Ambient (desorption/ionization) mass spectrometry methods for pesticide testing in food: a review

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Abstract

Ambient mass spectrometry refers to the family of techniques that allows ions to be generated from condensed phase samples under ambient conditions and then, collected and analysed by mass spectrometry. One of their key advantages rely on the ability to allow the interrogation of samples with minimal to no sample workup. This feature map well against the requirements of food safety testing, in particular, those related with the fast determination of pesticide residues in foodstuffs. This review addresses the application of different ambient ionization methods for the qualitative and (semi)quantitative determination of pesticides in foods, attending to the different specific methods used and their ionization mechanisms. The more popular techniques used are those commercially available including Desorption Electrospray Ionization (DESI-MS), direct analysis on real time (DART-MS), paper spray (PS-MS) and low-temperature plasma (LTP-MS). Several applications described with ambient MS have reported limits of quantitation approaching reference methods, typically based on LC-MS and generic sample extraction procedures. Some of them has been combined with portable mass spectrometers thus allowing *"in situ"* analysis. In addition, these techniques have the ability to map surfaces (Ambient MS imaging) to unravel the distribution of the agrochemicals on the crop.

Keywords: ambient mass spectrometry; pesticides; food; environment.

1. Introduction

Pesticides are plant protection products intended for preventing, destroying, repelling or mitigating any pest (harmful organism, such as insects, fungi, or weeds, among others) or disease. They may also influence the life processes of plants (e.g. growth regulators, nitrogen stabilizers) or preserve crops during production, storage and transport.[1,2] Annual pesticide sales in the period 2011-2016 were close to 400 000 tons of active ingredients, only in the European Union (EU).[3] As a consequence of this extended use, their residues may be found in foodstuffs of both vegetable and animal origin, and also as pollutants in the environment.[4,5] In order to asses food safety and to reduce any risk to human and animal health arising from pesticide exposure, pesticide residues have been restricted in developed countries. Public organizations such as EU, the United States Environmental Protection Agency (USEPA) or Codex Alimentarius have established maximum residue levels (MRLs) permitted in food, taking into consideration the acceptable daily intake of pesticides (amount of pesticide ingested daily during the whole life without leading to noticeable adverse effect).[6]

This framework fosters the development of analytical methods enabling the detection of pesticides at concentration levels below the MRLs set.[7] Multiresidue methods, the preferred option for food analysis, rely on hyphenated techniques such as gas chromatography/mass spectrometry (GC-MS) or high performance liquid chromatography/mass spectrometry (HPLC-MS)[6]. Nowadays, the feasibility of real-time pesticide testing, performed *"in situ"*, with little or no sample preparation and avoiding the chromatographic separation step, remains a challenge which focus the attention of food safety researchers. This greener approach, which fulfils many Green Analytical Chemistry principles, is feasible using Ambient MS techniques as captured in **Figure 1**.[8]

<Figure 1>

Ambient MS[9] is a rapidly growing field started with the development of desorption electrospray ionization (DESI)[10] and direct analysis in real time (DART)[11]. Since its inception, over eighty different Ambient MS approaches have been proposed for high-throughput testing and also for MS-imaging, being their connection the fact that analyte desorption and ionization steps take place under ambient open-atmosphere conditions with no (or scarce) sample workup; yet there is no consensus on classifying them[12].

Primary ionization mechanism is the more frequently used classification criterion, breaking down ambient MS techniques into (i) those closely related to electrospray ionization (ESI) and (ii) those resembling atmospheric pressure chemical ionization (APCI), generally plasma-based techniques.[13,14] Alternatively, ambient MS techniques may be organized by desorption or sample processing method (*i.e.*, thermal desorption, liquid extraction, use of lasers for desorption, etc) [15,16], and the combination of different criteria leads to establish subcategories. Readers interested in fundamentals of the different techniques and their classification according to the driving forces of both desorption and ionization steps are referred to different general reviews.[17,18,19,20,21,22,23,24,25] More detailed information about a particular subcategory of ambient ionization techniques may be found in specific reviews on spray-based,[26,27] plasma-based[28,29,30] and laser-based methods.[15,16]

This review article is focused on the application of ambient MS to pesticide residue analysis in food and environmental samples. The review is broken down in two main sections: ESI-related and APCI-related ambient MS methods, providing an overview of different ambient desorption/ionization MS methods as well as representative examples of their application to pesticide residue determination[31,32]. The different approaches, applied in the field, are presented, highlighting the advantages and limitations for their application in pesticide testing.

2. Electrospray-related ambient mass spectrometry methods applied to pesticide testing

In ESI-related ambient methods, the analytes are desorbed from the sample, and transferred to the atmospheric pressure inlet of the MS as charged solvent microdroplets. An overview of the more popular methods is represented in **Figure 2**. Selected applications in pesticide residue analysis are summarized in **Table 1**.

< Figure 2 >

2.1 Desorption Electrospray Ionization Mass Spectrometry (DESI-MS)

DESI was the first ambient ionization mass spectrometry method developed by Takats and Cooks[10]. It is commercially available[33]. In DESI experiment (**Figure 2a**), a charged high-velocity spray of microdroplets is directed towards sample (condensed-phase), and secondary droplets, including the species of interest, are then transferred through air to the atmospheric pressure interface of a mass spectrometer where solvent evaporation occurs, yielding gas-phase ionized compound(s). A solvent layer created by the initial spray dissolves the compounds deposited on the surface; subsequent spray droplets collide with the solvent layer, ejecting droplets containing the analyte from the surface towards the MS inlet.[10] More detailed discussions on DESI operation can be found in selected specific reviews.[34,35]

DESI has been applied to interrogate pesticides from both untreated crop surfaces and extracts obtained from dedicated sample workup procedures (*e.g.* QuEChERS (quick, easy, cheap, effective, rugged, and safe)).[36,37] Representative agrochemicals including insecticides (*e.g.* isofenphos-methyl, malathion), herbicides (e.g. ametryn, atrazine), and fungicides (*e.g.* imazalil, prochloraz, triazoles) were detected at similar or lower concentrations than MRLs set. The use of isotopically labelled internal standards (ILIS) provided quantitative results in agreement with those obtained by reference methods using LC-MS/MS or GC-MS.[36,37] DESI-MS fruit peel analyses were found a useful screening method to interrogate samples containing pesticide residues, either analysing directly the fruit peel surface[36] or by rubbing the peel with a glass slide subsequently used as substrate for DESI-MS.[37] Likewise, DESI-MS was used to determine chlorpropham on potato surfaces,[38] dimethoate, tebuconazole, and trifloxystrobin on olive and vine leaves,[39] and atrazine residues on Chinese cabbage leaf[40] (see **Table 1**). The main limitations for quantitative analysis on surfaces are low precision and the presence of matrix effects.[39]

A challenging pesticide such as thiram could not be directly detected on the surface of pear leaves,[41] but surface extraction with acetonitrile was appropriate for DESI-MS/MS. Using ILIS, semi-quantitative results could be demonstrated in spiked samples. Extraction of the homogenized fruit by QuEChERS method was inappropriate, due to severe suppression effects.

The feasibility of high-throughput *in situ* screening methods would be a convenient and cost-effective approach, as the number of samples subjected to a comprehensive evaluation would be significantly reduced. The combined use of ambient ionization methods and portable (handheld) mass spectrometers represents an interesting option to move the food control from the laboratory to the market shelves. This was first demonstrated by Mulligan *et al.*[42] using DESI to detect DEET, alachlor and atrazine in leaves and vegetable surfaces with no sample treatment. Sensitivity, selectivity and rapid detection could be satisfactorily achieved for the detection of target compounds in relevant field of analysis. Thus, DEET on the surfaces of cornstalk leaves or tomato was detected below 10 ng.

< Table 1>

The implementation of ESI-related ionization sources in portable mass spectrometers for *in situ* analysis of real samples is a very interesting approach that has been explored for pesticide residue testing, using not only DESI but also PS techniques.[42,43] Another interesting feature explored with DESI is the development of chemical images (mass spectrometry imaging (MSI)) of pesticide residues in crops (DESI-MSI). The distribution of pesticides in different parts of *Cotoneaster horizontalis* and *Kalanchoe blossfeldiana* was investigated by Gerbig *et al.*[44] using DESI-MSI. The distribution of contact pesticides (pyrethrins, rapeseed oil, imidacloprid, and methiocarb) on the plant surface and redistribution in plant stem and leaf of a systemic pesticide (dimethoate) were analyzed by DESI-MSI. A mass range from *m/z* 300 to 1500 was acquired to detect pyrethrins and triglyceride (TG) ions present in rapeseed oil. The TG showed non homogeneous covering on leaf surface. Also, pyrethrins showed different distribution on leaf surface. It was due to differences in polarity and size between them. When the same experiment was performed using an insecticide which contains imidacloprid and methiocarb, the pesticide distributions found on the leaf were distinctly more homogenous. The systemic incorporation of dimethoate in a *Kalanchoe blossfeldiana* plant was studied, and dimethoate was detected in the transport system of the plant at 25 days of treatment, and homogenously distributed in a leaf section after 60 days.

2.2 Extractive Electrospray Ionization (EESI) and nanoEESI

EESI was introduced for the first time by Chen *et al.*[45] (**Figure 2b**). It is based on the use of two separate sprayers, one of them (1-10 µL min^{-1}) nebulizes the sample solution and the second one generates charged microdroplets of solvent (extractive ESI) which continuously extracts the analytes from the sample solution into the solvent spray. It can be also modified to allow the analysis of solid samples (through neutral desorption EESI) or gas phase samples. This technique is very interesting for fast analysis of complex samples, being able to detect traces of atrazine in raw urine,[45,46] and of more than 200 toxicants, including pesticides, in urine, blood and stomach content or liver samples.[47]

Nanoextractive electrospray ionization (nanoEESI)[48] mass spectrometry is based on the use of a nanospray to generate the microdroplets (**Figure 2c**), using solvent flows in the range 0.05 – 0.1 µL min^{-1}. This avoids the use of the sheath gas, so reducing the parameters needing optimization and allowing hyphenation to portable mass spectrometers. Sample contamination and memory effects are reduced by using a disposable and manual sample injector. NanoEESI was applied to ambient mass analysis of paraquat and β-cypermethrin in spiked farmland water.[48]

2.3 Paper spray and related methods

In Paper spray (PS),[49] a piece of paper ending with a sharp point (held in front of the mass spectrometer inlet) is wetted with a solvent; a high electric field applied and the capillary action allow analyte transport and ionization (**Figure 2e**). Samples are loaded onto the paper by direct addition (a volume below 10 µL is appropriate), or the paper can be used as swab to sampling surfaces. The solvent is then applied once and mass spectra is recorded continuously until the signal disappears. With regards to the actual mechanisms, according to Espy et al.[50] , two spray operation modes have been described in positive ion PS-MS, spray mode 1, and spray mode 2 -after significant solvent depletion-. In the first mode, multiple Taylor-cone jets are observed, which depends on the paper cut and the solvent composition with ions from proton transfer reactions dominating the mass spectra. In spray mode 2, single cone-jet and a corona discharge coincide, with electron-transfer ions and radicals being observed (it is supposed mode 2 to occur always in negative ion MS).

Although most PS applications have been performed with in-house built setups,[51] commercial devices based on PS ionization (eg. VeriSpray™ PaperSpray ion source) are available and have been tested for pesticide analysis in whole milk, olive oil and leek homogenate.[52,53] PS has been used for the determination of methaldehyde (molluscicide)[54] and herbicides[55] in environmental waters by direct addition of a sample aliquot onto the paper substrate. Acidification of the solvent favored the formation of protonated molecules against sodium adduct, thus lowering LODs.[54] The use of isotopically labeled IS allowed the quantification of atrazine and metolachlor in the low microgram per liter range by PS-MS/MS. Complex matrices, such as soil extract[55] or fruit homogenates[55,56] showed higher limits of detection. In contrast, Guo *et al.* [57] supported that wine samples directly on the paper substrate allowed better detection and quantification (using ILIS) than when QuEChERS extracts were prepared. In a recent study, a semi-quantitative approach based on an extraction of tomato peels, instead of the whole vegetable, allowed to distinguish between stored or field samples.[58]

For screening purposes, PS-MS/MS allowed the detection of fungicides present on real samples by swabbing fruit peel with paper wetted with solvent, which is further used as substrate.[43,59] The spectra obtained for some citrus fruits showed the presence of imazalil and thiabendazole, identified by MS/MS analysis.[59] The sampling by paper wiping shows the advantage of collecting larger amount of analyte from larger surface area, so higher intensities may be obtained compared to surface analysis of agrochemicals by other ambient techniques such as DESI or LTP[59].

PS has been combined with portable mass spectrometers to perform *"in situ"* analyses, including pesticide testing in food surfaces[43,60]. Soparawalla *et al.*[60] determined thiabendazole by PS-MS in oranges using commercially available lens wipes paper (pre-moistened with isopropyl alcohol) to sample oranges surface and as ionization substrate. Nevertheless, signals, as well as their duration were a third lower than those obtained from filter paper, which was explained as consequence of the different porosity of both paper substrates.[60] Indeed, the substrate plays a key role in PS-MS, and although both filter [55, 60] and chromatographic paper[49,59] have been widely used, many modifications in the composition of the substrate have been proposed and are described as follows.

The use of a capillary emitter embedded on the paper substrate showed positive influence on the sensitivity and reproducibility comparing with standard PS.[61] Pu *et al.*[62] developed a method for pyrazole fungicides (penflufen, isopyrazam, fluxapyroxad, and pyraclostrobin) in wine using this PS variation; 10 μL of sample with no treatment and bixafen as IS. LOQs of 2 ng mL^{-1} were obtained, in compliance with the required regulatory limits. Microfluidics technologies, such as photolithography and wax patterning, have been also tested in order to increase sensitivity.[63,64] Photolithography produced a high background signal, but wax barriers improved sensitivity in the detection of atrazine and propazine in spiked tap water, compared to standard PS.[63] Paraffin microchannels also showed good results in pesticide analysis (atrazine, diuron and methomyl) in vegetable extracts.[65]

The chemical modification of the substrate was also tested. For instance, urea-modified paper substrate improved sensitivity in negative PS-MS because it retains anions from sample solution, thus reducing adduct formation[66]. In positive ion mode, silica-coated paper substrate improved LOQs for 7 pesticides in milk compared to commercial paper substrate[67] Molecularly imprinted polymers (MIP) has been also combined with PS ionization for herbicide analysis in food.[68] MIPs were directly synthesized on cellulose membranes, which were loaded (with sample) by dipping on different fruit methanolic extracts (apples, bananas and grapes), then, being used as PS substrate after washing and drying. Remarkable selectivity and LOQs below the established MRL (100 $\mu g\ L^{-1}$) were achieved for diuron and 2,4-dichlorophenoxyacetic acid (2,4-D), in positive and negative ion mode, respectively.[68] It is also worth mentioning the use of substrate paper coated with carbon nanotubes (CNTs) [69] which enabled the ionization of pesticides on orange peel with low voltages -in the range of volts instead of kilovolts commonly used in PS-MS-.

Finally, a smart and environmentally friendly modification of PS consists on the replacement of the paper by a natural porous substrate, the sample itself. In this regard, leaf spray (LS)[70] is a variation of the PS where the plant tissue acts simultaneously as substrate, sample and ion source. In this method, the gas phase ions are generated directly from the plant tissue, no other ionization device or support is needed beside the application of HV and a solvent. The direct determination of agrochemicals in fruit and vegetable tissues with no sample pre-treatment was demonstrated.[65,71] Signals were observed even without solvent addition, due to the presence of natural juice on fruit and vegetables, but more intense signals and better signal to noise ratios were obtained by adding solvent.[71] LODs below EU MRLs were reported[65,71] and discrimination between organic and conventional samples was shown,[71] providing also a semi-quantitative estimation of the concentration of pesticides in non-organic samples by external calibration. Another variation of paper spray for pesticide analysis is the wooden-tip ESI,[72] in which the porous substrate is a toothpick. The narrow-stick shape allows the generation of sharp electrosprays. Sample loading can be carried out by pipetting or directly dipping the wooden-tip into the sample solution. When a high voltage is applied and few microliters of solvent added to the tip, spray generation takes place and analyte ions are transferred to the MS. Analysis of beta-cypermethrin in spiked apple juices was satisfactorily performed as a proof of principle of this approach[73].

2.4 Other electrospray-based ionization methods: PESI and TD-EDI

A solid needle electrospray probe for liquid samples analysis called probe electrospray ionization (PESI) (**Figure 2d**) was developed by Hiraoka *et al.*[74]. A small amount of liquid sample is picked by the needles, with an automated movement on the vertical axis. Then, the needle is positioned in front of the MS inlet and an applied HV leads to ESI of the sample. PESI is free from clogging problems compared to ESI-based ion sources using capillaries. This source, commercially available[75], has been applied to the determination of polar pesticides (glufosinate, and paraquat) in human serum from real poisoning cases[76,77] with results consistent (using IS) to those obtained by standard methods. A variant (sheath-flow probe electrospray ionization (SF-PESI))[78] using a sheath liquid flow with a solid probe was applied to pesticide analysis in real-time from living plant tissues. Acephate, acetamiprid and thiophanate-methyl applied to the plant were detected, finding intense signals of sodium and potassium adducts together with the protonated molecule. However, the presence of these adducts and the lack of reproducibility in the sample amount loaded in the needle probe, prevent SF-PESI from providing absolute quantification values.

A relatively similar approach was proposed by Shiea *et al.*, so called thermal desorption electrospray ionization (TD-ESI-MS).[79] A metal probe is used to sample analytes; then, the probe is located in a pre-heated oven (**Figure 3**), with the analytes being desorbed with a nitrogen gas stream, transferred into an ESI plume to be ionized, and subsequently detected by MS.

<Figure 3>

TD-ESI has been used to detect pesticide residues from the surfaces of fruit and vegetables.[80,81] The decay, distribution, and removal of pesticides from fruits and vegetables surfaces by soak in water or detergent baths were studied.[80] The technique was useful for the screening of pesticides, but quantitative results cannot be provided by TD-ESI in solid samples due to the inhomogeneous distribution of the analytes throughout the surface.[80,81] TD-ESI has been also applied in the forensic field for the rapid identification of ingested pesticides. [82,83] A set of pesticides commonly detected in self-poisoning patients in Taiwan have been analysed by TD-ESI in gastric juice and oral fluid, achieving LODs in the parts per billion level (see **Table 1**). This involves a quick analytical process, which allows the rapid identification of pesticides before they reach the blood stream in self-poisoning patients, thus offering a promising tool for point-of-care based on ambient mass spectrometry.

3. Atmospheric pressure chemical ionization (APCI)-related ambient mass spectrometry methods applied to pesticide testing

APCI-related ambient MS methods include those which use an electric discharge to generate the species responsible for analyte ionization. Analyte ions are formed through series of gas-phase ion-molecule reactions with environment reagent species produced by a type of discharge. Additionally, in plasma-based techniques, ionization is also produced by energy-transfer reactions between the activated reagent species (e.g., helium metastables) and the analyte molecules.[14] Positive ionization is mainly attributed to Penning ionization and proton transfer from water cluster ions, whereas a variety of mechanisms such as electron capture and anion attachment, have been proposed for negative ionization.[84]

In these ionization sources, a gas flow (*e.g.* He, N_2 or air) is excited by an electrical discharge produced between two electrodes by applying either a direct-current (DC) or an alternating-current (AC) voltage at frequencies from kilohertz to several megahertz. Here, APCI-related ionization sources are sorted out in three groups, according to the featured discharge: a) glow discharge (GD) which is generated by DC voltages originating currents from hundreds of microamperes to several milliamperes and heating of the plasma gas; b) corona discharge (CD) which is produced around the tip of a needle electrode by DC supply and generates currents in the low microampere range; and c) dielectric barrier discharge (DBD) which is generated by an AC supply between two electrodes separated for at least one dielectric layer, providing a plasma close to room temperature and currents in the microampere range. For details about the fundamentals of plasma physics the readers are referred to specific literature.[85] Schematic representations of APCI-related ionization sources following discussed are shown in

Figure 4 and **Figure 5**. A summary of different methods developed for pesticide analysis using these sources is shown in **Table 2**.[87-141]

< Figure 4> and <Table 2>

3.1 Plasma sources based on an atmospheric pressure glow discharges (APGD)

3.1.1 Direct Analysis on Real Time (DART)

DART is a commercially available ionization source[86] and probably the more extended ambient MS method for pesticide residue testing, first described by Cody *et al.*[11] It consists of a tube divided in different chambers through which a gas (typically N_2 or He) is flowing through. A DC corona-to-glow discharge in the first chamber induces the formation of electrons, excited-state species and ions.[28] The gas flows through one or two chambers that can be used to filter ions and to heat the discharge gas before it impinges the sample placed near the atmospheric pressure inlet of the MS instrument (**Figure 4a**).

A set of different sampling assemblies have been also developed together with DART including the, so called, transmission mode DART (TM-DART)[86], and different autosamplers and pipette-based devices for sampling solid, liquid or gas samples. Thus, strobilurin fungicides residues were determined in wheat samples by Schurek et *al.*[87] by DART- TOF-MS. The utility of DART-TOFMS method for a rapid qualitative screening of the target fungicides in wheat grains without sample preparation requirements was attempted at concentration levels close or higher than the established MRLs. For quantitative purposes, the extraction of pesticides was carried out with ethyl acetate prior to DART-TOFMS analysis. The obtained LOQs (ranging 5 to 30 $\mu g\ kg^{-1}$) were lower than MRLs, and approached the results obtained by conventional LC-MS/MS using QuEChERS extraction.

The same group also showed the applicability of this methodology for the analysis of two dithiocarbamate fungicides (thiram and ziram) in pears.[41] Solvent extraction of the fruit surface with acetonitrile was preferred to QuEChERS procedure. The obtained LOQs comply with the EU-MRLs of fruit crops, and quantitative analysis was possible using

ILIS. These results were compared to surface analysis of fruits by DESI-MS/MS, which was suitable for thiram but not for ziram.

DART-Q-TOF-MS/MS was used in a collaborative study of Zhang and Dong[88] for the confirmation and quantification of dicyandiamide in powdered milk, using simple extraction with a mixture of water and acetonitrile. Quantitative analyses were performed with a high reproducibility without ILIS (commonly used to correct fluctuations in the desorption step) using TM-DART (**Figure 4b**). The results showed that TM-DART was useful for semi-quantitative analysis of pesticides in insecticide-treated nets at concentration levels lower than 0.5 mg·m^{-2} (10 ng) of deltamethrin, using either He or N_2 as discharge gas. The use of a fixed geometry eliminated the need of sample position optimization.

Zhang and Dong also reported that TM-DART provided enhanced precision compared to other sampling devices for the determination of pesticide residues in wine samples.[89,90] Quantitative analysis of the targeted pesticides was performed with a triple quadrupole instrument operated in multiple reaction monitoring mode. Direct determination of pesticides in red or white wine was achieved in 3 min with LOQs ranging from 25 to 500 ng mL^{-1}. However, QuEChERS treatment was found useful to minimize matrix effects and improve sensitivity (for 31 out of 50 pesticides) and LOQs (decreased up to 1-100 ng mL^{-1}).[90] Likewise, Lara *et al.*[91] also implemented the use of the Quick Polar Pesticide Extraction (QuPPe) method[92] with an additional clean up step in order to enable the determination of a group of polar pesticides in lettuce and celery by DART coupled to HRMS.

The use of foam swabs wetted with a solvent as sampling method on surfaces of fruits and vegetables has been tested. Polyurethane foam swabs were proven to be effective for the analysis of pesticide mixtures containing over two hundred species.[93,94,95]. A temperature gradient in the DART gas heater allowed the detection of such a great number of pesticides in a 3-min run. Cotton and polyester cleaning swabs were also useful[96] although polyester swabs have the disadvantage that its “background” ions itself dominate the spectrum.

Desorption temperature provided by the gas heater is one of the most critical analyte-dependent factors to be optimized, since it must be compatible with the sampling method (i.e. not degrading swabs or solid substrates) while providing effective desorption with high signal (which may include thermally labile compounds).

Solid-phase microextraction (SPME) has been combined with DART for analyte preconcentration and reduction of matrix effects for liquid samples. Wang *et al.*[97] analyzed triazine herbicides in lake water and orange juice by coupling of in-tube SPME (IT-SPME) with DART-MS. IT-SPME is based on the use of a carbon-nanotubes-incorporated polymer monolith and the online analyte desorption by the DART-MS system, leading to analyte desorption and ionization. Method precision was improved using an ILIS, and LOQs ranged from 0.06 to 0.46 ng mL^{-1}. The direct hyphenation of SPME to TM-DART (SPME-TM-DART) was introduced by Gómez-Ríos and Pawliszyn,[98] based on a metallic mesh coated with adsorbent particles which extracts the target analytes. SPME-TM DART devices were used for screening and quantification of pesticides in food (grape juice, orange juice, and cow milk) and environmental matrices (river water).[99] The total analysis time did not exceed 2 min per sample with LOQs in the range 0.1 – 5 µg kg^{-1}.

Therefore, to some extent, the analysis of pesticide residues in complex samples by DART-MS, and also by most of the ambient MS methods described, requires some sample treatment in order to reduce matrix effects to achieve both LOQs complying with the stringent regulations and to improve precision. Notably, some approaches that utilize minimal sample manipulation (e.g. surface extraction, SPME) give satisfactory quantitative results, particularly when ILIS are used.

3.1.2 Flowing atmospheric-pressure afterglow (FAPA)

Andrade *et al.*[100] proposed the use of the flowing afterglow (FA) of an APGD (first named FA-APGD and later FAPA) for the soft ionization of molecules. Like in DART, the discharge is not directly in contact with the sample. The reagent species are formed through the interaction of the ambient air with the excited species from the discharge and are transported outside the discharge chamber (see **Figure 4h**), which is mounted in a Teflon body into which typically He flows. As a consequence of the generated GD, the gas is heated (even above 200 ºC) by collisions with electrons, so no additional heating isrequired for sample desorption.[100]

For instance, thiabendazole was detected on lemon skin by wiping the surface with a swab and exposing it to FAPA.[101] The direct exposure of apple skin spiked with a mixture of pesticides (alachlor, atrazine, carbendazim, carbofuran, dinoseb, isoproturon, metolachlor, metolcarb, propoxur, and simazine) yielded LODs in the range 0.01 – 2.0 ng g^{-1}, below the MRLs set by the EU for the entire crop (in the range 50-100 ng g^{-1}).[102] Trace analysis of pesticides in spiked fruit juices from apple, cranberry, grape, and orange were performed pipetting 1 μL of the juice into pieces of filter paper subsequently exposed to the afterglow. A hybrid Q-TOF was used, but the response of spiked fruit juices at different concentrations was not linear and the precision was around 20%. A standardized method for sample positioning, together with the use of ILIS may solve the problems associated to reproducibility.

Shelley *et al.*[103] developed an improved design of the FAPA source (**Figure 4h**) leading to background signal reduction in both positive and negative ionization modes (89% and 99%, respectively), and, in addition, the capillary anode reduced the quantity of atomic oxygen (responsible of analytes oxidation in the pin-to-plate configuration). LODs obtained were *ca.* one order of magnitude better than related plasma-based methods.

An approach, conceptually similar to FAPA, that has been also reported for pesticide testing is microfabricated glow discharge plasma (MFGDP). It consists of a small planar ceramic chamber with DC voltage applied between two plate electrodes.[104] It features lower gas temperatures than FAPA. Semi-quantitative analysis of pesticides was performed with QuEChERS extracts of fruits and vegetables by MFGDP-MS/MS.[105] The solutions were spotted onto a filter paper and exposed to the plasma, achieving LODs between 0.13 and 3.1 ng g^{-1} and linearity up to two orders of magnitude.

3.2 Ambient mass spectrometry methods based on corona discharge ionization

Amongst these methods, Desorption Atmospheric Pressure Chemical Ionization (DAPCI) [106,107] (**Figure 5a**) is based on the same principle as APCI. A corona discharge is generated on the tip of the sharp needle (by applying a DC voltage of few kV), and reagent species are subsequently generated in its surrounding environment. Both gases and liquid solvents (introduced through an evaporation chamber) may be used to form reagent ions.

DAPCI has shown excellent results for detection of different drugs and biological samples,[108,109] with signal improvement compared with both DART and DESI. As an example, signals for cinchocaine and hydrocortisone (the main ingredients of an analysed ointment) were 5 and 50-fold higher with DAPCI than with DESI.[108] Chen *et al.*[110] used DAPCI to detect picograms of atrazine directly on unripe pumpkin surface and in cloths. MS/MS analyses together with chlorine isotope pattern were used to confirm the presence of the herbicide.

< Figure 5>

Besides DAPCI, other corona-based ambient MS methods are also shown in **Figure 5**. Thermal dissociation atmospheric chemical ionization (TDCI) was developed in 2011 by Han *et al.*[111]. Ionic liquids (green solvents) are used to produce reagent ions by thermal dissociation processes; these reagent ions interact with the analytes of the raw samples yielding analyte ions that are transferred to the MS. The original design of this source included two electrode plates assembled in a 90-degree configuration in front of the MS inlet and a heatable sample holder (see **Figure 5b**). The detection of both polar and nonpolar (nonvolatile) compounds was demonstrated.[111] A second design was used by Ouyang *et al.*[112] for dimethoate in orange juices, achieving a low LOQ (0.9 $pg\cdot mL^{-1}$) with no sample workup. Nevertheless, the authors reported some constraints of the technique due to the use of ILs, such as the possible contamination of the ion source with the continued used of these solvents and their high proton affinity, which hinders its application.

Another corona-based approach described by Wang *et al*[113] is desorption corona beam ionization (DCBI) (**Figure 5d**). It has similarities with DART source, such as the use of He (discharge gas) and the need of heating the gas for sample desorption. DCBI source produces a visible corona beam, allowing sampling area localization, thus being useful for imaging/surface experiments. In addition, it also allows gradient temperature operation, which permits sequential sample desorption to achieve a rough separation of analytes from complex mixtures. Pesticides were studied using this source, achieving absolute LODs ranging between 1 to 9.6 ng. In order to avoid sampling difficulties in liquid or gaseous matrices, the use of polydimethylsiloxane (PDMS) was also proposed as sampling substrate (by immersion in water)[114]. An improvement in LODs (1 $\mu g\cdot L^{-1}$)

for pesticide (acephate, isoprocarb, dimethoate, dichlorvos, and dicofol) detection in water, together with an increase in the number of identifiable compounds were achieved. Likewise, other improvements were proposed by Wang *et al.*[115] based on room temperature ionic liquids (RTILs) matrix-assisted DCBI.

3.3 Ambient mass spectrometry methods based on dielectric barrier discharge

Dielectric barrier discharges (DBDs) are widely used for plasma generation, because they offer some attractive features such as stable operation at atmospheric pressure, small size, low power consumption and a cold plasma production.[28] Several designs of DBDs have been proposed for Ambient MS including one or two dielectric barriers between the electrodes.[116,117] Amongst them, low-temperature plasma (LTP)[118] and the so-called DBDI[119,120] have been used and compared for pesticide residue testing. LTP is based on a ring-to-pin configuration and one dielectric barrier, whereas DBDI is based on a ring-to-ring configuration. Na *et al.*[121] reported the first ambient DBDI source (**Figure 4c**). It was a pin to plate configuration composed by a discharge needle (a hollow stainless-steel needle) and a copper sheet electrode, both separated by a glass slide acting as dielectric barrier and sample substrate. By applying an alternating voltage, a stable low-temperature plasma is formed between the discharge electrode and the glass surface[28] and the analytes (located on the glass slide) are desorbed and directly introduced into the MS. This initial configuration (pin-to-plate) was followed by LTP (pin-to-ring) and DBDI (ring-to-ring)

3.3.1 Dielectric Barrier Discharge Ionization (DBDI) (ring-to-ring)

This configuration consists of a glass capillary of small dimensions surrounded by two outer ring electrodes. The plasma jet dimensions depends on the gas flow (0.1 – 0.25 L min^{-1}), and cover a few millimeters.[119] The back electrode is grounded, while an AC high voltage is applied to the front electrode (closer to the MS inlet) with all the system being isolated with a Teflon casing. This probe was primarily utilized as ionization source for both ion mobility spectrometry[122] and LC-MS by Franzke and coworkers,[120] but also applications were performed for ambient MS analysis of pesticides. Gilbert-López *et al.*[123] proposed the combination of desorption by a continuous wave near-infrared diode laser with subsequent ionization by DBDI probe (LD-DBDI) as an ambient ionization method for detection of non-volatile chemicals on surfaces by MS (**Figure 4d**). A group of non-volatile pesticides (spinosad, prochloraz, and propazine) and other molecules with low vapor pressure were selected as analytes. The approach was applied to solvent standards and fragment confirmatory ions were obtained along with the protonated molecules of the studied pesticides. The results obtained by LD-DBDI-MS were distinctly superior to those obtained by thermal-assisted desorption.[123]

3.3.2 Active capillary plasma ionization (ACaPI)

The active capillary source designed by Zenobi *el al.* consists of a quartz capillary connected directly to the MS inlet, and the desorbed molecules are ionized in the gas phase during ion transfer into the vacuum. Different configurations have been tested for the electrodes,[124] and in the final design the DBD discharge occurs between an outer ring electrode connected to an AC high voltage and an inner ring grounded electrode (**Figure 4e**). This source has been recently commercialized under SICRIT® acronym (Soft Ionization by Chemical Reaction in Transfer).[125] In contrast to the ring-to ring DBDI[120,122], in ACaPI source the analytes flow through the capillary into which the discharge is produced, and are in contact with the grounded electrode. N_2 is usually employed as discharge gas in ACaPI, although regular air (doped with a low percentage of humidity) may be also used[126].

Ambient MS applications of ACaPI source include the analysis of the pesticide dichlorvos, by a handheld mass spectrometer.[127] Pesticide testing using ACaPI source involves so far, the use of hyphenated LC-MS or GC-MS techniques[126], or the use of solid-phase microextraction (SPME)[128] with the SPME fibers used as as substrate for subsequent thermal desorption and analyte ionization.

3.3.3 Low Temperature Plasma (LTP)

LTP probe was developed by Harper *et al.*[118] using a glass capillary of higher dimensions than that used in DBDI[120,122]. A stainless-steel grounded pin electrode axially centered inside the capillary and a copper outer HV electrode located in the opposite extreme of the tube generate a dielectric barrier discharge induced by an AC voltage. The inverse electrode configuration has been also described (inverse LTP)[129]. He and N_2 are commonly used as discharge gases, and the plasma jet formed interacts with the sample, prompting the desorption and ionization of molecules located on the surface (**Figure 4f**). Amongst the different LTP assemblies used, it is worth to mention a miniaturized version of LTP (glass capillary of 40 mm x 1.0 mm i.d., 1.6 mm o.d.) reported recently and applied to the analysis of gases or aerosols[130] and a 3D-printed holder design[131] with the aim of providing a reproducible model for LTP probes construction with potential application in MS imaging.

The first thorough study of LTP-MS applied to pesticide testing in fruit extracts deposited over a glass surface and fruit peels was performed by Wiley et al.[132]. Notably, the peak signal in LTP experiments was distinctly enhanced when the substrate was heated[118, 132]. LODs in the range from 0.2 to 200 ng g^{-1} were obtained for pesticides in spiked QuEChERS extracts of pepper, tomato and orange using LTP-MS/MS with heated substrate at *ca.* 100°C.[132] With a high-resolution Orbitrap MS instrument, LOQs in the range 1-7 ng g^{-1} were obtained for a group of pesticides in grape and raspberry QuEChERS extracts, distinctly below the MRLs.[133] Moreover, some authors have reported successful results in the direct analysis of samples without pretreatment. As an example, simple dilution applied to wines was enough to obtain LODs between 15 and 300 ng mL^{-1} for ten fungicides by LTP-MS/MS using an ion trap mass spectrometer.[134] These values fulfilled the established MRL values, highlighting the usefulness of LTP-MS for the qualitative analysis of real samples with no sample treatment.

Wang *et al.*[135] named thermal desorption LTP (TD-LTP) a coupling between a thermal desorption sample injector and an LTP probe. A PTFE swab is used to wipe out a solid sample surface, or it is wetted by a liquid sample or extract, and finally the swab is inserted into the TD module. The desorbed molecules are transported by an air current into the LTP plasma jet, which interacts only with sample in gas phase, originating an increase in sensitivity and stability comparing with conventional LTP. TD-LTP was used for the detection of 12 pesticides in broomcorn, using an ultrasound-assisted extraction with methanol and the extract was deposited on a PTFE swab prior TD-LTP-MS analysis. LODs ranging between 0.01 and 1 μg mL^{-1} for solvent standards.[135]

A different approach, proposed by Usmanov *et al.* [136]*,* studied the desorption of low-volatility compounds by liquid-solid friction. Microdroplets (*ca.* 30 μm diameter) of water/methanol (1:1) were produced by a piezoelectric generator and spotted on the flat surface of an ultrasonically vibrating blade (**Figure 4g**); microdroplet cavitation at the hitting interface was supposed to be the cause of the neutral desorption of the analytes. The vaporized analytes were subsequently ionized by a modified LTP quartz capillary probe in which the pin electrode extends outside the capillary, so the plasma jet is cut off. The analytes gave strong signals, which are not observed when either the blade vibrator or the piezoelectric microdroplet generator were off. LODs ranged from 0.1 to 100 ng (**Table 2**).

One of the most attractive features of ambient ionization sources is the possibility to perform *"in situ"* analysis. The combination of LTP with a portable MS has been proven useful as a high throughput screening method to differentiate between organic and non-organic apples.[60] Wiley *et al.*[137] developed a handheld LTP source powered by a small battery and either helium or compressed air were used as discharge gases. As expected, helium provided better LODs than air. Despite the reduction of gas and power consumption, the handheld source showed similar or slightly better analytical performance that the standard LTP, LODs, ranged between 0.001 to 0.9 ng, increasing up to 0.1 - 200 ng when a portable mini-MS was used.

3.4 Desorption atmospheric pressure photoionization (DAPPI)

DAPPI was developed by Haapala *et al.*[138] for rapid surface analysis of compounds with a wide range of polarities (from polar to nonpolar analytes) (**Figure 5c**).[139] It involves the use of a heated nebulizer microchip, which supply a heated jet of vaporized solvent, and a photoionization lamp. Sample spots on a surface are desorbed by the solvent jet, which is focused to the surface, subsequently, the analytes are ionized by APPI processes, and finally, they are detected by the MS. Luosujärvi *et al.*[140] studied species commonly found in environmental or food samples, including PAHs and pesticides (aldicarb, carbofuran, ditalimfos, imazalil, methiocarb, methomyl, oxamyl, pirimicarb, and thiabendazole). Three different spray solvents (with APPI dopants) were used in positive (acetone and toluene) and negative (anisole) ion mode. LODs for the studied pesticides ranged from 30 to 300 pg (corresponding to 0.14 to 1.4 pmol). Orange peel was directly analysed cutting a small slice and attaching it onto the sample substrate; an abundant ion at *m/z* 297, corresponding to protonated ion of imazalil, was observed and confirmed by MS/MS.

Vaikkinen *et al.*[141] compared the use of DAPPI and DESI to analize neonicotinoid compounds (thiacloprid, acetamiprid, clothianidin, imidacloprid, and thiamethoxam). DAPPI gave signal-to-noise ratios from 2 to 11 times better than DESI. LODs ranged from 0.4 to 5.0 fmol for neat standard solutions. DAPPI was also used to detect thiacloprid on fresh rose leaves and turnip rape flowers. Analysis of plant material was performed by DAPPI with no further requirements of extraction or sample preparation.

4. Concluding remarks and future perspectives

The application of ambient desorption/ionization MS methods for the determination of different pesticides in foodstuffs have been extensively studied in recent years. One of the major attractive features of ambient MS sources is the possibility of direct analyte determination on sample surfaces (*i.e.* determination of contact pesticides on crops). The first consequence of real-time surface analysis of trace amounts of organic compounds is the ability to map chemicals on surfaces, and eventually, the acquisition of chemical images with moderate lateral resolution, which might be highly informative, for instance, to understand the application of agrochemicals on crops and their mechanisms (degradation, persistence, distribution, …). For instance, the use of DESI for MS imaging[44] or the the combination of laser ablation with FAPA-MS[142] and LTP-MS[143] may be cited as examples of this feature.

In contrast, three main limitations may be observed for direct determination on foodstuffs with ambient MS methods. Firstly, direct surface analysis is affected by the nonhomogeneous pesticide distribution on the sample surface, which makes quantification efforts and method validation highly challenging. Secondly, in most ambient MS methods, only a small portion of the surface is interrogated so the analysis may not achieve the requested detection levels (MRLs values, normally provided in $mg \cdot kg^{-1}$ for the whole crop) depending on the interrogated surface (sweet spot effect). These limitations are usually avoided by the use of extraction techniques, such as surface liquid extraction, the use of dedicated procedures such as QuEChERS procedure, or sampling the targeted surface with swabs, paper or foam disks wetted with an appropriate mixture of solvents, with the subsequent determination directly on the sampling substrate by an ambient MS method. A relatively low portion of the literature address the quantitative analysis at low concentration levels, for instance with the use of ILIS. This issue yet remains as one of the main challenges to solve given the lack of homogeneity in the distribution of the pesticides in the sample. Thirdly, the occurrence of matrix effects in quantitative ambient MS methods should not be overlooked. There is a lack of thorough evaluation of matrix effects, although some studies have addressed this aspect.[144]

Finally, one of the most attractive features of ambient ionization sources is their use in portable mass spectrometers to perform *in situ* analysis. Amongst the ionization sources that has been coupled to a portable mass spectrometer we should mention DESI[42], PS[60], LTP[137] and ACaPI[127]. This is, definitely one of the most promising venues where ambient MS is expected to grow, as the availability of reliable portable MS instruments increases[8].

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Table 1. Summary of relevant methods for pesticides analysis by ESI-related ambient mass spectrometry.

Compounds	**Matrix**	**Ambient ionization technique/ spray solvent**	**Sample preparation**	**MS analysis**	**Analytical performance/matrix**	**Ref.**
DESI						
16 pesticides	(i) Fruit or vegetable extracts; (ii) Fruit peels	DESI (4.5 kV, 5 μL min^{-1}), ACN/water (8:2) (1% FA)	Two approaches: (i) QuEChERS; (ii) direct peel analysis	LIT-MS/MS	LODs 1 - 90 μg kg^{-1} in extracts	36
17 pesticides	Fruits (mango, papaya, passion fruit, apple and strawberry), and honey	DESI (3.5 kV, 125 μm/s), ACN/water (4:1) (0.1% FA)	Two approaches: (i) QuEChERS, and (ii) on fruit surface	Orbitrap MS	LODs (pg·mm^{-2}): 1, on Teflon; 33 on apple peel	37
Chlorpropham	Potato surface	DESI (5 kV, 0.5 μL min^{-1}), methanol/water (1:1) (1% acetic acid)	Not required	IT-MS/MS	LOD: 6.5 μg·kg^{-1}	38
Dimethoate, tebuconazole, and trifloxystrobin	Olive and vine leaves	DESI (5.5 kV, 1 μL min^{-1}), methanol/water (8:2) (10 mM FA)	Not required	QTRAP-MS/MS	LOQ (ng): Dimethoate (50), tebuconazole (150), and trifloxystrobin (60)	39
Atrazine	Chinese cabbage leaf	DESI (4.5 kV, 4 μL min^{-1}), ACN/water (1:1) (0.1% FA)	Not required	IT-MS/MS	LOQ < 63.13 pg·mm^{-2}	40
Dithiocarbamate fungicides: thiram and ziram	Fruit	DESI (5 kV, 5 μL min^{-1}), methanol/water (1:1) (0.1% FA and 10 mM ammonium formate)	Surface extraction with acetonitrile	LIT-MS/MS	LCL: thiram, 1 mg kg^{-1}; ziram, not detected	41
Alachlor, and atrazine and DEET	Leaf and vegetable surfaces	DESI, methanol/water (1:1)	Not required	Portable IT-MS	10 ng of DEET detected on cornstalk leaf	42
Insecticides: Dimethoate, imidacloprid, methiocarb, pyrethrins, and rapeseed oil,	Plant stem and leaves	DESI-MSI (3.5 – 4 kV, 2.5 – 3 μL min^{-1}), mixtures of methanol/water (containing FA, $(NH_4)HCO_3$ and $NaHCO_3$)	Cryosectioning to study the pesticide incorporation into the plant	Orbitrap-MS	Not available	44

EESI						
Atrazine	Spiked urine (2 μL min^{-1})	EESI (5 kV, 5 μL min^{-1}), methanol/water/acetic acid (5:5:1)	Not required	LIT-MS/MS	LOD: 0.4 fg atrazine	46
204 toxicants, including 47 pesticides	Urine, blood, stomach content, liver	EESI (4 kV, 5 μL min^{-1}),	Dilution and centrifugation (when needed)	LIT-MS/MS	LOD 0.002~0.09 μg L^{-1}	47
β-cypermethrin and paraquat	Spiked farmland water	nanoEESI (5 kV, 0.05 – 0.1 μL min^{-1}) with methanol/water (1:1)	Not required	LIT-MS/MS	LODs (μg L^{-1}):β-cypermethrin (6), and paraquat (10)	48
Paper Spray (PS) and related methods						
Atrazine, boscalid, clothianidin, diphenylamine, imidacloprid and thiamethoxam	Whole milk, olive oil, and leek homogenate	VeriSpray[52] Paper Spray system (3.8 kV), methanol:water (9:1) (0.1% FA)	Not required/ leek homogenization in a blender followed by solvent addition (1 mg μL^{-1})	QqQ-MS/MS	Calibration curves from the low μg L^{-1} (1-25) to the low mg L^{-1} (25-50) in milk and olive oil, and from 20 μg kg^{-1} to 10 mg kg^{-1} in leek homogenate	53
Methaldehyde	Environmental water	Paper spray (3.5 kV), methanol/water (0.1% FA) (1:1)	Not required. Only filtration	LIT-MS/MS	LOD: 0.05 μg L^{-1}	54
Atrazine, propazine, and metolachlor	Ground water, lake water, soil extracts, and crop extracts	Paper spray (3.5 kV), ACN	Soil and crop extracts by solid-liquid extraction with a mixture of acetonitrile/water (80:20, v/v)	IT-MS/MS	LODs in surface water: atrazine, 3.53 μg L^{-1}; metolachlor, 1.70 μg L^{-1}	55
Aldicarb, imazalil, methiocarb, methomyl and thiabendazole	Oranges, grapefruits, lemons, limes, mandarins, tomatoes, apples, pears, strawberries, grapes, and sweet peppers	Paper spray (3.2 kV), H_2O (0.1% FA)/ACN (2:8)	Two sampling approaches: (i) wiping with the paper; (ii) samples homogenized with acetonitrile	QqQ-MS/MS	LODs < 5 mg kg^{-1} in homogenates of orange, tomato and grapes	56

36 pesticides	Red wine	Paper spray (3.5 kV), methanol or ACN	(i) Off-line QuEChERS; and (ii) On-line Paper-Adsorption	QqQ-MS/MS	LOQs: (i) 0.3-375.5 µg L^{-1} (23 analytes); (ii) ACN as spray solvent: 0.6-272.9 µg L^{-1} (34 analytes); MeOH as spray solvent: 0.9-280.4 µg L^{-1} (31 analytes)	57
Acephate, chlorpyrifos, and cyazofamid	Tomato peels	Paper spray (4.0 kV), methanol (0.1% FA)	Remove the peel of the tomato and perform an extraction with ACN, or water (acephate)	IT-MS/MS	LOQs: 30 ppb	58
Imazalil and thiabendazole	Peel of lemon	Paper spray (4.5 kV), methanol/water (1:1)	Not required	LIT-MS/MS	Not available	59
Thiabendazole	Peel of treated oranges	Paper spray (4 kV), methanol/water (9:1)	Not required (surface wiping)	Portable MS (ion trap)	Not available	60
Pyrazole fungicides: isopyrazam, fluxapyroxad, penflufen and pyraclostrobin	Spiked wines	Capillary paper spray (2.5 kV), methanol	Not required	QqQ-MS/MS	LOQs: 2 µg L^{-1} for each analyte	61
Atrazine and propazine	Spiked tap water	Paper spray with wax-printed channels (4.5 kV), methanol/water (1 : 1)	Not required	Orbitrap-MS	LOD < 1.25 pmol	64
Acetochlor, alachlor, benzeneacetamide, butachlor, metolachlor, napropamid, pretilachlor	Spiked milk	Paper spray with silica-coated substrate, methanol/water (8:2)	Not required	QqQ-MS/MS	LOQs: 10.9 - 242.4 µg L^{-1}	67
Herbicides: diuron, and 2,4-dichlorophenoxyacetic acid (2,4-D)	apple, banana, and grape	Paper spray with MIP membrane substrate (3.5 kV), methanol (0.1% FA for positive ionization; 0.1% ammonium hydroxide for negative ionization)	Extraction with methanol	Q-Orbitrap-MS/MS	LLOQs: diuron, 0.41 – 0.99 µg L^{-1}; 2,4-D, 1.02 - 2.0 µg L^{-1}	68
Carbofuran, methyl parathion, parathion	Spiked orange surface (50 ppm)	Paper spray using paper coated with CNTs as substrate (3 V), methanol/water (1:1)	Not required (surface swabbing)	LIT-MS/MS	Not available	69

Atrazine, diuron and methomyl	Arugula, basil, cabbage, lettuce and kale vegetable samples	Paper spray with a paraffinned microchannel (3.5 kV), methanol (0.1% FA)	Extraction with methanol	Q-Orbitrap-MS	LOQs: 4.12 – 83.33 ppb	65
Atrazine, diuron and methomyl	Arugula, basil, cabbage, lettuce and kale vegetable samples	Leaf spray (3.5 kV), methanol (0.1% FA)	Not required	Q-Orbitrap-MS	LOQs: 0.11 – 120 ppb	65
Acetamiprid, diphenylamine, imazalil, linuron, and thiabendazole	Peel and pulp of different fruits and vegetables	Leaf spray (3.5 kV), isopropyl alcohol	Not required	LIT-MS/MS	LODs : 5-50 μg kg^{-1}	71
beta-Cypermethrin	Spiked apple juice	Wooden-tip ESI (3.5 kV), methanol (0.1% FA)	Not required	QTRAP-MS/MS	LOD: 30.0 μg L^{-1} (30.0 pg)	73
PESI						
Glufosinate and glyphosate	Human serum	PESI (1.7 kV), ammonium formate (10 mM)/ethanol (1:1)	Dilution	QqQ-MS/MS	LOQs: 1560 μg L^{-1} for both herbicides	76
Paraquat	Human serum	PESI (1.7 kV), ammonium formate (10 mM)/ethanol (1:1)	Dilution	QqQ-MS/MS	LCL: 15 μg L^{-1}	77
Acephate, acetamiprid, clothianidin, thiophanate-methyl	Living plants	SF-PESI (2.5 kV), ACN/water (1:1) (0.1% FA)	Not required	TOF-MS	LOD of acetamiprid in methanol solution over Teflon substrate < 50 pg	78
TD-ESI						
8 fungicides, 12 insecticides, 2 herbicides	Fruits and vegetables	TD-ESI (4.5 kV), water (0.1% FA)/methanol (1:1)	Not required	QqQ-MS/MS	LOD: 0.5 - 100 μg L^{-1} for aqueous pesticide standards	80
308 pesticides	Tomato and bell pepper	TD-ESI (4.5 kV), 5 mM NH_4OAc in 40% MeOH	Not required	QqQ-MS/MS	LOD < 50 ppb, for benthiazole standard solution	81
Acephate, chlorpyrifos, diazinon, dimethoate, iprobenfos, and methamidophos	Gastric juice	TD-ESI (3.5 - 4.5 kV), water/methanol (1:1) (0.1% acetic acid)	Not required	QqQ-MS/MS	LOD: 4.3 – 9.9 μg L^{-1}	82
Chlorpyrifos, dimethoate, methamidophos, methomyl, paraquat	Human oral fluid	TD-ESI (3.5 - 4.5 kV), water/methanol (1:1) (0.1% acetic acid)	Sampling with a cotton swab and subsequent pesticide	QqQ-MS/MS	LODs: 1 – 10 μg L^{-1}	83

extraction with methanol

Abbreviations: ACN, acetonitrile; FA, formic acid; LCL, lowest calibration level; LIT, linear ion trap; LLE, liquid-liquid extraction; MS, mass spectrometry; QTRAP, hybrid triple quadrupole/ion trap; QqQ, triple quadrupole; TOF, time-of-flight.

Table 2 Summary of relevant methods for pesticides analysis by APCI-related ambient mass spectrometry.

Compounds	**Matrix**	**Ambient ionization technique**	**Sample preparation**	**MS analysis**	**Analytical performance**	**Refs**
DART						
Strobilurins fungicides: Azoxystrobin, dimoxystrobin, kresoxim-methyl, picoxystrobin, pyraclostrobin, trifloxystrobin	Wheat	DART, He; Confirmatory analysis: DESI, methanol/water (1:1) (0.1% formic acid)	DART-TOFMS: Extraction with ethyl acetate. DESI-MS/MS: Microextraction with a C18 pipet tip using methanol as extracting solvent	TOFMS	LOQs 5-30 µg kg^{-1}	87
Dicyandiamide	Powdered milk	TM-DART using He as ionization gas	Extraction with acetonitrile/water (8:2)	Q-TOFMS	LOQ: 250 µg kg^{-1}	88
50 pesticides (positive and negative ionization)	Red and white wine	TM-DART, He	Modified QuEChERS procedure	QqQ-MS/MS and TOFMS	(i) DART-QqQ MS/MS, LOQs 1-100 µg L^{-1}; (ii) DART-TOFMS, LOQs 25-250 µg L^{-1}.	89
31 pesticides (positive ionization)	Red and white wine	TM-DART, He	Direct determination	QqQ-MS/MS and TOFMS	(i) DART-QqQ MS/MS, LOQs 25-500 µg L^{-1}; (ii) DART-TOFMS, LOQs 100-500 µg L^{-1}.	90
Amitrole, cyromazine, diethanolamine, melamine, propamocarb, 1,2,4-triazole, triethanolamine,	Lettuce and celery	DART using He as ionization gas	Modified QuPPe procedure	Orbitrap MS	LOQs 50 - 190 µgkg^{-1}	91

Thiram and ziram	Fruit	DART, He	Surface extraction with acetonitrile	TOFMS and OrbitrapMS	LOQs: (i) DART-TOF: 1000 and500 µg kg^{-1} for thiram and ziram, respectively; and (ii) DART-Orbitrap: 100 and 1000 µg kg^{-1} for thiram and ziram, respectively.	41
132 pesticides	Surfaces of grapes, apples, and oranges	TM-DART using He as ionization gas	Sampling by foam swabs	Orbitrap MS	Using foam swabs: 86% target analytes detected at levels of 2 µg kg^{-1} (apple or orange) and 10 µg kg^{-1} (grape)	93
Mixtures of 240, 140, 132 and 60 pesticides	Surfaces of apples, kiwis, peaches and tomatoes	DART using He as ionization gas	Sampling by foam swabs	Orbitrap MS	More than 80% of target analytes were detected at levels of 2, 5 and 10 µg kg^{-1}	94
164 pesticides	Surfaces of apples, oranges, and broccoli	TM-DART using He as ionization gas	Sampling by polyurethane foam disks	Q-Orbitrap MS	Spiked pesticides at concentration of 10 µg kg^{-1} were 100% detected onto apples and oranges, and 80% onto broccoli	95
Dimethoate, malathion, methamidophos,	Surfaces of cherry tomatoes, oranges, peaches, and carrots	TM-DART using He as ionization gas	Sampling by two kinds of swabs: (i) cotton, and (ii) polyester	Orbitrap MS	Concentrations (µg L^{-1}): dimethoate (20 and 200), methamidophos (200), and malathion (80 and 800)	96
Ametryn, atrazine, prometon, prometryne, propazine, simazine,	Lake water and orange juice	DART using N_2 as ionization gas	IT-SPME	TOFMS	LOQs: 0.06 - 0.46 µg L^{-1}	97
19 pesticides	Concord grape juice, orange juice, cow milk, and river water	TM-DART using He as ionization gas	SPME extraction performed onto the coated mesh	QqQ-MS/MS	LOQs, Concord grape juice and surface water (0.1-5 µg kg^{-1}); orange juice (0.1-0.5 µg kg^{-1}); cow milk (0.1-1 µg kg^{-1})	99
APGD						
Thiabendazole	Lemon skin	FAPA (pin-to-plate design), He gas flow, 0.8 L min^{-1}; operating current, 25 mA	Surface rubbed with a polyester swab	TOFMS	Not available	101
10 pesticides	Spiked fruit juices and fruit peel (apple, cranberry, grape, orange, and salad leafs)	FAPA (pin-to-plate design), He; DC 0.5 kV, 40 mA	Fruit juices spotted on filter paper; pesticide solution spotted on fruit/vegetable surface	Q-TOF-MS/MS	LODs, (i) fruit juices, 1 - 500 µg L^{-1}; (ii) apple skin, 0.01 - 5 µg kg^{-1}	102

Ametryn, diphenylamine, ethoxyquin, isofenphos-methyl, isoproturon, malathion, parathion-ethyl, terbuthylazine	Standards	FAPA (pin-to-capillary design), He,	Not required	LIT-MS/MS	LODs: 0.004 - 9.2 fmol	103
Ametryn, amitraz, buprofezin, dimethoate, diphenylamine, imazalil, isoproturon, malathion, parathion-ethyl	Peels and extracts of apples, oranges, tomatoes, green peppers, grapes, and celery	MFGDP, He 0.6 L min^{-1}; DC 820 V, 15 mA.	Two approaches: (i) QuEChERS, and (ii) direct determination on peel	IT-MS/MS	LODs, 0.13-3.09 μg kg^{-1} for fruit and vegetable extracts (QuEChERS)	105
Corona discharge						
Atrazine	Unripe pumpkin surface and cloths	DAPCI using ambient air as discharge gas	Not required	LIT-MS/MS	1-10 pg of atrazine detected	110
Dimethoate	Orange juices	TDCI using ionic liquid (1-butyl-3-methylimidazolium bromide salt)	Not required	LIT-MS/MS	LOD 0.9 ng L^{-1}	112
12 pesticides	Standards	DCBI source using He as discharge gas	Not required	Q-MS	LODs 1 - 9.6 ng	113
Acephate, isoprocarb, dimethoate, dichlorvos, and dicofol	Spiked water, river water, tap water, and wastewater	DCBI source using He as discharge gas	Microextraction in PDMS substrate		LODs of 1 μg L^{-1}	114
Dicrotophos, pirimicarb, carbaryl, and triazophos	Standards	RTILs matrix-assisted DCBI,using He as discharge gas	Not required	Q-MS	LODs: 2 - 10 ng	115
DBD						
Prochloraz, propazine, spinosad	Standards	LD-DBDI, He 0.2 L min^{-1}; AC, 20 kHz, 4.5 kV,	None	ITMS	Not available	123
Dichlorvos, diethyl ethylphosphonate, diisopropyl methylphosphonate, dimethyl	Standards	ACaPI, 1.6 kV, 5.75 kHz	None	Portable LIT-MS/MS	LODs: 1.0 – 6.3 μg L^{-1}	124

methylphosphonate, diethyl phosphoramidate						
13 agrochemicals	Fruit peels, fruit/vegetable extracts and water	LTP, He 0.4 L min^{-1}; AC, 2.5 kHz, 5-10 kV; 150 ºC heated surface (except direct peel analysis)	Two approaches: i) direct determination on fruit peel or spiked water, and ii) QuEChERS extracts	LIT MS/MS	LODs QuEChERS extracts: pepper (0.4-200 µg kg^{-1}); orange (0.4-20 µg kg^{-1}); tomato (0.2-20 µg kg^{-1})	132
Acetamiprid, cyprodinil, fenhexamid, fludioxonil	Grapes and raspberries	LTP, He 0.3 L min^{-1}; AC, 10 kV, 30 kHz; 150 ºC heated substrate	QuEChERS (citrate buffer) extracts	Orbitrap MS	LOQs ranged from 1 to 70 µg kg^{-1}	133
10 multiclass fungicides	Red wine	LTP, He 0.45 L min^{-1}; AC, 6.2 kV, 2.5 kHz; 120 ºC heated substrate	Dilution (1:5) with ACN	IT-MS/MS	LODs, ranged between 15 to 300 µg L^{-1}	134
12 pesticides	Broomcorn	TD-LTP, He 0.15 L min^{-1}; 180 ºC for TD; 0.1 L min^{-1} air flow for sample transport.	Methanolic extraction in ultrasonic bath	QqQ MS	LODs ranged between 10 and 1000 µg L^{-1}.	135
Carbaryl, gramicidin S, imazalil, spinosad,	Standards	modified LTP, He 0.25 L min^{-1}; desorption by ultrasonically vibrating blade	None	Orbitrap MS	LODs 0.1 – 100 ng	136
Diphenylamine	Apples	LTP (reduced size), He 0.3 L min^{-1}; AC, 17 kV, 6 kHz;	None	LIT-MS/MS (portable)	--	60
11 pesticides	Standards	Handheld LTP, 7.4-V, 900 mAh Li-polymer battery; (i) Air, 0.1 L min^{-1}; (ii) and (iii) He, 0.1 L min^{-1}	None	(i) and (ii) LIT MS/MS; (iii) Mini MS	(i) LTP (air)-MS/MS, LODs 0.004-300 ng; (ii) LTP (He)-MS/MS, LODs 0.001-0.9 ng; (iii) LTP (He)-MS (mini), LODs 0.1-200 ng	137
Photoionization						
Aldicarb, carbofuran, ditalimfos, imazalil, methiocarb, methomyl,	Standards and orange peel	DAPPI using different solvents (acetone, toluene, and anisol) as spray solvent. For orange	Not required	IT-MS	LODs: 30-300 pg (0.14 to 1.4 pmol)	140

oxamyl, pirimicarb, thiabendazole		peel analysis, acetone was selected as spray solvent				
Acetamiprid, clothianidin, imidacloprid, thiacloprid, thiamethoxam	Standards and thiacloprid detection on fresh rose leaves and turnip rape flower	DAPPI using acetone as spray solvent	Not required	IT-MS	LODs: 0.1 – 1 µg L^{-1} (0.4-5.0 fmol) for standard analytes	141

IT, ion trap; IT-SPME, in-tube solid phase microextraction; LIT, linear ion trap; Q, single quadrupole; QqQ, triple quadrupole; Q-TOF, quadrupole time-of-flight;

Figure Captions

Figure 1 Typical workflow of a routine pesticide testing method using chromatographic techniques and the role ambient MS may play to speed up these procedures, allowing even on-site sample analysis when portable MS instrumentation is used. Adapted from Ref. [8] with permission from Elsevier.

Figure 2. Schematic representations of (a) DESI (Ref. [10]); (b) EESI (Ref. [45]); (c) nanoEESI (Ref. [49]; (d) PESI (Ref. [74]); (e) PS-MS (Ref. [59]). For details, see text. Adapted with permission from the publishers (Wiley, Royal Society of Chemistry, ACS and .

Figure 3. Schematic diagram of the TD-ESI-MS analytical procedure. Adapted from ref. [83], with permission from Wiley.

Figure 4. Schematic representations of (a) DART (Ref. [11])]; (b) Sample holder and upper view of TM-DART (Ref. [86]); (c) DBDI (pin-to-plate) (Ref. [121]); (d) LD-DBDI (Ref. [123]); (e) ACaPI source (inner (I.E.) and outer electrodes (O.E.) are shown) coupled to SPME desorption chamber (Ref. [128]); (f) LTP (Ref. [118]); (g) Ultrasonic-assisted desorption DBDI-MS (Ref. [136]); (h) Pin-to-plate and pin-to-capillary configurations of FAPA (Ref. [103]). For details, see text. Adapted with permission from the publishers (ACS, Elsevier and Royal Society of Chemistry).

Figure 5. Schematic representations of: (a) DAPCI (Ref. [110]); (b) TDCI (Ref. [111]); (c) DAPPI (Ref. [138]); (d) DCBI (Ref. 113). For details, see text. Adapted with permission from the publishers (Wiley, Elsevier, Royal Society of Chemistry and ACS respectively).

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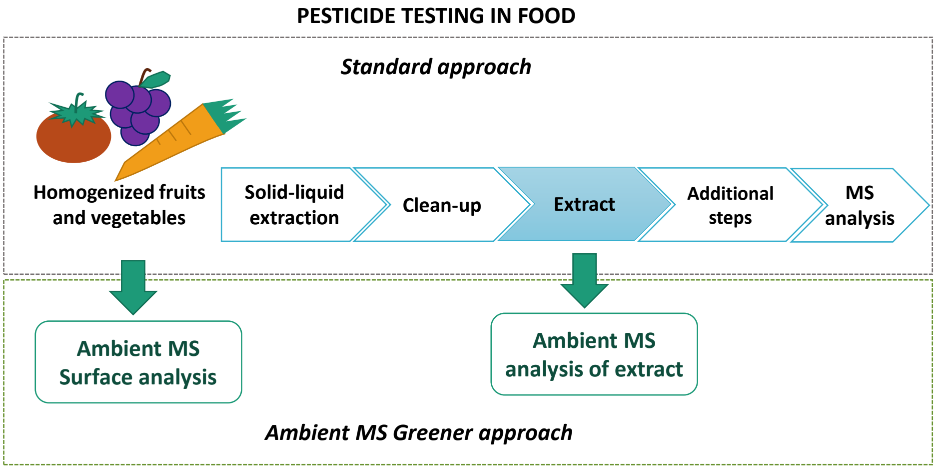


Figure 1

Figure 2

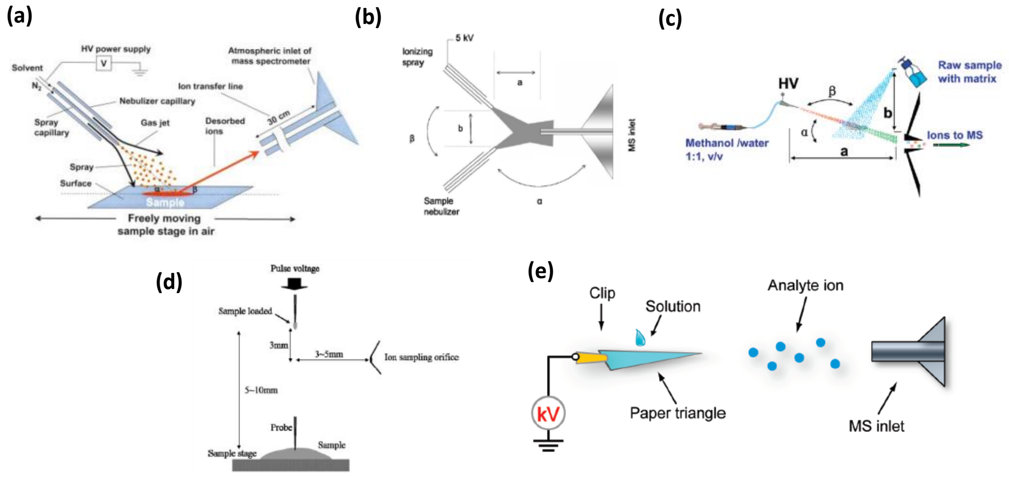


Figure 3

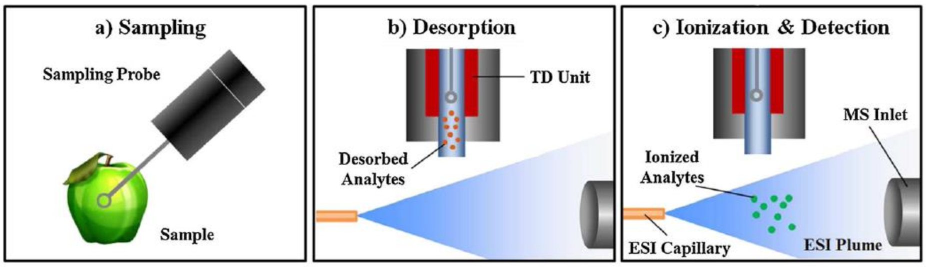


Figure 4

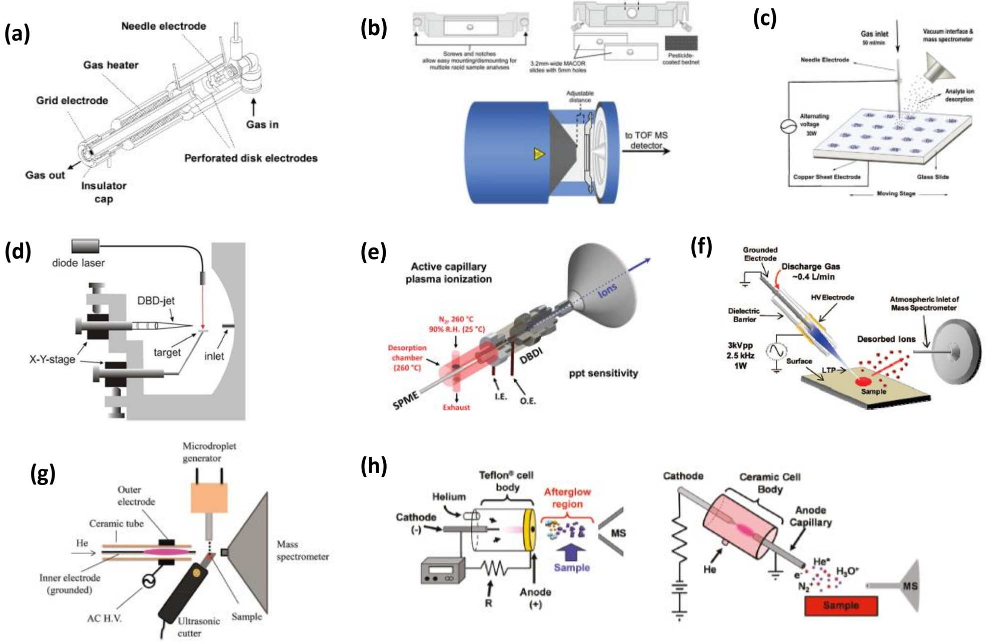
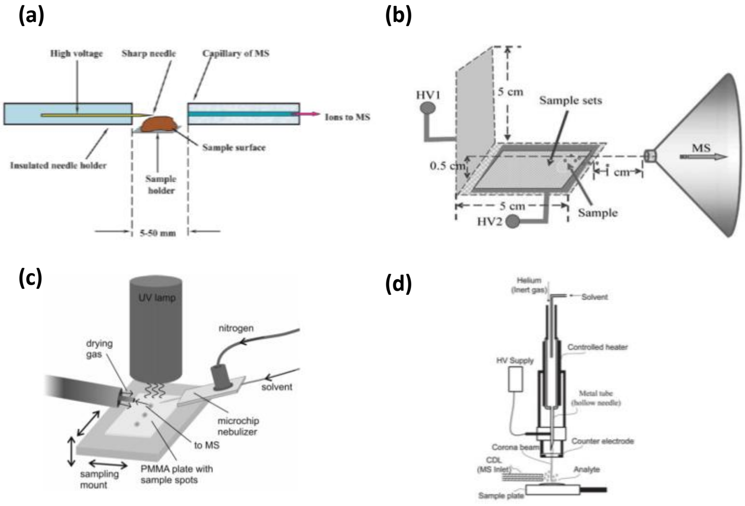


Figure 5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High voltage
Sharp needle
Capillary of MS
Ions to MS
Insulated needle holder
Sample surface
Sample holder
5-50 mm
(b)
HV1
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MS
0.5 cm
1 cm
5 cm
HV2
Sample
(c)
UV lamp
nitrogen
drying gas
solvent
microchip nebulizer
to MS
PMMA plate with sample spots
sampling mount
(d)
Helium (Inert gas)
Solvent
Controlled heater
HV Supply
Metal tube (hollow needle)
Counter electrode
Corona beam
CDL (MS Inlet)
Analyte
Sample plate