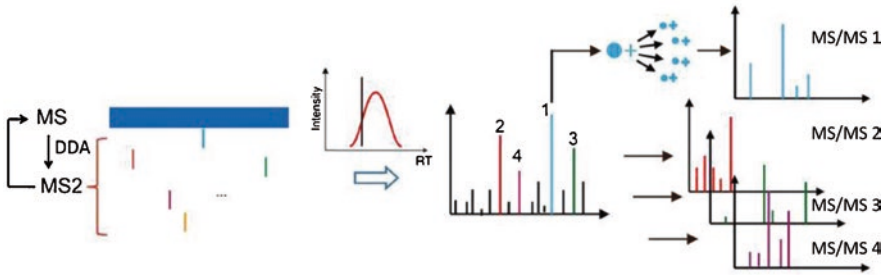

Fig. 3.3 A scheme of data dependent acquisition analysis. A MS full scan is acquired followed by MS^2 product ion scans of automated real-time selected ions. (Adapted from Ref. [17]. Copyright 2019, Springer)

same ions, a dynamic exclusion criterion (*i.e.* in the next 50 s doesn't select the same *m/z* value more than one time) has also to be defined (Fig. 3.3).

Different instrumental setup can be used for DDA analysis, such as sector instruments, ion traps, triple quadrupoles, Q-Orbitrap, QToF, FT-ICR.

DDA technique suffers from some limitations derived by low MS^2 spectral coverage due to its biased selection of high abundant precursor ions and to the undefined MS^2 spectral quality as the MS/MS spectra are not always acquired at the apex of a chromatographic peak.

High resolution mass spectrometry can be also used for a full mass spectrum acquisition in the *m/z* range defined by the operator.

3.5.1.2 Data Independent Acquisition (DIA)

Data independent acquisition methods have been generally used for target analysis. Some of them, and in particular those based on MS^{All}, MS^{E}, SWATH, PAcIFIC and MSX scan modes, are currently used for both target and untarget analysis (Fig. 3.4).

These approaches are not strictly MS^2 acquisition methods as no precursor ion selection is performed. In particular, ions in a narrow/wide *m/z* range are submitted all together to collision induced dissociations. Thus the resulting product ion

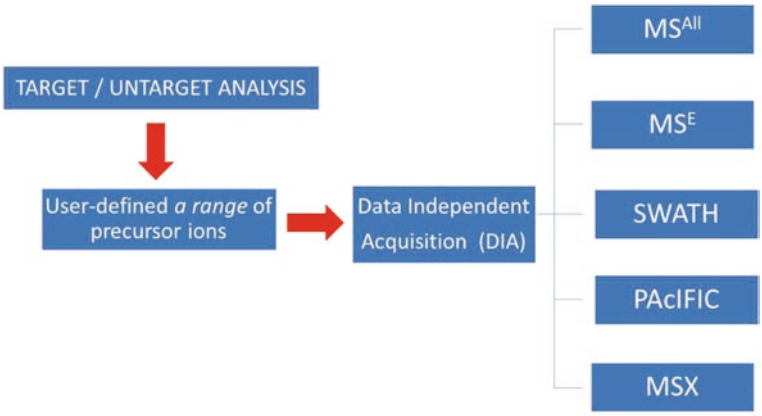

Fig. 3.4 Data independent acquisition modes based on user-defined ranges of precursor ions

spectrum contains all product ions, regardless of what the precursor ion is. It follows that the MS^2 spectrum is nonselective and it may lack specificity if more than one compound enters the ion source at the same time. It follows that these techniques generally require efficient chromatographic separations.

The produced data sets are very large, including a huge number of ions produced by also a huge number of analytes, which have to be entirely processed with appropriate algorithms and data analysis strategies.

The MS^{All} scan mode, also referred as MS^E [20], or All Ion Fragmentation (AIF) [21, 22] consists of two parallel alternating scan functions operating in a QqToF mass spectrometer: in the first, all ions coming from the ion source within a wide mass range (*e.g. m/z* 100–1000) are transmitted all together through a quadrupole, operating in a wide pass mode, to the collision cell, which has a low collision energy, so to avoid fragmentation, and finally to the ToF mass analyzer. All these ions form the precursor ion spectrum. The second scan function acquires data over the same mass range, but the collision energy is high (20–40 eV, for example) so to obtain product ions which are analyzed by the ToF analyzer. The result is a nonselective product ion spectrum of all precursor ions. By using a ToF analyzer, high resolution spectra are obtained for both the precursor ion and the product ion spectra.

If an efficient separative system, such as GC, HPLC or ion mobility, is coupled to MS, in most cases, the predominant fragment ions are produced by a single precursor ion.

The entire data set is then mined post-acquisition by assigning product ion spectra to their associated precursor ion peaks. This is done by aligning the precursor ion spectrum of each component with its corresponding product ion spectrum by retention time.

A scheme of the LC-MS^E method is depicted in Fig. 3.5.

SWATH (sequential window acquisition of all theoretical fragment-ion spectra) analysis is implemented on a QqToF instrumentation [24, 25]. In this technique, the

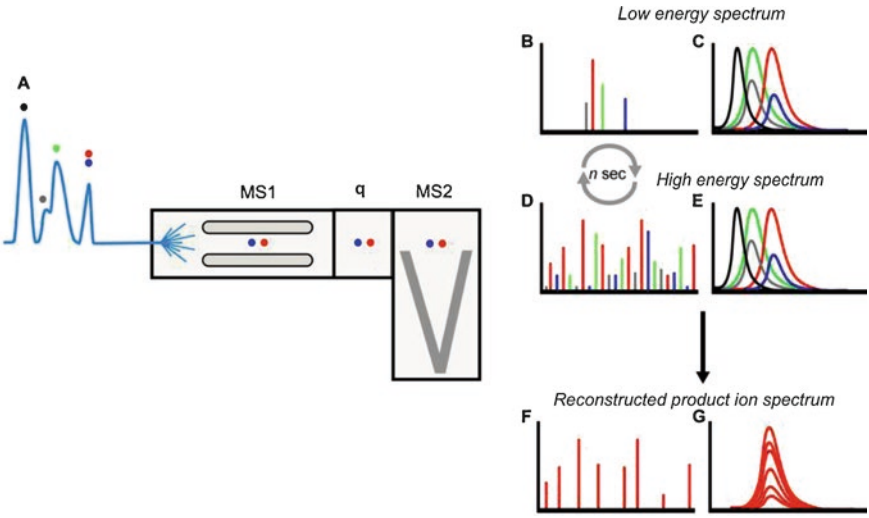

Fig. 3.5 An overview of LC–MS^E. Molecules coming from a separative system enter the mass spectrometer (**A**). They are ionized and ions pass through the quadrupole, operating in a wide pass mode (MS1), enter the collision cell (q) and then the ToF analyzer. When the collision energy is low, spectra of all precursor ions are obtained (**B**) together with their retention times (**C**); when the collision energy is switched to high, spectra of all product ions are obtained (**D**) together with their retention times (**E**). An ion-accounting algorithm compares the retention time profiles and intensity of all individual precursor ions (**C**) to all individual product ions (**E**) matching them on the basis of retention time profile and intensity (**G**) and creating a reconstructed product ion spectrum linked to a single precursor ion (**F**) that can be used by search engines to identify compounds. (Adapted from Ref. [23])

quadrupole analyzer is stepped continuously across the whole selected *m/z* range with a medium width mass window (20–30 Da) for precursor ion selection. Precursor ions are then transmitted to the collision cell, submitted to collision-induced dissociations and the resulting product ions are analyzed sequentially in high resolution by the ToF analyzer (Fig. 3.6).

The quadrupole isolation window can be (*i*) fixed (*e.g.* 25 Da width) (Fig. 3.6A); (*ii*) variable, with different isolation width based on equalizing the distribution of either the precursor ion population or the total ion current (Fig. 3.6B) [26], (*iii*) sequentially shifted with a small overlapping mass range (*e.g.* 5 Da), referred to as shift or offset SWATH, typically requiring five repetitive injections so to reconstruct more accurately the precursor/product ion relationship and improve the accuracy of compound identification and quantification (Fig. 3.6C) [27].

Other DIA methods are PAcIFIC and MSX, both applied in proteomics.

PAcIFIC, referred as precursor acquisition independent from ion count, has been developed on a LTQ-Orbitrap instrument and requires multiple injections for one sample analysis [28].

In the first injection, the ion trap performs MS^2 spectra at every *m/z* value at each of ten continuous intervals (each with a 1.5 Da width) across a range of 15 Da using

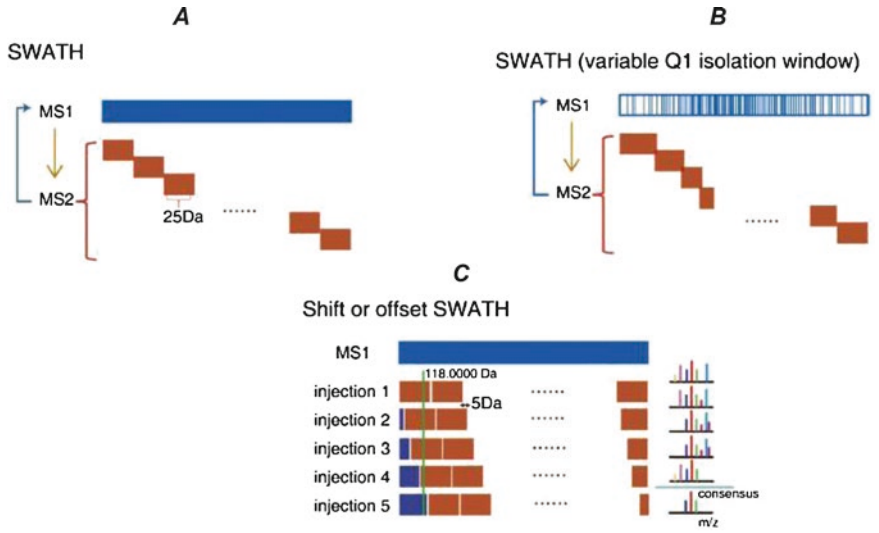

Fig. 3.6 Different SWATH scan modes. (Adapted from Ref. [17])

a 2.5 Da isolation width. The injections are repeated, in each shifting the *m/z* range 15 Da up, until the whole *m/z* range has been covered. This has the advantage to decrease the complexity of acquired MS^2 at cost of repeating multiple injections for each sample.

MSX is another data independent acquisition method mainly applied in proteomics and set up in the Q Exactive mass spectrometer [29]. It is developed by multiplexing five isolation mass ranges (4 Da each), randomly chosen from the predefined *n* possible non overlapping windows, and combined in one multiplexed MS^2 spectrum. The random selection is repeated until the whole *m/z* range is covered. MSX technique maintains the acquisition efficiency similar to SWATH technique, but higher selectivity similar to PAcIFIC, which is a good combination of data acquisition efficiency and computational deconvolution [17].

3.5.2 Confirm Presence/Absence of Known Analytes and Quantitation: Target Analysis

In the case of confirmation of presence/absence/suspicion of known analytes and/or for their quantitation, a target analysis can be performed (Fig. 3.7). In this case, the gas phase behavior of each analyte is known, so distinctive single ions or reactions are monitored.

A target analysis has advantages of high sensitivity, wide dynamic range, high reproducibility and allowing quantitative reproducibility. On the other hand, it is limited by the number of compounds which can be analyzed in a single experiment.

Fig. 3.7 Scheme of a MS and MS/MS data independent acquisition target analysis

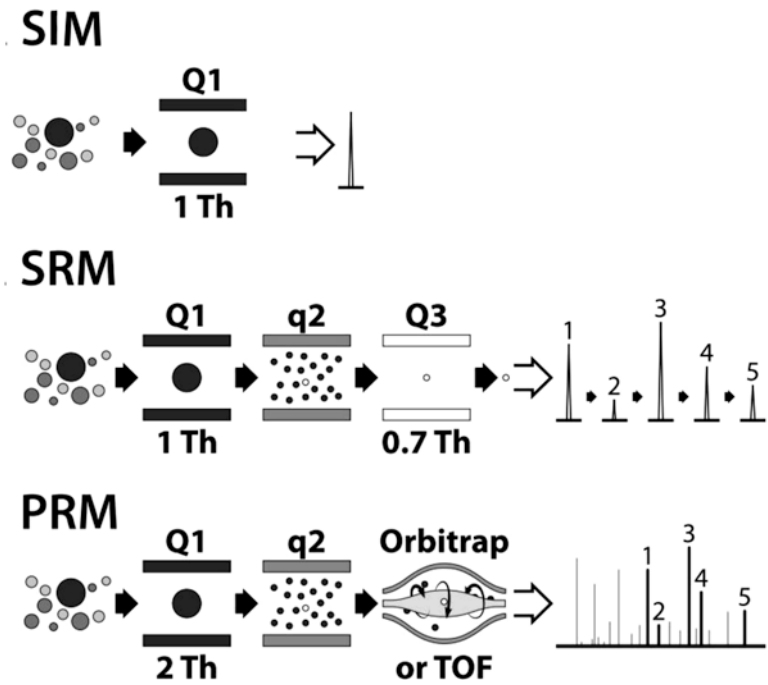

Fig. 3.8 Scheme of MS scan mode in selected ion monitoring (SIM), and of MS/MS scan modes in selected reaction monitoring (SRM) and parallel reaction monitoring (PRM). (Modified from Ref. [30])

In target analysis a *data independent acquisition* can be performed with single ions, precursor ions or reactions set by the user before the experiments starts.

The classical *selected ion monitoring* (SIM) approach is a MS method, requiring one analyzer and consisting in monitoring selected ions, one or more, of each analyte. It can be performed in low or high resolution mode. In SIM the analyzer is not scanning but fixed so to acquire only the ions of interest (Fig. 3.8). As more than one ion can be monitored, the analyzer "jumps" from one *m/z* value to the next. This ensures high sensitivity but scarce selectivity as a given ion might be produced by

different molecules. Combining SIM with retention time increases selectivity as very few molecules, if not one, will yield the same ions and will have the same retention time. Owing to the large diffusion of tandem mass spectrometry instruments, the use of SIM is actually limited in low resolution analysis but it is widely used in high resolution MS.

Tandem mass spectrometry methods, and in particular selected reaction monitoring (SRM), also known as multiple reaction monitoring (MRM), are widely used in target analysis. In selected reaction monitoring, typically occurring in triple quadrupole mass spectrometers, both analyzers don't make any scan but are fixed at given *m/z* values: the first at the *m/z* value of the precursor ion, the latter at *m/z* value of the product ion (Fig. 3.8). By monitoring one or more reactions for a single analyte, a SRM analysis is much more specific and selective than monitoring just single ions as it occurs in SIM. Furthermore SRM offers highly sensitive, and cost-effective analysis for simultaneous quantitation of several hundreds of targeted compounds in a single experiment.

Parallel reaction monitoring (PRM) [30] is also included in this group, being related to SRM, even if it can be used also in untarget analysis (Fig. 3.8).

As in a SRM assay, also in parallel reaction monitoring the first analyzer selects specific ions of interest for fragmentation. Unlike SRM/MRM, the second analyzer is not fixed on a given *m/z* value, but it scans over a wide *m/z* range so to detect all fragment ions at once (Fig. 3.8). Parallel reaction monitoring has been firstly set up on Q Exactive mass spectrometer having a quadrupole followed by an Orbitrap analyzer [30], but it has been used also with a ToF as a second analyzer.

So in PRM no any reaction pathway has to be defined, saving time in method development, and the use of high resolution and accurate mass measurements is an advantage when analyzing analytes in complex mixtures.

3.6 Food Safety/Detection of Toxins in Food

Toxins are represented by wide classes of molecules with different chemico-physical properties, ranging from volatile small molecules to polar big molecules, such as proteins. Among other analytical methods, mass spectrometry plays a key role and it is widely applied in the field of food safety for detecting and quantifying contaminants, residues and toxins in food [16, 31–35].

A targeted approach with data independent acquisition mode is aimed to detect the presence/absence of already known and well characterized contaminants, residues and toxins in food and it is limited to a user built compound list.

As an example, liquid chromatography coupled to mass spectrometry operating in multiple reaction monitoring with triple quadrupole instruments has been traditionally selected for mycotoxin analysis, monitoring in parallel quantitative and qualitative ion transitions. This approach provides both high sensitivity and high selectivity, and achieves limits of regulatory requirements for the official control methods. Anyway the method set-up is tedious and time-consuming when wanting to determine a large number of substances [36].

A targeted approach by using PRM has been developed for the characterization of six bacterial protein toxins of *Clostridium perfringens* of potential warfare significance [37].

Similarly an immuno-LC-MS/MS method, using PRM, for the simultaneous and specific quantification of the three potential biological warfare agents, ricin, staphylococcal enterotoxin B, and epsilon toxin, in complex human biofluids and food matrices has been setup [38].

On the other hand, an untarget analysis is able to detect both unexpected compounds, true unknowns, such as new emerging pesticides and toxins not yet integrated into current monitoring plans, and already known compounds. Among many others, some examples of untarget analysis are the use of the SWATH method for the identification and quantitation of pesticide residues in food [39]; a screening method based on a GC-APCI-MS^E approach for around 130 pesticides in fruit and vegetable samples; identification and quantification of domoic acid by UHPLC-QTOF MS^E tandem mass spectrometry, with simultaneous identification of non-target photodegradation products [40].

Looking for unknown and known analytes, high resolution should be used both in analysis of small molecules, such as contaminants and pesticides [41, 42] offering in this case the possibility to determine the accurate mass and the chemical formula, and in the case to big molecules, such as proteins, for a better certainty of identification and for the ability to detect polymorphisms and post-translational modifications.

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