Liquid and Gas Chromatography–Mass Spectrometry Methods in Food and Environmental Safety

Yelena Sapozhnikova

Contents

Abstract This chapter describes recent advances in applications of gas chromatography (GC) and liquid chromatography (LC) coupled with mass spectrometry (MS) for analysis of contaminants in the field of environmental and food safety during the last decade (2011–2021). Most employed MS analyzers with unit-resolution, different ionization modes, and improvements in liquid and gas chromatography techniques are discussed. Regulatory compliance for GC-MS/(MS) and LC-MS/(MS) identification as outlined by regulatory agencies is presented. Examples of innovative uses of state-of-the-art methods for analysis of diverse contaminants in the last decade are provided, and an opinion on future trends in the field is offered.

Y. Sapozhnikova (✉)
United States Department of Agriculture, Agricultural Research Service, Eastern Regional Research Center, Wyndmoor, PA, USA
e-mail: Yelena.Sapozhnikova@usda.gov

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1 Introduction

In environmental and food safety, contaminants analyzed by gas chromatography–mass spectrometry (GC-MS/(MS)) methods are non-polar, semi-polar, volatile, and semi-volatile compounds. These include pesticides, polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs) and other flame retardants, persistent organic pollutants (POPs), i.e. chemicals identified by the Stockholm convention as persistent, bioaccumulative, and toxic, and emerging contaminants, such as chlorinated paraffins, organophosphate flame retardants, plasticizers, and many others. Contaminants analyzed by liquid chromatography–mass spectrometry (LC-MS/(MS)) methods are semi-polar to polar and non-volatile. Examples are some pesticides, pharmaceuticals, personal care products, natural toxins such as mycotoxins, veterinary drugs, polar flame retardants, and many others.

Since pesticides are the most studied contaminants in food and environmental safety, a quick look into the past publication records provides a glance into when mass spectrometry coupled with LC and GC started to be routinely used in analytical laboratories. A search in Web of Science for "LC-MS pesticides" returned 1 paper published in 1989, describing confirmation of pesticides by LC-MS, then 2 hits for 1991 on applications of LC-MS for pesticide analysis. It was not until 2010 that 102 papers reporting LC-MS for pesticide analysis were published. A similar search for "GC-MS pesticides" in the Web of Science engine returned 1 paper published in 1990 on an analysis of 50 pesticides in water by GC-MS, growing to 100 papers per year published in 2003. At that early time of GC- and LC-MS analysis, most MS detectors were single quadrupole or ion traps. Since the 2010s, triple quadrupoles (QqQ) became more common tools in analytical laboratories. Additionally, different ionization techniques associated with both GC- and LC-MS instrumentation were developed to cover a wide range of polarity for analytes of interest (Fig. 1).

This chapter is covering advantageous developments in applications of GC-MS/(MS) and LC-MS/(MS) methods in analysis of small molecule organic contaminants (under 1,000 Da) in environmental and food safety with a focus on the last decade (2011–2021), with the emphasis on unit-resolution MS instrumental applications, with high-resolution MS applications described in a separate chapter.

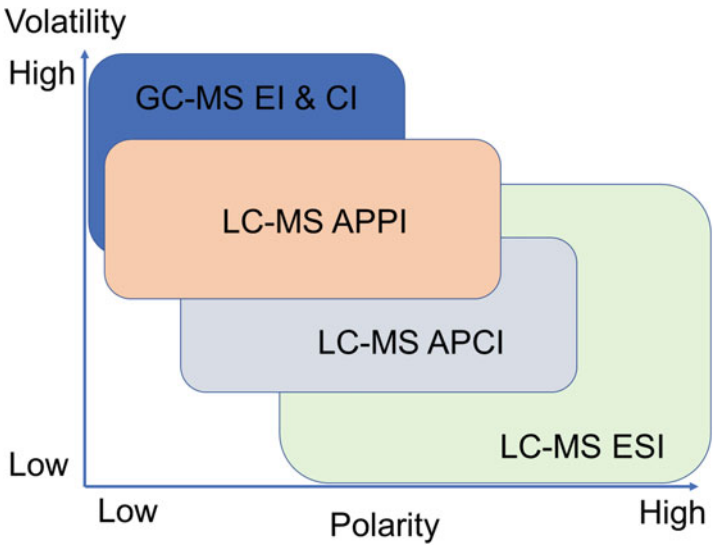

Fig. 1 Instrumental analysis and ionization modes based on analytes' volatility and polarity

2 Recent Advances in Gas Chromatography–Mass Spectrometry Analysis

2.1 GC-MS Analyzers

GC-MS/(MS) analyzers utilized for analysis of residual levels of contaminants in environmental and food safety encompass single and triple quadrupoles, ion trap, Orbital ion trap (Orbitrap), time of flight (TOF), and hybrid systems: quadrupole (Q)–ion trap (Q-trap), Q-TOF, Q-Orbitrap. In the last 10 years (2011–2021), GC coupled with triple quadrupole (QqQ) analyzers was most often applied for targeted analysis of contaminants and became a gold standard for environmental and food safety testing. Indeed, a Web of Science search for "pesticide analysis GC-MS" with different MS analyzers for 2011–2021 showed 59% of the published articles used GC-MS/MS with QqQ analysis, followed by 15% using GC-MS with single quadrupole MS. The remaining 12% and 15% of the published articles used TOF and ion trap MS, respectively. Starting from the 2010s, many laboratories transitioned from GC-MS in single ion monitoring (SIM) mode to GC-MS/MS analysis operated in multiple/selected reaction monitoring (MRM/SRM) mode, which provided greater sensitivity, selectivity, and specificity compared to GC-MS with single quadrupole analyzers.

Main vendors of GC-MS/(MS) instruments are Agilent Technologies, Thermo Fisher Scientific, LECO, and Shimadzu. The biggest advances in GC-MS instruments in the last decade are improvements in MS analyzers' sensitivity and scan speed (Da/s). The latest GC-MS/MS QqQ instruments provide instrument detection

limit (IDL) sensitivity for octafluoronaphthalene (OFN) < 0.4 fg, MRM speed of up to 800 MRM transition/s, minimum MRM dwell time of 0.5 s, and scan speed ≤20,000 Da/s. In addition, to reduce down time needed to vent the instrument for ion source cleaning and/or GC column change, Agilent 7010D QqQ offered an automated, self-cleaning ion source, and Thermo Fisher Scientific TSQ 9000 enabled changing ion source and GC column without venting the instrument.

Recent improvements in detectors' scan speed and acquisition rates translate to more acquired MRMs per unit time, resulting in a greater number of contaminants analyzed in a single run, thus increasing the scope of the method. For example, a multi-residue method was developed and validated for 192 pesticides in animal feed by GC-MS/MS [1] with 2 MRM transition for each analyte in a 22 min GC run time. A total of 32 contaminants including PCBs, PBDEs, PAHs, and organochlorine pesticides were analyzed by GC-MS/MS in mussels and clams with 3 MRM transitions/analytes in a 45 min GC run [2]. A multi-class method for pesticides, PCBs, PAHs, PBDEs, and other flame retardants in meats, poultry [3], and catfish [4] covered 232 analytes with 3 MRMs/analytes in a 10 min fast low pressure GC run. In a recent study, 4 MRM transitions/analytes were applied for analysis of 400 pesticides in food samples in a 60 min GC run [5]. These examples demonstrate how modern GC-MS analyzers provide wide scope of analysis by covering hundreds of contaminants and multiple classes of analytes in a single GC-MS/(MS) run, thus increasing throughput and laboratory efficiency.

Taking advantage of improvements in MS detector's speed, 3 MRMs instead of 2 MRMs/analytes are acquired to improve selectivity and provide more confidence in the identification based on additional MRM transitions and their ion ratios (see Sect. 4), thus increasing identification reliability and minimizing false negative findings in complex samples with matrix interferences.

Additional advantage in acquisition of multiple MRMs is software improvements for GC-MS/MS with dynamic/scheduled MRM algorithms, allowing the user to specify retention time and time window for acquiring selected MRMs compared to laborious division of MRMs into time segments.

Modern MS analyzers provide great sensitivity, and each next version is at least 2–3 times more sensitive than the previous version. Agilent 7000 MS/MS QqQ introduced in 2014, for example, has IDL ≤4 fg while 7010B version, introduced in 2016, has IDL ≤0.5 fg for 2 fg OFN injected, thus offering an eight-fold sensitivity increase in just 2 years. Increased sensitivity provides greater signal to noise (S/N) ratio and lower limits of detection (LODs), allowing to measure contaminants at lower levels. This is especially valued in the environmental field where a general rule of thumb is to measure the lowest quantities possible. In the food safety arena, most chemical contaminants are regulated and have established tolerances or maximum residue limits (MRL). For example, for most pesticides, MRLs are 10 ng/g, thus the lowest amounts needed to be quantified are ½ MRL, or 5 ng/g, and the lowest calibration curve point is usually at 0.5–1 ng/g. In this case, increase in MS sensitivity permits injection of more diluted final extracts without resulting in increased LODs, decreased matrix effects, and improved robustness. This advantage can result in fewer sample preparation steps, sample dilution instead of

concentration/evaporation, smaller sample equivalent injected on column, and consequently, less instrument maintenance.

2.2 GC-MS/(MS) Ionization Modes

Electron ionization (EI) is most commonly used with GC-MS analyzers. The advantage of EI is its universal applicability. Mass spectra generated in EI mode with 70 eV are highly reproducible with any GC-MS/(MS) instrument and are used for identification and confirmation with existing commercial EI spectral libraries. One of the most utilized spectral databases is the NIST/EPA/NIH EI-MS library containing 306,643 compounds (2020 release), including pesticides, industrial chemicals, petrochemicals, surfactants, drugs and metabolites, toxins, etc. The main disadvantage of EI is in its harsh ionization causing extensive fragmentation, and in most cases lack of a diagnostic molecular ion. Softer ionization techniques, such as chemical ionization (CI) in positive (PCI) or negative (NCI) mode, atmospheric pressure chemical ionization (APCI), and cold EI overcome this challenge and provide highly diagnostic molecular ion.

GC-MS with NCI in selected ion monitoring (SIM) mode using methane as a chemical reagent was used for determination of organochlorine pesticides and PBDE congeners in air particulate matter [6]. In another study, a multi-residue method for 51 pesticides in green coffee beans was developed with GC-MS-NCI [7], and high MS selectivity was achieved, while matrix effects were high for this difficult food matrix. Gonzalez-Gago et al. compared sensitivity of GC-MS-EI with GC-MS-NCI for PBDE congeners and concluded that GC-MS-NCI had lower LODs, especially for higher brominated congeners [8]. Ayala-Cabrera et al. compared GC-MS with positive (PCI) and negative chemical ionization (NCI) modes and EI mode for the determination of fluorotelomer olefins, fluorotelomer alcohols, perfluoroalkyl sulfonamides, and sulfonamido-ethanols in water [9]. For most of the analytes, PCI worked the best generating protonated molecules and low fragmentation compared to high fragmentation observed in EI and NCI modes.

Applications of APCI in GC-MS(/MS) published by 2020 are summarized in three recent reviews [10–12]. These reviews highlighted APCI as an advantageous soft ionization technique for generating spectral data with protonated molecular ions for improved identification and low LODs. Li et al. discussed advantages and drawbacks of GC-MS-APCI [12], while Fang et al. [10] reviewed its applications for the analysis of persistent organic pollutants (POPs) and Niu et al. [11] covered applications in non-targeted analysis and targeted analysis for pesticides, flame retardants, PAHs, PCBs, dioxins and furans, sterols, esters, pharmaceuticals, and cannabinoids. Cherta et al. first studied application of GC-MS/MS-APCI for 25 pesticides selected based on high fragmentation and low/no molecular ion in EI mode [13]. Under APCI conditions with water as a modifier, abundant protonated ions $[M + H]^+$ were observed for most of the selected pesticides and used as precursors for MS/MS, thus resulting in increased selectivity and sensitivity. Among pesticides,

pyrethroids are especially difficult to analyze with EI due to the lack of molecular ion and extensive fragmentation. GC-MS/MS-APCI was shown to improve analysis of pyrethroids [14] based on the formation of highly abundant protonated molecular ions with low LODs. One disadvantage of APCI is a strong interference of matrix components leading to matrix-induced suppression or enhancement. In the study of pyrethroids in fruits and vegetables, average signal reduction was 55% [14]. GC-QTOF-APCI was used in a non-targeted study to investigate chemicals migrating from food packaging in combination with GC-TOF-EI to increase confidence of identification by using two complementary ionization modes [15]. Other soft ionization techniques with high potential for future applications in GC-MS/(MS) analysis are atmospheric pressure photo-ionization (APPI) [16], dielectric barrier discharge ionization (DBDI) [17], and supersonic molecular beam (SMB) also known as cold EI [18].

2.3 Improvements in Gas Chromatography

Modern analytical laboratories demand fast sample turnaround time and higher throughput to analyze as many samples as fast as possible. Typical GC run with the most often used analytical column: (5%-phenyl)-methyl-polysiloxane, 30 m × 0.25 mm internal diameter (i.d.) × 0.25 μm film thickness can take 30–60 min depending on the selected analytes and GC conditions. Increasing the speed of GC separation while reducing total run time is important to achieve greater productivity.

Zocalli et al. reviewed GC-MS techniques from the last decade [19] and Pico et al. reviewed recent innovations in GC-MS for pesticide analysis [20], and both reviews presented several fast GC approaches and their applications. One way to reduce GC run time is to alter GC column dimensions, i.e. reduce length, internal diameter (i.d.), and film thickness. To discuss reduction of i.d. here, classification of GC capillary columns was based on the following parameters [21] – microbore: i.d. 0.1–0.2 mm, narrow bore: i.d. 0.2–0.3 mm, wide bore i.d. 0.3–0.5 mm, and megabore: i.d. ≥0.5 mm. Use of microbore column (20 m × 0.18 mm i.d. × 0.18 μm) and pulsed pressure injection was reported for analysis of 356 pesticides by GC-MS/MS [22]. Analysis time was 18 min, plus significantly higher and narrower peaks were observed, resulting in greater signal to noise (S/N) and lower sensitivity. In another study with GC × GC-MS, 10 m × 0.1 mm × 0.1 μm column was used for cryogenic modulation [23] to evaluate rapid two-dimensional comprehensive GC × GC analysis with single quadrupole MS for cosmetic allergens. Low polarity 8.9 m × 0.1 mm × 0.1 μm and medium polarity 1.1 m × 0.1 mm × 0.1 μm GC columns were used in first and second dimension, respectively, with analysis time of 11.4 min. The well-known drawbacks of microbore columns are reduced sample capacity and method robustness.

In contrast to microbore column, narrow bore GC columns (i.d. 0.2–0.3 mm) are widely used in environmental and food safety applications. GC runtime of 12 min

was reported for the analysis of PBDEs and their methoxylated metabolites by Cruz et al. [24] with 10 m × 0.25 mm × 0.1 μm GC column and triple quadrupole MS/MS using EI and NCI modes. In another study GC separation <10 min for pesticides and PCBs was achieved with 15 m × 0.25 mm × 0.25 μm by GC-MS/MS-APCI [25]. Several factors were optimized to reduce GC analysis run time: short GC column (15 m), high starting oven temperature (120°C), fast rate of temperature programming (30°C/min), and high flow rate (6 mL/min).

High flow rate in addition to increased velocity of carrier gas is the main characteristic of low pressure (LP) vacuum outlet GC-MS/(MS) technique [26]. LPGC-MS/(MS) uses short (5–15 m) megabore (i.d. > 0.5 mm) analytical column connected to a restrictor at the inlet and vacuum at the MS outlet. By extending vacuum conditions through LPGC column, carrier gas (helium) linear velocity becomes 10 times greater compared to under atmospheric pressure, thus speeding up GC separation. In addition, higher flow rates, rapid heating, thicker film thickness provide faster separation, more sensitivity, high sample capacity, greater ruggedness, and less degradation of thermally labile compounds [26, 27]. Khan et al. compared LPGC-MS/MS and conventional GC-MS/MS for analysis of 259 pesticides in tobacco [28]. A fast separation of 14 min was achieved for LPGC-MS/MS analysis with 15 m × 0.53 mm × 1 μm column and flow rate of 4 mL/min compared to 42 min using conventional GC-MS/MS with 30 m × 0.25 m × 0.25 μm column. Additionally, low sensitivity with limit of quantitation (LOQs) < 2 ng/g was demonstrated for all pesticides. Recent studies using LPGC-MS/MS with 15 m × 0.53 mm × 1 μm LPGC column connected to 5 m × 0.18 mm guard column and carrier gas at 2 mL/min for analysis of >200 pesticides, PCBs, PBDEs, and other flame retardants had a total run time of 10 min with LOQ ≤ 5 ng/g, and low matrix effects in complex samples of meat, poultry, and fish [3, 4]. Figure 2 illustrates fast separation of PBDE and PCB congeners relevant to environmental and food safety using LPGC-MS/MS in 7 min. On the other hand, disadvantages of LPGC-MS/(MS) are decreased separation efficiency, greater potential for leaks, and typically only MS-based detection since vacuum conditions are required.

Among other recent developments in GC-MS worth mentioning is column backflushing GC-MS/MS method [29] to eliminate unwanted matrix components from GC column by reversing the column flow with a pressure-controlled tee device. Fast analysis of pesticides in dietary supplements with column backflushing resulted in increased sample throughput (50%), decreased instrument maintenance, and greater ruggedness [29]. In another study, column backflushing was used for analysis of nitrosamines in bacon [30] with reporting limits of 0.1 ng/g, and backflushing was demonstrated to be rugged for long-term use with minimal maintenance.

Another advantageous technique for analysis of challenging complex samples is multi-dimensional GC, which offers improved resolution for analytes with greater separating power, higher peak capacity, improved identification, and lower detection limits compared to one-dimensional GC separation. A recent review outlined the use of comprehensive two-dimensional (2D) GC in environmental analysis in targeted and non-targeted applications [31]. In non-targeted screening of surface water by GC × GC-TOFMS, over 3,000 chemicals were detected, including pharmaceuticals

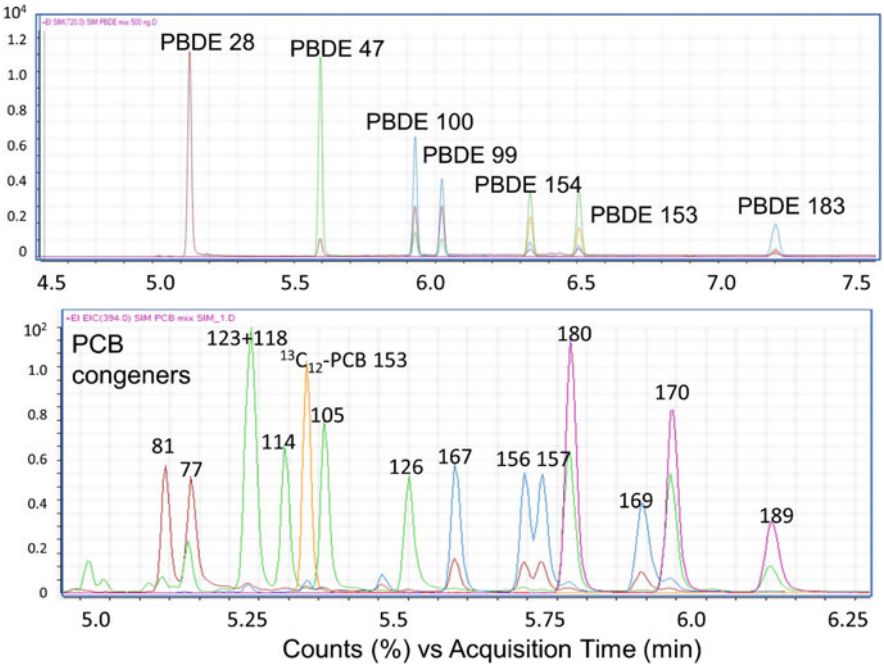

Fig. 2 Example of fast separation of PBDE and PCB congeners using low pressure vacuum outlet GC-MS/MS

and personal care products (PPCPs), sunscreens, pesticides, hormones, fragrances, and emerging endocrine disrupting chemicals [32]. In another study, 327 persistent and bioaccumulative compounds were identified in blubber bottlenose dolphins by GC × GC-TOFMS non-targeted analysis, with 280 identified chemicals not typically monitored in environmental surveys [33]. In food safety applications, non-targeted analysis with GC × GC-TOFMS was used to screen for chemicals migrating from food packaging with 91 chemicals identified [34].

While most GC × GC-MS/(MS) studies to date used EI to utilize common MS databases, some reports have emerged with alternative ionization modes. Pulsed flow modulation GC × GC-MS with cold EI (supersonic molecular beam) was reported for pesticide analysis in agricultural products [35]. The identification with this technique improved NIST library identification probabilities. Another study explored milder EI conditions, e.g. 20 eV vs. 70 eV for GC × GC – quadrupole MS for analysis of pesticides, sterols, linear alkanes, etc. [36]. Lower energy resulted in increase of the relative abundance of higher-mass diagnostic ions and fragments. GC × GC coupled with TOF with APCI was evaluated for analysis of flame retardants and plasticizers with direct probe [37].

GC × GC-TOFMS is a powerful tool for targeted and especially non-targeted analysis in complex and difficult matrices which can tolerate little/no sample preparation, however tentative identification of thousands of compounds can be a long

and overwhelming process, and software improvements are expected in the future to streamline and improve data analysis.

3 Liquid Chromatography–Mass Spectrometry

3.1 Analyzers

Just as for GC-MS/(MS) analysis, the most common LC-MS/(MS) analyzers are single and triple quadrupoles, ion trap, Orbitrap, TOF, and hybrid instruments combined with a quadrupole: QTRAP, Q-TOF, Q-Orbitrap. Based on Web of Science search for papers on "pesticide analysis LC-MS" with different MS analyzers in the last decade, 57% used QqQ, followed by 19% TOF, 16% ion trap, and 8% single quadrupole. Major vendors of LC-MS/(MS) instruments are Agilent Technologies, Shimadzu, Sciex, Thermo Fisher Scientific, and Waters.

LC-MS/MS with QqQ instruments have become "workhorses" of modern laboratories for analysis of LC-amenable contaminants. Common characteristic of modern LC-MS/MS QqQ (based on Agilent QqQ 6495C) are: MRM speed is 500 MRM transitions/second, minimum MRM dwell time is 0.5 s, polarity switch <25 ms, collision cell clearance time <0.5 s, scan speed ~17,000 Da/s, and IDL sensitivity is <0.6 fg based on reserpine on column. Other advances in the last years, besides improved sensitivity and speed, are improvements in ion source design and diversity of ion source ionization modes.

3.2 LC-MS/(MS) Ionization Sources

The most frequently used ionization sources in LC-MS(MS) analysis are electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), and atmospheric pressure photo-ionization (APPI). ESI dominates in the published LC-MS/(MS) methods for LC-amenable contaminants due to high selectivity, sensitivity, and efficient ionization for a wide range of diverse analytes. ESI can be operated in positive (+) and negative (−) modes, and ESI (+) is generally preferred mode based on most compounds ionization efficiency producing $[M + H]^+$ or other adduct ions, resulting in wider scope of analysis. ESI (−), on the other hand, creates deprotonated ions $[M\text{-}H]^-$ and is characterized by lower background noise [38]. Liigand et al. [39] challenged the assumption that most compounds are better suited for ESI (+) by comparing ionization efficiency of 33 compounds ionized in both ESI(+) and ESI (−) modes. Their findings showed that ESI (−) provided better sensitivity for almost half of the selected analytes. To take advantage of both ESI polarities in one LC run, polarity switching is employed. A recent study demonstrated simultaneous analysis of 52 multi-class illegal dyes in food [40] with ESI polarity switching in one LC-MS/MS run of 12 min for acidic, neutral, and basic

analytes. Another interesting investigation of this study was a 100-fold dilution of the extracts then taking advantage of the instrument sensitivity while eliminating matrix effects. In another study, ESI polarity switching was applied to acquire 27 and 710 scheduled MRM transitions in ESI(−) and ESI (+), respectively, in 10 min LC run to determine pesticides, veterinary drugs, and their metabolites in catfish [41].

Four ionization sources: ESI, heated ESI (HESI), APPI with and without dopant, and multi-mode source with ESI and APCI were compared for analysis of 40 pesticides in tomato and garlic [42]. The lowest LODs were achieved with ESI and HESI, and ESI was significantly less affected by matrix effects compared to HESI.

Softer, but currently less utilized ionization sources are APCI and APPI. The applicability of three ionization sources: ESI, APCI, and APPI was tested for analysis of five pharmaceuticals in wastewater samples [43], and ESI provided the best ionization efficiency, lower LODs, greater S/N, and lower matrix effects. Tokumura et al. compared analysis of 14 organophosphorus flame retardants by LC-MS/MS with APCI and ESI, as well as by GC-EI-MS and GC-NCI-MS [44]. LC-MS/MS with APCI afforded the lowest LOQs for 12 analytes. In contrast, Silva et al. compared efficiency of ESI and APCI ionization sources for analysis of 22 pesticides in food and found two- to four-fold lower LOQs for ESI vs. APCI, and greater matrix effects in APCI [45]. These examples highlight the differences between ionization efficiency of various chemicals, depending on their properties and the impact of matrix effects for different ionization mechanisms.

Ramirez et al. reported the determination of 28 parent and 15 alkylated PAHs in environmental waters by LC-MS/MS-APPI with chlorobenzene as a dopant on a polymeric C18 column [46]. Brecht et al. reported the development of a fast-switching dual source operating ESI and APCI simultaneously or in switched mode [47] with potential for routine use in LC-MS/(MS) analysis in the future. Similarly, Galani et al. evaluated a new ionization interface, UniSpray, in comparison with ESI [48] for 81 pesticides in food and water samples. The UniSpray was shown to achieve better sensitivity and improved S/N, but overall, LODs were similar to ESI, while signal suppression from matrix effects was lower with UniSpray compared to ESI.

3.3 Improvements in LC Analysis

Since ultra-high performance (UHP) LC instruments were introduced in 2004, they became routine LC instruments in analytical laboratories. UHPLC instruments operate at high pressure (up to 1,500 bars) with small column particle size (typically <2–5 μm) and high flow rates (up to 5 mL/min), which allows short separation time (typically 10–15 min) with high efficiency and resolution [49]. Among LC developments in the last decade, the introduction of sub-2 μm particles, novel monolithic columns, superficially-porous (core-shell) particles, and elevated temperatures are some of the most significant advances to meet demands for efficient separation in multi-class, multi-residue analytical methods.

Hundreds of UHPLC-MS(MS) applications have been reported for pharmaceuticals, personal care products, pesticides, drugs, flame retardants, and many other emerging contaminants. Kachhawaha et al. reviewed recently developed LC-MS/(MS) methods for detection and quantitation of PPCPs in environmental waters [50]. UHPLC-MS/MS with ESI was the most extensively used analysis for PPCPs at trace levels (ng/L). UHPLC-MS/MS methods for brominated flame retardants in food [51] and for organophosphorus flame retardants/plasticizers in mussels [52] were reported, achieving low detection limits at sub ng/g levels. Quantitative LC-MS/MS method was reported for 295 bacterial and fungal metabolites, including mycotoxins, in food using "dilute and shoot" approach [53]. The method LOQs for all analytes were below the established regulatory tolerance levels of these contaminants.

To speed up LC analysis, flow injection (FI) coupled to MS was tested in various FI-MS/(MS) applications. FI-MS(MS) eliminates LC separation taking advantage of modern MS detectors used as a "separation" tool. Nanita and co-workers pioneered FI-MS/MS high-throughput analysis of pesticide residues in foods, biological matrices, and water [54], and Mol and van Dam developed an FI-MS/MS method for polar pesticides not amenable to multi-residue methods [55] with run time of 30–60 s. In a recent study, FI-MS/MS was evaluated for simultaneous analysis of selected pesticides and mycotoxins in food and feed samples in 2 min [56]. Despite high complexity of the samples, the method achieved LODs below the established regulatory values. The main advantages of FI coupled with MS are speed, simplicity, high throughout, and low cost, however, it can suffer from high ion suppression caused by matrix interferences in absence of chromatography. FI-MS/MS was utilized for the analysis of organophosphate esters (OPEs), used as flame retardants and plasticizers to avoid background contamination from common LC solvents [57]. Garcia-Ac et al. compared FI-MS/MS with ESI, APCI, and APPI [43] for analysis of five pharmaceuticals in wastewater and found that ESI performed the best among the three in terms of S/N ratio and peak areas.

With increasing complexity of samples and greater demand to analyze more chemicals, comprehensive two-dimensional LC (LC × LC) is becoming a more popular and attractive approach to increase separation power with enhanced peak capacities. Selectivity can be dramatically increased when different retention mechanisms are employed for two dimensions. These reviews outlined recent developments and successful applications in LC × LC [58, 59], however, no practical applications can be found for environmental or food safety applications, but applications in polymers, peptides, natural medicine, metabolomics [58], and food composition are described [60].

Another interesting approach to meet the challenge for complex samples is LC column backflushing. This approach helps to avoid ghost peaks, reduce matrix effects in high-throughput methods, and reduce instrumental maintenance. Michlig et al. [61] applied LC column backflushing for 3 min followed by 3 min re-equilibration between every injection in the analysis of pesticides in complex samples of hemp and hemp products.

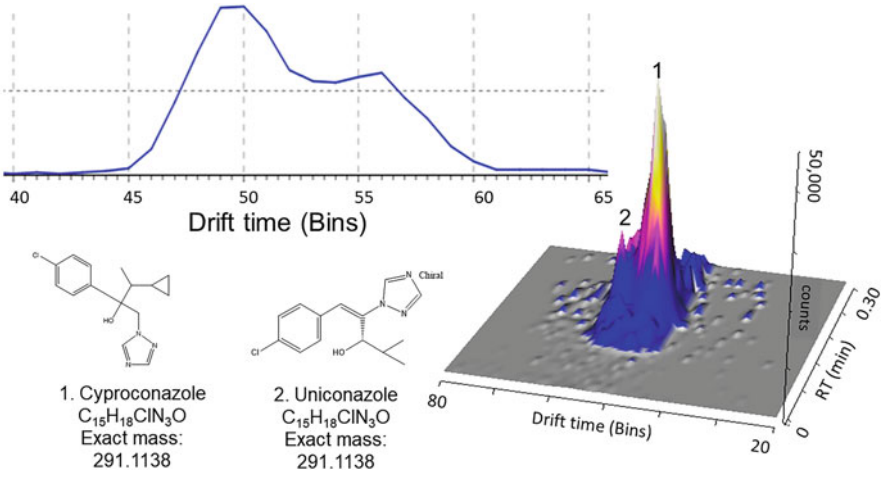

Fig. 3 Example of partial separation of structurally isomeric pesticides – cyproconazole and uniconazole with flow injection ion mobility TOF-MS in parent trap MS mode for $[M + H]^+$ ion 292.112

Additionally, ion mobility (IM) spectrometry should be mentioned as an additional dimension to LC-MS, as its hyphenation to LC-MS is drawing more interest and attention recently [62]. Applications of IM for environmental analysis of perfluorocarbons, PAHs, pesticides, terpenes, chlorophenols, etc. in air, water, and soil were reviewed [63]. UHPLC-(Q)TOFMS with traveling-wave ion mobility spectrometry was evaluated for >200 pesticides in fish feed [64] and for screening of multi-class pesticides in fruits and vegetables [65]. In another study, FI-IM-TOFMS was evaluated for separation of structurally isomeric pesticides [56]. Figure 3 shows an example of partial separation of two pesticides used in agriculture, cyproconazole and uniconazole using FI-IM-TOF [56]. Both pesticides have the same formula $C_{15}H_{18}ClN_3O$ and exact mass 291.1138, which challenges their differentiation. However, their identification and accurate measurement are extremely important in food trade as two pesticides have different regulatory values in different countries. Thus, cyproconazole has MRL = 0.05–0.2 mg/kg in the EU, and MRL = 0.05 mg/kg for corn and wheat grain in the USA, while uniconazole has MRL = 0.01 mg/kg in the EU, and no regulatory value in the USA. False positives and other incorrect results in the analysis of these or other structurally isomeric pesticides can lead to detrimental economic and health consequences, and advanced techniques such as ion mobility in this case can increase confidence of identification and reduce false findings.

4 Regulatory Compliance for Identification with GC-MS/(MS) and LC-MS/(MS)

In regulatory testing, compliance with the identification criteria established by governing agencies is required [66, 67]. Table 1 summarizes identification criteria for liquid and gas chromatography with various MS analyzers to meet regulatory compliance as established by some regulatory agencies worldwide in environmental and food safety. For retention time (RT) compliance, most criteria require RT within 6–12 s of RT in midpoint calibration standard in the same sequence, although the International Organization for Standardization (ISO) criteria is different, and RT tolerance highly depends on RT range [68]. Ions selected for MS should be characteristic or structurally significant, and $\geq$3 ions should be selected for MS, and $\geq$2 product ions with S/N $\geq$3 should be selected for MS/MS, and analyte peaks from all product ions in the extracted ion chromatogram must overlap. For ion ratios, most regulators use relative tolerance of $\pm$30%, while others use absolute tolerance, and ISO uses a formula: [$<\pm(0.1 \times I_{std} + 10)\%$] to calculate relative tolerance, where I_{std} is a relative ion intensity for calibration standard (Table 1).

Recently, Angeles and Aga pointed out that not all official methods require ion ratio tolerance [69]. For example, the EPA methods 542 and 1694 for PPCPs and method 537.1 for selected per-and polyfluorinated alkyl substances by LC-MS/MS do not have ion ratio requirements, but methods 8270E and 8260B for semi-volatile and volatile compounds by GC-MS/MS do have ion ratio tolerance. The authors attributed this to the lack of the established guidelines, which are still developing and evolving.

In summary, regulatory compliance parameters for identification of analytes by GC- and LC-MS/(MS) are presented in Table 1. In any testing, regulatory or not, the use of these criteria should be implemented to increase the confidence of identification.

5 Orthogonal Applications of GC-MS and LC-MS

In an interesting study, Schürmann et al. reported a false positive finding of pesticide sebuthylazine in tarragon sample [76] with LC-MS/MS analysis based on retention time, 2 MRM transitions and their ratios. A co-eluting matrix interference resulted in a false positive by producing product ions corresponding to 2 MRM transitions of the compound. However, a 3rd LC-MS/MS MRM transition and a separate analysis by orthogonal GC-MS/MS revealed the false positive findings. Many chemicals are both GC- and LC-amenable (Fig. 1) and can be routinely analyzed by both instrumental techniques. Thus, GC-MS and LC-MS can be not only complementary, but also confirmatory for these compounds. For example, pesticides and veterinary drugs in animal feed were analyzed by GC-MS/MS (192 analytes) and LC-MS/MS (187 analytes) with >50 overlapping analytes analyzed by both techniques

Table 1 Regulatory compliance with retention times and ion ratios for identification by GC-MS and LC-MS (single quadrupole, ion trap, TOF) and GC- and LC-MS/MS (MS/MS triple quadrupole, ion trap, Q-Trap, Q-TOF) with unit mass resolution

		Criteria		
Regulatory source	Guidelines for	Chromatography: retention time (RT)	Mass spectrometry: # of required ions	Ion ratio tolerance, %
US EPA methods	8270E: semi-volatile organic compounds (PAHs, PCBs, pesticides) [70] 8260B: volatile organic compounds [71]	*GC:* RT within ±10 s of RT in midpoint calibration standard from the same sequence; or within ±10 s relative to the shift of the associated internal standard (IS) (delta RT of the IS ±10 s)	≥2 ions	MS/MS: ±30% (relative) of expected ion ratio in reference spectrum
EU SANTE 12682/2019 (2020) [72]	Pesticides in food and feed	*GC & LC:* RT ± 12 s	MS: 3 ions MS/MS: ≥2 product ions with S/N ≥ 3	±30% (relative) of average of calibration standards from same sequence
US FDA Office of regulatory affairs (ORA) [73]	ORA-LAB.5.4.5. (2020): methods, method verification and validation	Not specified	MS: 3 ions MS/MS: ≥2 product ions with S/N ≥ 3	± 30% of average of calibration standards from same sequence
USA: FDA guidance for industry 118 confirmation of identity of animal drug [74] residues (2003)	Animal drug residues	LC: RT ≤ 5% GC: RT ≤ 2%	MS: ≥3 ions	3 ions ±10% (absolute)
				≥ 4 ions: ±15% (absolute)
				2 product ions: ±10% (absolute)
			MS/MS: ≥ 2 product ions	≥3 product ions: ±20% (absolute)
USDA Agricultural Marketing Service Science & Technology Pesticide Data Program (2021) [75]	Pesticides in agricultural commodities	*GC & LC:* RT ± 6 s if an external standard is used	MS: 3 ions MS/MS: ≥2	±30% (relative) when compared to the same relative

		RRT ± 0.1 min if an internal standard is used	product ions with S/N ≥ 3	abundances observed from a standard solution injection made during the same analytical run
The International Organization for Standardization (ISO) 22,892:2006 (confirmed in 2016) [68]	Contaminants in soil	*GC:* RT < 500 s: ±1 s RRT = 500–5,000 s, ±0.2% RT > 5,000 s, ±6 s	MS: 3 ions MS/MS: ≥2 Product ions	<±(0.1 × I_{std} + 10)% (relative)

RT retention time, *RRT* relative retention time, *S/N* signal to noise, I_{std} relative ion intensity for calibration standard

[1]. Similarly, 302 contaminants, including pesticides, PAHs, PCBs, PBDEs were analyzed in catfish, with 128 and 219 by UHPLC-MS/MS and GC-MS/MS, respectively, and 45 overlapping contaminants were analyzed by both. Orthogonal applications of GC-MS and LC-MS provide an additional degree of confidence by employing different chromatographic mechanisms and different ionization modes and are especially important when analyzing complex samples where matrix interferences can result in false negatives or false positives.

6 Future Trends

Evolving challenges to analyze more contaminants faster, more efficiently, with low detection limits and to reduce false positive/false negative rates in complex samples place high demands on future improvements in LC- and GC-MS/(MS) instrumentation and techniques.

Just like in the past, improvements in MS detectors' sensitivity, speed, selectivity, specificity, and wider dynamic linear range are expected. We may see new features aimed to reduce instrumental downtime needed for maintenance, and new and improved ionization sources and interfaces, plus combinations of existing ion sources used simultaneously.

With continually improving modern powerful LC- and GC-/MS(MS) instruments, 1,000 contaminants from different classes with various properties may be covered in one analytical method providing a wide scope of analysis. While triple quadrupole instruments have been "workhorses" in analytical laboratories in the last decade, a transition to high-resolution MS systems will likely occur to avoid shortcomings associated with QqQ instruments in terms of developing ion transitions, their optimization, limited amount of transitions due to the scanning speed of QqQ. Kaufmann et al. conducted direct comprehensive comparison of LC-MS/MS and LC-HRMS [77], and found that selectivity of LC-HRMS at 50,000 FWHM was superior to LC-MS/MS. Analysis with modern HRMS instruments allows virtually unlimited amount of analytes based on the full scan data, plus retrospective analysis. Recent improvements in sensitivity of HRMS instruments put them on par with modern MS/MS.

Other trends expected and desired by the analytical community in the future are software improvements that make it easier for analytical chemists to deal with an enormous amount of generated data. Software packages with streamlined and flexible workflows for different types of applications are expected.

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