RECENT DEVELOPMENTS IN ATMOSPHERIC PRESSURE PHOTOIONIZATION-MASS SPECTROMETRY

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Recent developments in atmospheric pressure photoionization (APPI), which is one of the three most important ionization techniques in liquid chromatography-mass spectrometry, are reviewed. The emphasis is on the practical aspects of APPI analysis, its combination with different separation techniques, novel instrumental developments - especially in gas chromatography and ambient mass spectrometry - and the applications that have appeared in 2009–2014. © 2015 Wiley Periodicals, Inc. Mass Spec Rev 36:423–449, 2017

Keywords: *ambient mass spectrometry; atmospheric pressure photoionization; dopant; gas chromatography-mass spectrometry; liquid chromatography-mass spectrometry*

I. INTRODUCTION

Atmospheric pressure photoionization (APPI), together with electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI), is one of the three most-important atmospheric-pressure ionization (API) techniques. APPI was introduced in 2000 as a novel ionization method for liquid chromatography-mass spectrometry (LC-MS), and it has been shown to markedly widen the range of compounds that can be ionized in LC-MS towards nonpolar compounds (Robb, Covey, & Bruins, 2000; Syage, Evans, & Hanold, 2000). Since then, numerous applications and theoretical studies on the ionization mechanism of APPI have been reported. Besides LC-MS, APPI has been used in gas chromatography-mass spectrometry (GC-MS), capillary electrophoresis-mass spectrometry (CE-MS) and ambient MS. Several excellent reviews have been published that discuss the theoretical aspects of APPI, as well as its numerous applications (Raffaelli & Saba, 2003; Bos, van Leeuwen, & Karst, 2006; Robb & Blades, 2008; Marchi, Rudaz, & Veuthey, 2009). Six years have passed since the publication of the last review, and therefore we saw the need to provide an update on the recent developments in APPI research. In this review, the emphasis is on the practical aspects of APPI analysis, its combination with different separation techniques, novel instrumental developments – especially in GC-MS and ambient MS – and the applications that have appeared after the review of Marchi, Rudaz, and Veuthey (2009). Because the theoretical aspects of APPI have been very comprehensively discussed in a review by Robb and Blades (2008); they are touched on here only briefly.

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II. APPI ION SOURCE

The APPI source has been described in several research papers and review articles (Raffaelli & Saba, 2003; Robb & Blades, 2008; Syage, Short, & Cai, 2008; Marchi, Rudaz, & Veuthey, 2009), and therefore only a short description is given here. An example configuration of an open-source APPI relative to the vaporizer and the mass spectrometer inlet is illustrated in Figure 1. APPI is similar to APCI in that the analyte molecules must be vaporized for effective ionization, and therefore in essentially all commercial MS systems, APPI uses the same nebulizer/vaporizer assembly as APCI. Current commercial APPI sources utilize vacuum ultraviolet (VUV) lamps that are based on discharge of a gas mixture that consists primarily of Kr, and operate on the atomic emission lines at 10.0 and 10.6 eV. The discharge can be driven by a variety of means, but the most common are radiofrequency electrodeless excitation and high voltage direct current electrode excitation. Often, an additional solvent that is primarily ionized by the photons, a dopant, is introduced to the APPI source to enhance the ionization efficiency. The dopant can be delivered through a T-piece to heated gas line, or the solvent line.

III. GENERAL PRINCIPLES OF APPI

A. Ionization Mechanism in Positive-Ion APPI

The ionization in APPI is initiated by 10.0 eV (and minor proportion 10.6) photons emitted by a krypton discharge lamp. The photons can ionize compounds with ionization energies (IEs) below this energy, which includes most organic compounds, but leaves out atmospheric gases and the most typical LC solvents. Therefore, APPI is more selective than, e.g., APCI, which also ionizes gases and LC solvents by corona discharge-initiated ionization reactions.

The initial ionization reaction in direct APPI is the photoionization of the analyte, and formation of a molecular ion ($M^{+\cdot}$; Scheme 1, Reaction 1). In case a solvent with ionization energy below 10.6 eV is present (i.e., many normal-phase (NP) LC solvents), the solvent can also be ionized (Scheme 1, Reaction 2). After the initial photoionization reaction, compounds with high proton affinities (PAs) tend to form protonated

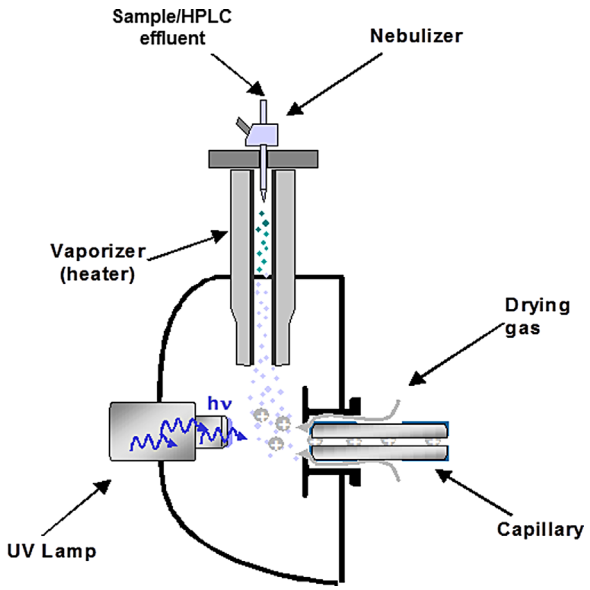

FIGURE 1. Standard configuration of an orthogonal APPI source in positive ion mode. Adapted with permission from Hanold et al. (2004), Copyright 2004 [American Chemical Society].

molecules ($[M+H]^+$) by self-protonation, or in reactions with solvent or water clusters.

At atmospheric pressure, direct photoionization is often inefficient, because the photons tend to become absorbed by neutral molecules and lose their energy by radiationless decay processes. To increase the ionization efficiency, APPI often utilizes a dopant – an additional solvent that has an IE below 10 eV, and that can, therefore, be efficiently ionized by the lamp photons. In photoionization, the dopant forms dopant molecular ions ($D^{+\cdot}$) (Scheme 1, Reaction 3), which can react further with the analytes or other species present in the ion source. For analytes with IEs below the IE of the dopant, a possible route of ionization is charge-exchange (Scheme 1, Reaction 4). Water (and solvent) clusters, which are ubiquitous in atmospheric pressure ion sources, have been shown to play a crucial role in APPI (Klee et al., 2013). Following photoionization, the $D^{+\cdot}$ ions can be solvated by water or (if present) solvent clusters (Scheme 1, Reaction 5). Extremely fast intracluster chemistry can lead to decomposition of the initial cluster, and formation of charged solvent cluster and neutral radical dopant species (Scheme 1, Reactions 6 and 7). The charged solvent clusters can react with the analytes by ligand-switching or association reactions that cause the analytes to enter the clusters (Scheme 1, Reactions 8 and 9, respectively). At the MS entrance, the clusters will break due to electrical-field driven collisional decomposition reactions, and the proton will end up with the species of highest PA, to form $[M+H]^+$ (analyte), $[S+H]^+$ (solvent), or $[D+H]^+$ (dopant) (Scheme 1, Reaction 10).

B. APPI Dopants

The most commonly used APPI dopants are toluene, acetone, anisole, and chlorobenzene. Besides these, there are numerous solvents or combinations of solvents that have been tested, such as various substituted benzenes, tetrahydrofuran (THF), and carbon disulfide (Robb, Smith, & Blades, 2008; Cai, McConnell, & Bach, 2009; Smith, Robb, & Blades, 2009; Dousty et al., 2013). Some examples of APPI dopants are shown in Table 1. The discussion here is limited to the most-common dopants.

In the presence of toluene, the analytes can form either molecular ions or protonated molecules. For a particular compound, the route of ionization might depend on other species present in the ion source, such as LC solvents (Kauppila et al., 2002). Charge-exchange between toluene $D^{+\cdot}$ and the analyte can be highly efficient in the presence of low PA solvents or in a gas chromatographic system, which is free of solvents. In the presence of high PA solvents, such as methanol or acetonitrile, however, toluene $D^{+\cdot}$ ions react with the solvent (Scheme 1, Reaction 7), which leads to neutralization of $D^{+\cdot}$ and formation of protonated solvent molecules (and clusters). Neutralization of $D^{+\cdot}$ hinders ionization of analytes through charge-exchange. Instead, the analytes can undergo ligand-switching and ligand-association reactions with proton-bound solvent molecules, which lead to formation of protonated molecules of the analytes. The molecular ion of anisole does not transfer a proton to methanol or acetonitrile in Reaction 7 (Kauppila, Kostiainen, & Bruins, 2004). As a consequence, the charge-exchange reaction with anisole is efficient even when high PA solvents (e.g., methanol, acetonitrile) are present. The molecular ion of toluene is a better proton donor than the molecular ion of anisole: in toluene $D^{+\cdot}$ a benzylic C–H bond is broken more easily than a $–O–CH_3$ C–H bond or an aromatic C–H bond in anisole. The resulting $[D-H]^{\cdot}$ radical in Reaction 7 (Scheme 1) for toluene has a benzyl structure or a seven-membered tropylium ring structure. This favorable structure of the $[D-H]^{\cdot}$ radical is another driving force for deprotonation of the molecular ion of toluene. On the other hand, anisole is more polar than toluene and therefore a more-suitable ligand

$M + h\nu$	→	$M^{+\cdot} + e^-$	if IE (M) < 10.6 eV	(1)
$S + h\nu$	→	$S^{+\cdot} + e^-$		(2)
$D\ (dopant) + h\nu$	→	$D^{+\cdot} + e^-$		(3)
$D^{+\cdot} + M$	→	$M^{+\cdot} + D$	if IE (M) < IE (D)	(4)
$D^{+\cdot} + nS$	→	$[D^{+\cdot}S_n]$		(5)
$[D^{+\cdot}S_n]$	→	$S_n^+ + D^{\cdot}$		(6)
$[D^{+\cdot}S_n]$	→	$[S_n+H]^+ + [D–H]^{\cdot}$		(7)
$[S_n+H]^+ + M$	→	$[M+S_{n-1}+H]^+ + S$		(8)
$[S_n+H]^+ + M$	→	$[M+S_n+H]^+$		(9)
$[M+S_n+H^+]$	→	$[M+H]^+ + nS$		(10)

SCHEME 1. The ionization reactions in positive-ion APPI (M = analyte, S = solvent, D = dopant) (Kauppila et al., 2002; Hanold et al., 2004; Klee et al., 2013).

TABLE 1. Examples of APPI dopants. IE, ionization energy, PA, proton affinity (P.J. Linstrom and W.G. Mallard, Eds., NIST Chemistry WebBook, NIST Standard Reference Database Number 69, National Institute of Standards and Technology, Gaithersburg MD, 20899, http://webbook.nist.gov, retrieved February 3, 2015).

Dopant	IE (eV)	PA (kJ/mol)	Ref.
Toluene	8.83	784.0	(Robb, Covey, & Bruins 2000)
Acetone	9.70	812.0	(Robb, Covey, & Bruins 2000)
THF	9.40	822.1	(Rauha, Vuorela, & Kostiainen 2001)
Anisole	8.20	839.6	(Kauppila, Kostiainen, & Bruins 2004)
Chlorobenzene	9.07	753.1	(Robb, Smith, & Blades 2008)
Bromobenzene	9.00	754.1	(Robb, Smith, & Blades 2008)
Fluorobenzene	9.20	755.9	(Robb, Smith, & Blades 2008)
1,3,5-Trimethylbenzene	8.40	836.2	(Robb, Smith, & Blades 2008)
2,4-Difluoroanisole	n.a.	n.a.	(Smith, Robb, & Blades 2009)
3-Trifluoromethylanisole	n.a.	n.a.	(Smith, Robb, & Blades 2009)
CS_2	10.073	681.9	(Dousty et al. 2013)
Toluene/anisole (95.5:0.5)	n.a.	n.a.	(Lung & Liu 2011)
Ethanol/bromobenzene/anisole (98.975:0.1:0.9:0.025)	n.a.	n.a.	(Amad & Sioud 2012)

for the solvent clusters (Klee et al., 2013). Anisole has been suggested to expel the analytes from the clusters, which can sometimes result in reduced efficiency for protonation. The IE of anisole is rather low, and therefore there is a large amount of compounds that cannot be ionized through charge-exchange with anisole. Chlorobenzene was suggested as an APPI dopant in order to overcome this problem: it has higher IE than anisole, and it can therefore ionize a larger group of compounds through charge-exchange; in addition it is equally unreactive as anisole towards high PA solvents (Robb, Smith, & Blades, 2008). Acetone, on the other hand, goes through a self-protonation reaction after the initial photoionization (Tzeng, Wei, & Castleman, 1989), and therefore acetone $M^{+\cdot}$ ions are not at all available for charge-exchange. However, the protonated acetone molecules and clusters can react efficiently with the analytes through proton transfer. These reactions are often more selective than the ionization with, e.g., toluene and result in a much lower background.

C. Ionization Mechanism in Negative-Ion APPI

In negative-ion APPI, the ionization is initiated by thermal electrons that are either released in the photoionization of the dopant (Scheme 2, Reaction 1), or from metal surfaces of the ion source (Basso et al., 2003; Kauppila et al., 2004a). Subsequently, the ionization follows similar routes as in APCI (McEwen & Larsen, 2009). The thermal electrons can be captured by gases, solvents, or analytes that exhibit positive electron affinities (EAs; Scheme 2, Reactions 2–4). Compounds that have positive EAs typically have halogenated or nitro groups, or a high degree of conjugation (e.g., quinones). Besides compounds with positive EAs, acidic analytes are efficiently ionized by proton transfer in negative-ion APPI. In electron capture, a negative molecular ion ($M^{-\cdot}$) is formed. Oxygen has positive EA, and has been shown to play an important role in negative-ion APPI. In electron capture it forms superoxide ions, $O_2^{-\cdot}$ (Scheme 2, Reaction 4), which can react with the analytes through charge-exchange (Scheme 2, Reaction 5), or be solvated by water or solvent clusters (Derpmann, Albrecht, & Benter, 2012). Charge-exchange is possible in case the analyte has higher EA than $O_2^{-\cdot}$. $O_2^{-\cdot}$ has also elevated gas-phase basicity, and it can accept protons from analytes or solvents that have higher gas-phase acidities (Scheme 2, Reactions 6 and 7). $O_2^{-\cdot}$ is therefore an important reagent ion for proton transfer in the negative-ion mode. Also solvent-derived ions (e.g., acetate ions from the LC buffer) can act as reagent ions in negative-ion APPI, and react with analytes through proton transfer (Scheme 2, Reaction 8). Aromatic compounds sometimes form oxidation products that can complicate the negative-ion APPI mass spectra (Scheme 2, Reaction 10). For some compounds, ionization can be achieved

D (dopant) + hν	→	$D^{+\cdot} + e^-$		(1)
$M + e^-$	→	$M^{-\cdot}$	if EA (M) > 0 eV	(2)
$S + e^-$	→	$S^{-\cdot}$	if EA (S) > 0 eV	(3)
$O_2 + e^-$	→	$O_2^{-\cdot}$		(4)
$M + O_2^{-\cdot}$	→	$M^{-\cdot} + O_2$	if EA (M) > EA (O_2)	(5)
$M + O_2^{-\cdot}$	→	$[M\text{-}H]^- + HO_2^{\cdot}$	if $\Delta_{acid}G$ (M) < $\Delta_{acid}G$ ($HO_2^{\cdot}$)	(6)
$S + O_2^{-\cdot}$	→	$[S\text{-}H]^- + HO_2^{\cdot}$	if $\Delta_{acid}G$ (S) < $\Delta_{acid}G$ ($HO_2^{\cdot}$)	(7)
$M + [S\text{-}H]^-$	→	$[M\text{-}H]^- + S$	if $\Delta_{acid}G$ (M) < $\Delta_{acid}G$ (S)	(8)
$M + O_2^{-\cdot}$	→	$[M\text{-}X+O]^- + OX^{\cdot}$	X = H, Cl, NO_2	(9)
$M^{-\cdot} + O_2$	→	$[M\text{-}X+O]^- + OX^{\cdot}$		(10)
$M + A^-$	→	$[M+A]^-$		(11)

SCHEME 2. Ionization reactions in negative ion APPI (Kauppila et al., 2004a).

by anion attachment (Scheme 2, Reaction 11), as was shown for nitroaromatic compounds by introduction of halogen salts to the ionization area (Song et al., 2007). Because negative-ion APPI requires specific functionalities in the analyte structure in order to be efficient, it is more selective than positive-ion APPI and can be used to gain excellent signal-to-noise ratios (S/N). Negative-ion APPI has been used, e.g., for the analysis of explosives and environmentally interesting analytes, such as polybrominated flame retardants and polychlorinated biphenyls (Bacaloni et al., 2009; Song & Bartmess, 2009; Moukas, Thomaidis, & Calokerinos, 2014).

IV. APPI AS AN INTERFACE TO COUPLE SEPARATION TECHNIQUES WITH MASS SPECTROMETRY

A. Liquid Chromatography-Mass Spectrometry

APPI was originally developed as an interface for LC-MS, and it is still the most-important area where APPI is used. In comparison to the earlier introduced LC-MS ionization methods, ESI and APCI, which are efficient to ionize polar compounds, APPI has expanded the range of LC-MS-analyzable analytes towards completely nonpolar compounds. APPI has also been reported to have a broader linear range than ESI (Hakala et al., 2003) and show less baseline noise than APCI (Cai, Hanold, & Syage, 2007), as demonstrated in Figure 2 for benzoin enantiomers. In comparative studies among the three ionization methods, APPI has often been the most-sensitive technique for neutral and nonpolar compounds; however, for polar and ionic compounds, ESI usually gives the best sensitivity (see section V, Recent APPI applications).

Unlike in ESI, where the solvent must be electrically conductive, in APPI there are no such restrictions. Therefore, the range of solvents in APPI is broader, and even completely nonpolar NP-LC solvents can be easily combined with APPI-MS (Wang, Hsieh, & Korfmacher, 2005; Cai, Hanold, & Syage, 2007). However, the LC solvent often affects the ionization mechanism and sensitivity in APPI (Kostiainen & Kauppila, 2009). In reversed-phase liquid chromatography (RP-LC), the solvent is typically a mixture of water with methanol or acetonitrile, and often ammonium acetate or other volatile buffer is added to ensure optimal chromatographic behavior of the analytes. In dopant-assisted APPI, gas-phase reactions between dopant ions and neutral solvent molecules can take place (see discussion above). Therefore, it is difficult to achieve charge-exchange of the analytes in RP-LC conditions with toluene as the dopant, because the toluene molecular ions will be depleted in reactions with methanol- and acetonitrile-containing clusters, and ionization will turn to proton transfer (Kauppila et al., 2002). Of course, low-polarity compounds that can only be ionized with APPI, do not possess sufficiently high PAs for proton transfer – otherwise, one might as well use ESI or APCI – and, therefore, the charge-exchange route is often pursued instead of proton transfer. In the case of toluene as the dopant, the only way to promote this route is with low-PA solvents that do not react with the toluene molecular ions. These solvents include water, hexane, or chloroform, which are not the best choice for RP-LC. Anisole and chlorobenzene as dopants, however, allow the ionization of analytes through charge-exchange even in the presence of typical RP-LC solvents, as already concluded above (Kauppila, Kostiainen, & Bruins, 2004; Smith, Robb, & Blades, 2009). Nonpolar NP-LC solvents are well-suited for APPI, and many of them (e.g., hexane, heptane, octane, isooctane, isopropanol, and THF) also possess sufficiently low IEs that allow them to be ionized by the Kr lamp photons (Wang, Hsieh, & Korfmacher, 2005; Cai et al., 2007; Black et al., 2013). In that case, an additional dopant is not necessary. NP-LC with APPI ionization is well-suited to analysis of lipids (Gaudin et al., 2012; Black et al., 2013) and crude oil components (Lababidi & Schrader, 2014).

In negative-ion APPI, LC solvents that possess positive EAs (e.g., chloroform and other halogenated solvents) have been reported to suppress the ionization (Kauppila et al., 2004a). Also, acetate and formate buffers can cause signal suppression when the analyte has lower gas-phase acidity than the additive. However, for cases where the analyte has higher gas-phase

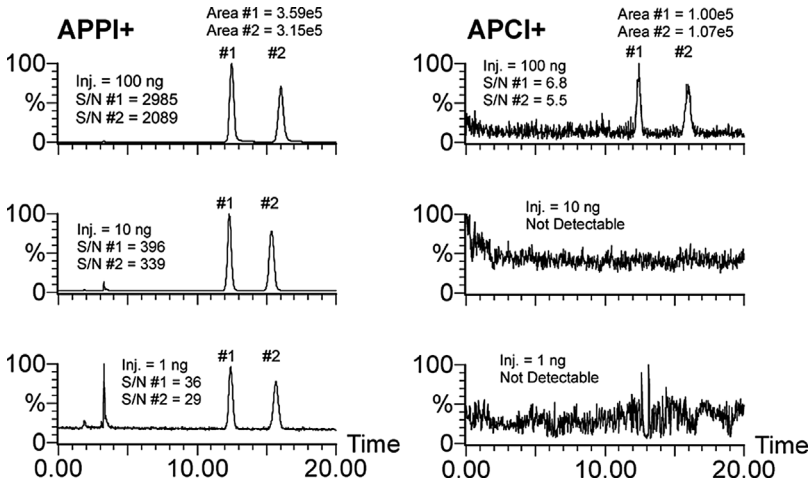

FIGURE 2. LC separation of benzoin enantiomers with APPI and APCI. Although the APPI and APCI peak areas differ by no more than a factor of 4, the S/N ratios differ by over two decades. Poor APCI sensitivity was mainly due to elevated baseline noise generated from ionization of column-bleeding components. Reprinted with permission from Cai, Hanold, and Syage (2007), Copyright 2007 [American Chemical Society].

acidity, the presence of acidic additives might increase the signal and decrease the noise due to enhanced selectivity. Buffers reduce the ionization efficiency also in positive-ion APPI, and therefore the concentration of LC buffer in LC-APPI-MS should be kept to a minimum (Rauha, Vuorela, & Kostiainen, 2001; Kauppila et al., 2002).

In LC-MS, an important issue that must be considered is the flow-rate of the LC solvent that is introduced into the APPI source. The signal of analytes in APPI saturates and even decays at higher solvent flow rates (above 200 μL/min, Fig. 3) (Yang & Henion, 2002). The signal saturation and decay have been suggested to be due to (i) absorption of photons by the increasing amount of solvent molecules, (ii) formation of larger solvent clusters with higher PAs, which can block the ionization of the analytes, and/or (iii) an increased number of recombination processes between positive and negative ions in the ion source (Hanold et al., 2004; Kauppila, Kostiainen, & Bruins, 2005; Robb & Blades, 2005). In dopant-assisted APPI, the analytes that are ionized through charge-exchange are more-severely affected by this phenomenon than compounds that form protonated molecules; that result might be due to depletion of dopant molecular ions by the increased amount of solvent and solvent impurities (Kauppila, Kostiainen, & Bruins, 2005). More efficient charge-exchange has been reported with a lower solvent flow rate (50 μL/min instead of 200 μL/min), because then the dopant molecular ions are not depleted, but are available for the charge-exchange reaction, even in the presence of high-PA solvents (e.g., methanol, acetonitrile) (Robb & Blades, 2006). Even lower solvent flow rate (0.5–10 μL/min) is used in microchip APPI (μAPPI), which can be used as an interface for capillary-LC-MS (Kauppila et al., 2004b; Haapala et al., 2007a).

B. Gas Chromatography-Mass Spectrometry

There are several advantages to couple GC with API-MS: GC can achieve a far higher number of theoretical plates than LC, and can therefore provide more efficient separation. Coupling GC with LC-MS mass spectrometers, on the other hand, allows a multitude of MS/MS scanning modes (single- and multiple reaction monitoring, neutral loss, precursor scan, MS^n) which can be utilized for retrieving structural information about the analyte.

APPI is a well-suited interface for GC-API-MS, because GC and APPI both require that the analytes are initially in neutral and gaseous form. GC is inherently a method for non-polar molecules (polar molecules are generally derivatized) for which APPI excels. Further, the odd-electron $M^{+\cdot}$ ions formed in APPI form similar fragments in MS/MS as those formed during EI, and therefore, it has been suggested that the APPI product-ion spectra could be compared with EI library spectra to identify unknowns (Hintikka et al., 2013). In GC-APPI-MS, there are no LC solvents that could deplete the dopant molecular ions from the APPI source, and ionization of analytes through charge-exchange is more likely than in LC-MS conditions (Kauppila, Kersten, & Benter, 2014). Commercial GC-MS products that use APPI are expected to become available in the near future, and the number of applications that use GC-APPI-MS is therefore likely to increase rapidly.

In the meantime, custom-made GC-APPI-MS designs have been introduced by several research groups. McEwen (2007), Lee, Smith, and Jun (2012), and Suominen et al. (2013) all used simple setups, where a heated GC transfer line delivered the gaseous sample to a commercial API-MS instrument (McEwen 2007; Lee, Smith, & Jun, 2012; Suominen et al., 2013). Lee used

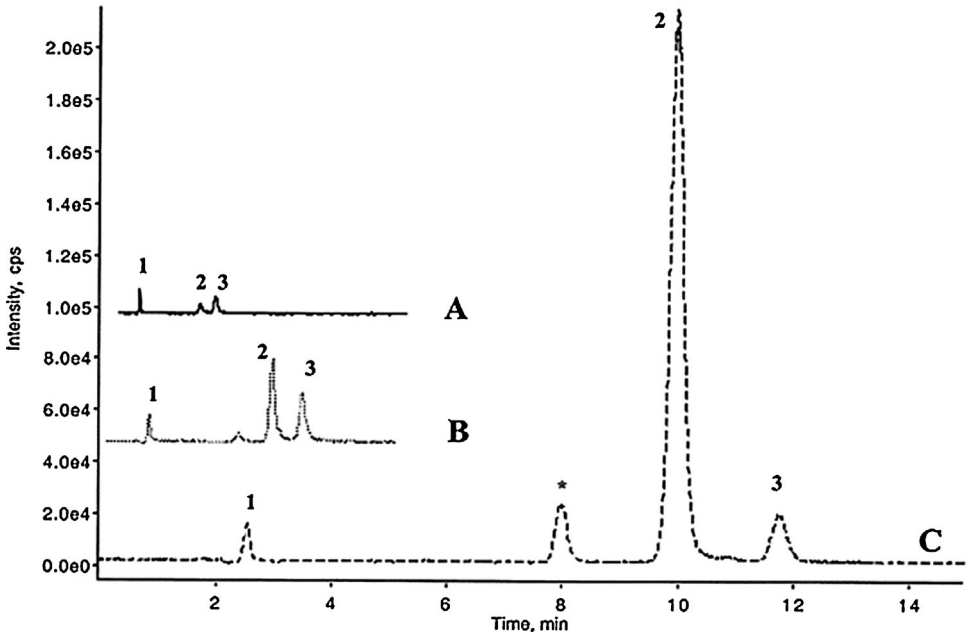

FIGURE 3. Effect of flow rate on the sensitivity of LC-APPI-MS towards (1) idoxifene and its metabolites (2) SB20, and (3) SB19. Mobile phase flow-rates: (A) 0.7 mL/min; (B) 0.35 mL/min; (C) 0.1 mL/min. Solvent: acetonitrile–H_2O 85:15 v/v (1% HCOOH). Reprinted with permission from Yang and Henion (2002), Copyright 2002 [Elsevier].

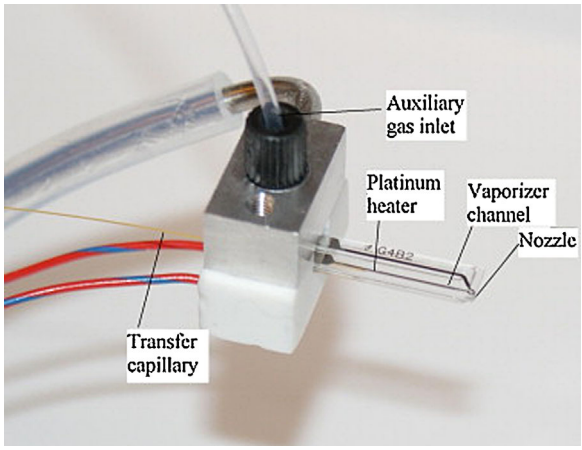

FIGURE 4. A photograph of the heated nebulizer microchip. Reprinted with permission from Kruve et al. (2011), Copyright 2011 [Elsevier].

the setup to analyze a perfume sample, McEwen perfume and EPA priority pollutants, and Suominen trimethylsilyl (TMS)-derivated neurosteroids from human urine. Another setup by Hintikka et al. (2010) used the heated nebulizer microchip (Fig. 4) originally developed for low flow rate LC-APPI-MS (see discussion above) as a GC-MS interface. The conventional ion source was replaced with a nano-spray stand and the microchip was placed to close proximity of the MS inlet. A heated transfer line was used to connect the GC column to the microchip, which was heated to approx. 300˚C. This setup has been used for the quantitative analysis of TMS-derivatized and underivatized anabolic steroids (Hintikka et al., 2010, 2013) and 2-quinolinone-derived selective androgen receptor modulators (Luosujärvi et al., 2010a) from urine.

Kersten et al. introduced another setup for GC-MS coupling, called capillary APPI (cAPPI) (Kersten et al., 2011). In cAPPI, a windowless miniaturized argon spark-discharge lamp was embedded into an ion transfer capillary, which separates the atmospheric and differentially pumped low-pressure regions of the mass spectrometer. Due to the close proximity to the MS inlet, the source had a temporal resolution of milliseconds, and can be used

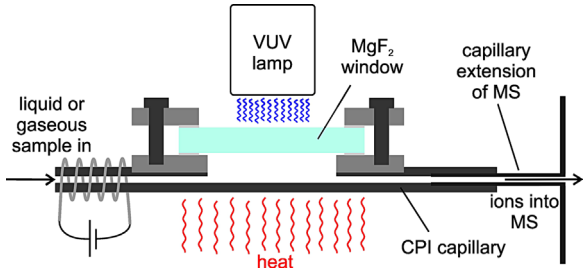

FIGURE 5. Schematic of the capillary photoionization device connected to a mass spectrometer. Reprinted with permission from Haapala, Suominen, and Kostiainen (2013), Copyright 2013 [American Chemical Society].

in real-time studies of rapidly changing chemical systems. Because ionization takes place inside the transfer capillary, ion-transmission efficiency is maximized and detection limits at low ppb range were achieved. Similar to cAPPI, in a setup called capillary photoionization (CPI), photoionization and the subsequent ionization reactions take place inside a transfer capillary (Fig. 5) (Haapala, Suominen, & Kostiainen, 2013). CPI uses a heated transfer capillary with a VUV transparent MgF_2 window, through which the photons from a krypton discharge lamp enter. The sample can be either liquid or gaseous, and is introduced together with a dopant directly into the heated transfer capillary, where it is vaporized (in case of a liquid sample) and photoionized. The setup was used for the highly sensitive analysis of TMS-derivatized steroids from biological samples with LODs in the range of 2–6 pg/mL. Figure 6 shows a schematic of another GC-APPI-MS interface that uses a gas-tight ionization unit and highly purified nitrogen for nebulization (Kauppila, Kersten, & Benter 2014). The ion source can achieve highly efficient photoionization without a dopant and with very low background, and has been used in a comparative study of the ionization mechanisms in direct and dopant-assisted APPI and atmospheric pressure laser ionization (APLI) in GC-MS environment.

C. Capillary Electrophoresis

Several groups have used APPI as the ionization method for capillary electrophoresis-mass spectrometry (CE-MS) (Nilsson

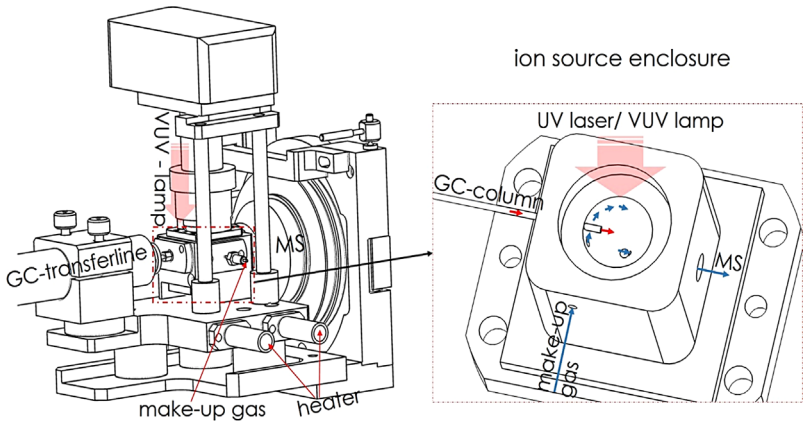

FIGURE 6. Schematic of the GC-API interface (left) and close-up of the ion-source enclosure with indicated volume flows and radiation entrance (right). Reprinted with permission from Kauppila, Kersten, and Benter (2014), Copyright 2014 [Springer].

et al., 2003; Mol, de Jong, & Somsen, 2005). ESI is traditionally the method of choice for CE, because CE separation demands that the compounds are in ionic form; nevertheless, APPI has some advantages over ESI as a CE-MS interface. Although nonvolatile phosphate and borate buffers that are common in CE can cause severe signal suppression in ESI, APPI is not as severely affected by the buffers and shows lower background than ESI (Nilsson et al., 2003; Zheng & Shamsi, 2006; Schappler et al., 2007; Hommerson et al., 2008). Recent publications, where APPI-MS is used as a CE interface, show ESI, APCI, APPI, and TSI as complimentary ionization techniques for drug impurity profiling (Hommerson et al., 2009).

D. Ambient Photoionization Mass Spectrometry

Ambient mass spectrometry is a family of techniques to directly sample compounds from solid surfaces. Although the most-prominent techniques in this family are desorption electrospray ionization (DESI) (Takáts et al., 2004) and direct analysis in real time (DART) (Cody, Laramee, & Durst, 2005), over thirty techniques that use different techniques for desorption and ionization of the analytes have been introduced (Van Berkel, Pasilis, & Ovchinnikova, 2008; Harris, Galhena, & Fernández, 2011; Monge et al., 2013). The methods that use photoionization are briefly introduced here, along with some of the applications that use them.

Desorption atmospheric pressure photoionization (DAPPI) was the first ambient MS technique that used photoionization and has thus far been the most explored (Fig. 7) (Haapala et al., 2007b). In DAPPI, the analytes are thermally desorbed from the surface under study, after which they are ionized with photon-initiated reactions in the gas-phase, similar to conventional APPI. The DAPPI setup uses a microchip heater to deliver hot vapor of nebulizer gas and dopant for thermal desorption and ionization. Thus far, DAPPI has been applied to analysis of pharmaceuticals in tablets (Haapala et al., 2007b) and dried blood spots (Räsänen et al., 2014), drugs of abuse in powder, tablet, resin, plant and paper form (Kauppila et al., 2008, 2011, 2013), anabolic steroids in oil (Kauppila et al., 2011), pesticides in fruit peel and plant surface, and polyaromatic hydrocarbons (PAHs) in soil (Luosujärvi et al., 2010b; Vaikkinen et al., 2015), as well as vitamins and other lipids from tablets, capsules, food products, and mouse tissue (Pól et al., 2009; Suni et al., 2012; Räsänen et al., 2014). DAPPI can be achieved also by holding the solid sample in front of a commercial APPI source, as shown by Podgorski et al.(2012a), who used this setup for the characterization of pyrogenic black carbon. A modification of DAPPI, which uses a DART source equipped with a VUV lamp and a dopant supply line, has also been introduced (Jorabchi, Hanold, & Syage, 2013). This source was compared to conventional DART, and the sensitivity of positive-ion DAPPI was 3–5 times better than that of DART. Nitrogen and helium could both be used as desorption gases, with similar performance. In another study, DAPPI showed better sensitivity for all the studied analytes and lower background than DART (Räsänen et al., 2014).

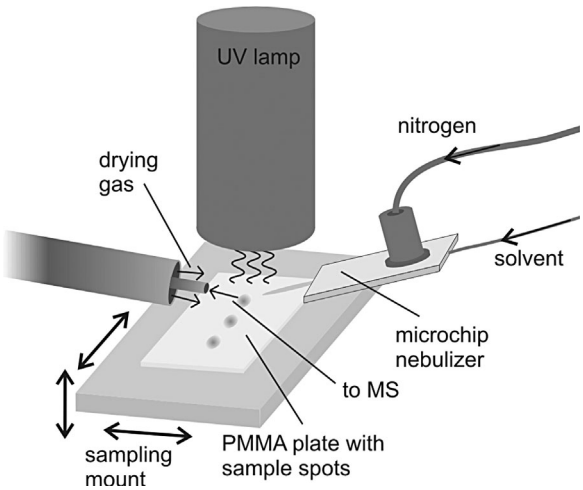

FIGURE 7. Schematic of the DAPPI source. Reprinted with permission from Haapala et al. (2007b), Copyright 2007 [American Chemical Society].

An ambient MS technique that combines photoionization with atmospheric solids analysis probe (ASAP) has been introduced, and is referred to as direct probe APPI (DP-APPI) (Ballesteros-Gomez et al., 2014; Syage & Jorabchi 2014). In ASAP, the sample – liquid or solid – under study is coated on the outside of the closed end of a melting-tube capillary and inserted inside an atmospheric pressure ionization source, where thermal desorption by the hot nebulizer gas takes place (McEwen, McKay, & Larsen, 2005). The technique is closely similar to direct chemical ionization, which in the 1970s was used in combination with EI/CI mass spectrometers (Cotter, 1980).

Although, originally ASAP used APCI for analyte ionization, DP-APPI uses APPI instead of APCI. In the work by Ballesteros-Gomez et al., DP-APPI was applied to analysis of plastic products, electronic waste, and car interiors, and deteted polybrominated diphenyl ethers, and brominated and organophosphorus flame retardants. Resorcinol bis(phenylphosphate) and bisphenol A were identified from consumer products. The glass probes were loaded with the solid sample by inserting them directly to the shredded material or by scratching the surface with the probe. DP-APPI was more selective and sensitive than DP-APCI, with a lower background, especially when low temperatures and dopant were used. In work by Syage and Jorabchi, pesticides, steroids, and pharmaceuticals were studied (Syage & Jorabchi, 2014). DP-APPI showed significant improvements in detectability and sensitivity compared to DP-APCI. A further benefit was that room-air flow instead of nitrogen gave comparable quality results, which overcomes the need for purified gas and makes DP-APPI better-suited for field applications..

Photoionization is also used in laser ablation atmospheric pressure photoionization (LAAPPI), where analytes are ablated from the surface of water-containing samples with an infrared laser (Fig. 8) (Vaikkinen et al., 2012). The laser can achieve spatial resolution of $\sim$300 μm, which is adequate for mass spectrometry imaging, as shown for phytocompounds from sage leaves (Vaikkinen et al., 2014).

V. RECENT APPI APPLICATIONS

A large number of publications that used APPI have appeared in 2008–2014, after the publication of the last APPI review (Marchi, Rudaz, & Veuthey, 2009). To keep the length of this

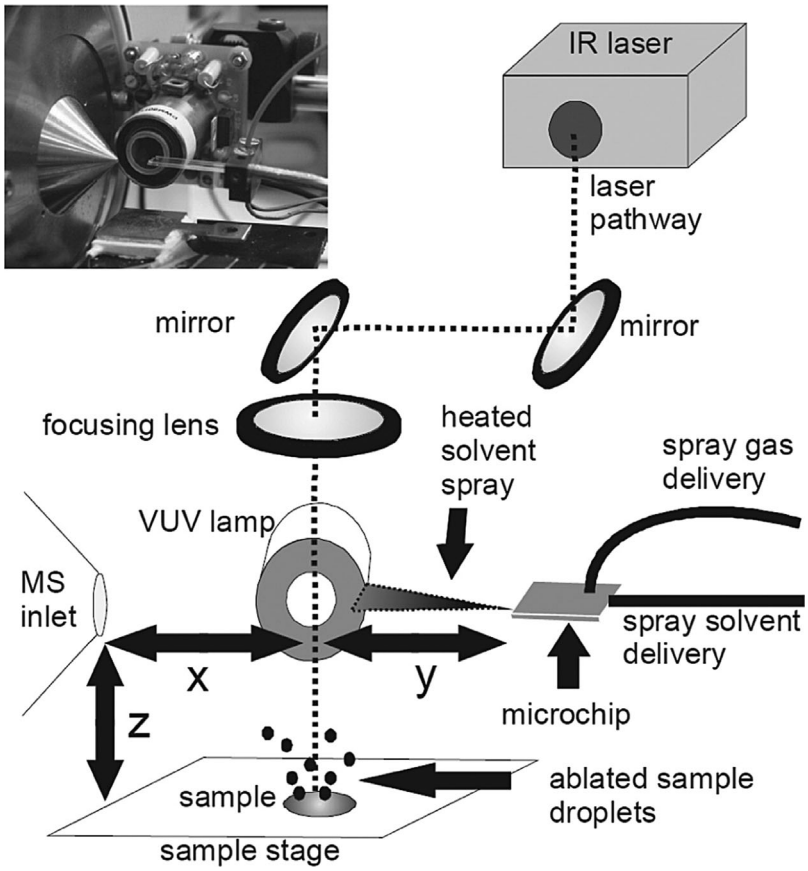

FIGURE 8. Schematic of the LAAPPI setup. Reprinted with permission from Vaikkinen et al. (2012), Copyright 2012 [American Chemical Society].

review reasonable, it is not possible to discuss all the cases individually. Instead, we show examples of the type of applications, where use of APPI has given added value. Of special interest are cases, where APPI and other techniques are compared. A more-comprehensive view of the applications is given in Tables 2–6.

A. Drug Analysis

After introduction of APPI for LC-MS in 2000 (Robb, Covey, & Bruins, 2000; Syage, Evans, & Hanold, 2000), pharmaceutical analysis fast became the most-explored field for APPI (Raffaelli & Saba, 2003; Bos, van Leeuwen, & Karst, 2006; Marchi, Rudaz, & Veuthey, 2009). Table 2 shows the APPI-related applications published in pharmaceutical and toxicological areas in 2008–2014. Most pharmaceuticals and their metabolites are polar molecules, and usually show higher signal response in ESI than in APPI. For neutral compounds, however, APPI sometimes proves more sensitive; other advantages of APPI are its wider linear range and tolerance of complex matrices.

Mascher and co-workers used APPI as the ionization method for LC-MS in the pharmacokinetic analysis of a corticosteroid drug ciclesonide and its metabolites (Mascher, Zech, & Mascher, 2008). They detected analytes as acetate adducts in negative-ion mode and achieved four-times greater sensitivity for the analytes with APPI than with ESI or APCI. In another pharmacokinetic study APPI was chosen over ESI and APCI due to more sensitive detection of neutral compounds, such as budesonide, a glucocorticoid steroid for treatment of asthma (Borges et al., 2011). Marchi and coworkers chose APPI over ESI for the analysis of benzodiazepins in haemolyzed blood, due to its lower susceptibility to signal alterations in biological samples, and wider linear dynamic range (Marchi et al., 2009). The latter was mentioned as especially important for benzodiazepines that have wide therapeutic and toxicity windows. In a study by Wang et al., ESI, APCI, and APPI were compared in the LC-MS analysis of 17 illicit drugs and their metabolites from oral fluid, and APPI showed the lowest LODs for most of the analytes; APCI and APPI were however observed to be more susceptible to matrix effects than ESI (Wang, Feng, & Chen, 2010). APPI has also been used for the LC-MS analysis of paraquat and diquat, which are widespread herbicides and popular suicide agents, in human serum (Yoshioka et al., 2012). When compared with ESI, APPI showed 7–10 times better sensitivity. The LC-APPI-MS method was finally applied to study authentic forensic cases.

Suni et al. tested the feasibility of DAPPI and DESI in fast forensic screening of benzodiazepins and opioids from urine samples (Suni et al., 2011). DAPPI showed better sensitivity and lower susceptibility towards the urine matrix than DESI, although sample preparation was required by both methods. DAPPI was used to analyze authentic post-mortem urine

TABLE 2. APPI in drug analysis.

Analytes/purpose of the study	Sample matrix	Ionization techniques	Polarity	Sample introduction	Dopant in APPI	Reference
			Pharmaceutical analysis			
Ciclesonide, ciclesonide-1-metabolite, fluticasone propionate	Human serum	APPI	-	LC	Acetone	(Mascher, Zech, & Mascher 2008)
β-blockers, central stimulants, diuretics, other doping substances		ESI, APPI	+/-	MEEKC	None	(Schappler et al. 2008)
Dihydropyridine calcium channel blockers	Human plasma	APPI	-	LC	Acetone (solvent)	(Pereira et al. 2008)
Basic amines, steroids, esters, phenones, a quaternary ammonium compound		ESI, APPI	+	MEKC	Toluene	(Hommerson et al. 2008)
Drug impurity profiling		ESI, APCI, APPI, TSI	+	CE	Toluene	(Hommerson et al. 2009)
Pharmaceuticals, drug discovery compounds		APPI	+	LC	Toluene, acetone, anisole, THF	(Cai, McConnell, & Bach 2009)
Budesonide (bioavailability)	Human plasma	APPI	+	LC	Toluene	(Borges et al. 2011)
Chloroquine	Dried blood spots	DAPPI	+	Desorption	Toluene	(Räsänen et al. 2014)
			Forensic and toxicological analysis			
Alprazolam, flunitrazepam, their main metabolites	Haemolyzed blood	APPI	+	LC	Acetone	(Marchi et al. 2009)
17α-methylepithiostanol, desoxymethyl-testosterone	Dietary supplements	APPI	+	LC	Toluene	(Okano et al. 2009)
Illicit drugs, their metabolites	Oral fluid	ESI, APCI , APPI	+	Isotope dilution UHPLC	None, toluene	(Wang, Feng, & Chen 2010)
Benzodiazepins, opioids	Human urine	DESI, DAPPI	+	Desorption	Acetone, toluene, anisole, toluene/anisole 99.5/0.5 (v/v)	(Suni et al. 2011)
Police confiscated drugs, pharmaceuticals, anabolic steroids	Tablet, powder, herb, oil	DAPPI	+/-	Desorption	Toluene, acetone	(Kauppila et al. 2008; Luosujärvi et al. 2009; Kauppila et al. 2011; Kauppila et al. 2013)
Paraquat, diquat	Human serum	ESI, APPI	+	LC	None	(Yoshioka et al. 2012)
Phenicol drugs		ESI, APCI, APPI	+/-	UPLC	Toluene, anisole, THF, chlorobenzene, acetone	(Alechaga, Moyano, & Galceran 2013)

samples and the results were compared to GC-MS. DAPPI could detect 15 out of the 16 analytes detected with GC-MS.

B. Steroids

Steroids are an important compound group in clinical, forensic, and environmental analysis, but because they lack easily ionizable groups, ESI ionization is challenging and often requires derivatization. APPI, however, can ionize steroids with high efficiency, as was shown early on, and analysis of steroids is still one of the most-popular APPI application fields. The clinical applications include determination of steroids and their metabolites from biological matrices, such as cell lines, plasma, serum, and tissue (Table 3). 17α-Ethinylestradiol (EE_2) was analyzed from incubation mixtures to support *in vitro* hepatic clearance studies with ESI and APPI (Li, Hsieh, & Korfmacher, 2008). Although ESI required derivatization, APPI ionized EE_2 directly, and anisole as the dopant gave a substantial increase in the analyte signal over toluene. For 27-hydroxycholesterol in plasma, APPI was more sensitive than APCI to allow quantitation from very low amounts of samples (Karuna, von Eckardstein, & Rentsch, 2009). In a study, where ESI, APCI and APPI were compared for the LC-MS analysis of estradiols in human serum and endometrial tissue, APPI in the negative-ion mode proved the most sensitive, and APPI and APCI were both less susceptible to ion suppression than ESI (Keski-Rahkonen et al., 2013).

Although most APPI applications have used LC-MS, there are some recent reports with GC-APPI-MS. Hintikka et al. coupled GC with a triple quadrupole with an API interface with μAPPI to quantitate anabolic androgenic steroids (AAS) in urine with and without derivatization (Hintikka et al., 2010; Hintikka et al., 2013). GC was preferred over LC due to its higher separation efficiency and narrower peaks. In APPI, the AAS formed $[M+H]^+$ or $[M-H]^+$ ions when analyzed without derivatization, whereas analysis of AAS-TMS derivatives with chlorobenzene dopant formed $M^{+\cdot}$ ions. Although derivatization added the complexity of the whole analysis process, the LODs for the derivatized AAS were an order of magnitude better than the LODs for the nonderivatized AAS, thanks to the high ionization efficiency and improved chromatographic performance. Also, the MS/MS fragmentation pattern of the TMS-derivatives was similar to that in EI, and could make possible the use of EI spectral libraries to identify unknown steroids.

In nature, natural and synthetic sex steroids are considered environmental contaminants due to their potential interference with the endocrine systems of aquatic organisms, and therefore sensitive analytical methods are needed to monitor them from a variety of environmental sources. Challenges to the analytical method are posed by the low abundance of these compounds in nature, as well as the complexity of the matrices. Similar to the clinical applications, many groups used APPI due to its high efficiency towards steroids. Viglino and coworkers compared ESI, APCI, and APPI for LC-MS analysis of natural and synthetic estrogenic compounds from environmental waters (Viglino et al., 2008). APPI yielded the highest sensitivity towards the hormones. Because addition of dopant did not improve the signal, measurements were performed without dopant. Dopant-assisted APPI was superior to ESI and APCI also for estrogens in terms of sensitivity and compatibility with optimum LC mobile-phase composition (Matějíček, 2011). In another study, ESI, APCI, and APPI were compared for analysis of pharmaceuticals and personal care products (PPCP), steroid hormones, and sterols in wastewater (Wang & Gardinali, 2012). APPI with toluene dopant was the most-sensitive ionization method for most analytes, and allowed detection of two otherwise difficult-to-ionize fecal-related sterols (coprostan-3-ol and coprostan-3-one). In a study by Snow et al., APPI was chosen for the LC-MS analysis of natural and synthetic steroids in environmental samples (Snow et al., 2013). Androgens and estrogens could both be detected in positive-ion APPI, while ESI demanded measurements in both positive- and negative-ion modes. APPI also reduced background interferences when compared to ESI. Groundwater, wastewater, run-off, and soil samples were analyzed with the method, and several androgens, estrogens, and other steroid-like compounds were detected that originated from animal waste. ESI, APCI, and APPI, and different LC modes have been compared for the quantitative analysis of estrogenic chemicals in water (Lien, Chen, & Wang, 2009). The chemicals were analyzed in their native form, as well as their dansyl chloride or pentafluorobenzyl bromide derivatives. Dansylated compounds with ESI and UPLC separation gave the highest sensitivity and smallest matrix effects. However, the ionization efficiency in all ionization modes was improved with dansyl chloride derivatization, and in APPI the dansylated analytes gave 300–4000 times higher signals than the native compounds. Dansyl derivatives of sex steroids have also been analyzed with LC-APPI-MS to monitor levels of endocrine disrupting steroids in fish plasma (Zhang et al., 2009b).

C. Biological Applications

The biological applications of APPI are highly diverse, and include analyses of human-, animal-, and plant-derived compounds, such as endogenic metabolites, lipids, large biomolecules, and plant metabolites (Table 4). Because steroids were already discussed as their own group of compounds (including also synthetic steroids), they are not included here.

ESI, APCI, and APPI have been compared for LC-MS analysis of global plasma endogenous metabolites of healthy volunteers (Tian et al., 2013). The measurements were performed in positive- and negative-ion modes. The three ionization techniques were complementary to each other: ESI detected efficiently glycerophosphocholines, glycerophosphoethanolamines, acyl carnitines, bile acids and sulfates; APCI-MS cyclic alcohols, fatty acids, and linoleic acids; and APPI steroids, sphingolipids, some amino acids, nucleosides, and purines. The widest range of metabolites was detected with APPI. For a global plasma-metabolomics assay, the authors recommended the combination of ESI and APPI, because it provided more-comprehensive information than any of the techniques alone. Recently, APPI was used in the metabolic screening of serum samples from Alzheimer patients (Gonzalez-Dominguez, Garcia-Barrera, & Gomez-Ariza, 2015). The APPI spectra showed an increase of diacylglycerols, ceramides, ceramide-1-phosphate, and free fatty acids to indicate membrane-destabilization processes, and reduction of fatty acid amides and several neurotransmitters related to impairments in neuronal transmission.

Earlier work by Cai and coworkers compared APPI, APCI, and ESI to detect a variety of lipids, such as free fatty acids and

TABLE 3. Analysis of steroids by APPI.

Analytes/purpose of the study	Sample matrix	Ionization techniques	Polarity	Sample introduction	Dopant in APPI	Reference
		Clinical applications				
17α-ethinylestradiol	Hepatocytes	ESI, APPI	+	LC	Toluene, anisole	(Li, Hsieh, & Korfmacher 2008)
27-hydroxycholesterol	Plasma	APPI, APCI	+	LC	None, toluene, acetone	(Karuna, von Eckardstein, & Rentsch 2009)
17-ethinylestradiol	Human plasma	APPI	+	LC	Toluene	(Borges et al. 2009)
Norethisterone	Human serum	APPI	+	LC	n.a.	(Zhang et al. 2009a)
Estrogens, androgens	Serum	APPI	+/-	LC	Toluene	(Harwood & Handelsman 2009)
Androgens	Prostate tissue, cell cultures	APPI (and ESI)	+	LC	Toluene	(Lih et al. 2010)
Anabolic steroids	Urine	μAPPI	+	CapLC	Toluene	(Ahonen et al. 2010)
Anabolic steroids	Urine	μAPPI	+	GC	Toluene	(Hintikka et al. 2010)
Selective androgenic receptor modulators	Urine	μAPPI	+	GC	Toluene	(Luosujärvi et al. 2010a)
Cholesterol oxidation products		APPI	+	LC	Toluene, acetone	(Ronsein et al. 2010)
Cholesterol, cholesterol esters	Mouse plasma and tissue	ESI, APPI	+	LC	Acetone	(Castro-Perez et al. 2011)
Testosterone, estradiol	Human cell line	APPI	+	LC	Toluene	(Zhang et al. 2011)
Anabolic steroids (trimethylsilyl derivatives)	Urine	μAPPI	+	GC	Chlorobenzene	(Hintikka et al. 2013)
Estradiol	Human serum, endometrial tissue	ESI, APCI, APPI	+/-	LC	Toluene	(Keski-Rahkonen et al. 2013)
Neurosteroids (trimethylsilyl derivatives)	Human urine	APPI	+	GC	Toluene, anisole, chlorobenzene	(Suominen et al. 2013)
		Environmental applications				
Natural and synthetic estrogenic endocrine disruptors	Environmental waters	ESI, APCI, APPI	+/-	LC	None, toluene, acetone	(Viglino et al. 2008)
Testosterone, estradiol, ethinyl estradiol, 11-ketotestosterone	Fathead minnow fish plasma	APPI	+	LC	Toluene	(Zhang et al. 2009b)
Estrogenic chemicals	Environmental waters	ESI, APCI, APPI, APCI/APPI	+/-	LC, UPLC, 2D-LC	Toluene	(Lien, Chen, & Wang 2009)
Estrogenic compounds	Wastewater	ESI, APCI, APPI	-	LC	Toluene, acetone	(Chen, Kuo, & Ding 2009)
Estrogens	Sediments	ESI, APCI, APPI	+/-	2D-LC	Toluene, acetone, anisole	(Matějíček 2011)
Endocrine disrupting compounds (e.g. estrogens)	River water	APPI	+	LC	Anisole	(Matějíček 2012)
Steroid hormones and sterols	Aqueous matrices	ESI, APCI, APPI	+/-	LC	Toluene, acetone, anisole, chlorobenzene	(Wang & Gardinali 2012)
Natural and synthetic steroids	Water and solids	ESI, APCI, APPI	+/-	LC	Toluene	(Snow et al. 2013)

TABLE 4. Biological applications of APPI.

Analytes/purpose of the study	Sample matrix	Ionization techniques	Polarity	Sample introduction	Dopant in APPI	Reference
Endogenic metabolites	Human plasma	ESI, APCI, APPI	+/-	RR-LC	Acetone	(Tian et al. 2013)
Metabolites in Alzheimer's disease	Human serum	APPI	+/-	FIA	Toluene, anisole, chlorobenzene	(Gonzalez-Dominguez, Garcia-Barrera, & Gomez-Ariza 2015)
Sphingolipids	Stratum corneum of house sparrows	APPI	+/-	LC	Toluene	(Muñoz-Garcia et al. 2008)
Juvenile hormone II	Mediterranean Corn Borer hemolymph	ESI, APCI, APPI, TSI	+	UHPLC	None	(Vilaró et al. 2012)
Lipidomics		APPI	+/-	NP-LC	None	(Gaudin et al. 2012)
Lipidomics	Leishmania donovani promastigotes	ESI, APCI, APPI	+/-	LC	Toluene, acetone	(Imbert et al. 2012)
Lipids	Fish oil,α-tocopherol capsules, butter	DAPPI, DESI	+/-	Desorption	Toluene, acetone, anisole, chlorobenzene	(Suni et al. 2012)
Fingerprinting	Iberian ham	ESI, APPI	+	Direct infusion		(González-Dominguez, García-Barrera, & Gómez-Ariza 2012)
Vitamin D forms and metabolites	Serum	APPI, APCI	+	LC	None, toluene, toluene/acetone	(Adamec et al. 2011)
Vitamin D, triacylglycerols	Dietary supplements	ESI, APCI, APPI			Acetone	(Byrdwell 2013)
Vitamins	Almond, multivitamin tablets	DAPPI-TWIMS-MS	+	Desorption	Toluene	(Räsänen et al. 2014)
Antifungal lipids produced by lactobacilli	Crude lipid extracts and their hydroxylated derivatives	APPI	+/-	NP-LC	Hexane, IPA (solvent)	(Black et al. 2013)
Oxysterols, vitamin D metabolites	Mouse brain	APPI	+	UHPLC	Toluene	(Ahonen et al. 2014)
Peptides, proteins		AP-ECD	-	Direct infusion	Acetone	(Robb et al. 2010)
Peptides		APPI	+/-	FIA	None	(Bagag, Giuliani, & Laprévote 2011)
Protein palmitoylation		SR-APPI	+	FIA	Toluene	(Bagag et al. 2012)
Hydrophobic peptides		ESI, SR-APPI	+	FIA	Toluene	(Bagag et al. 2013)
O-methylated oligosaccharides		APPI, TSI	+	FIA	n.a.	(Bagag et al. 2008)
Sterol profiles of vegetable oils	Vegetable oil	ESI, APPI	+	Direct infusion	Acetone (solvent)	(Lerma-García et al. 2008)
Monoterpene hydroperoxides		ESI, APCI, APPI	+/-	FIA	Acetone	(Nilsson et al. 2008)
Pentacyclic triterpenes	Tree extracts	ESI, APCI, APPI	+/-	LC	Toluene, acetone, anisole	(Rhourri-Frih et al. 2009)
MS imaging of phytochemicals	Sage leaves	LAAPPI	+	Laser ablation	Anisole	(Vaikkinen et al. 2014)
Carotenoids		ESI, APCI, APPI	+	UHPLC	None, toluene, acetone, anisole, chlorobenzene	(Rivera, Vilaró, & Canela 2011)
Phytoestrogenic isoflavones, lignans (biomonitoring)	Urine	APPI	-	LC	Toluene	(Parker, Rybak, & Pfeiffer 2012)
Polyisoprenoid alcohols		ESI, APPI	+/-	LC	None, toluene	(Kania et al. 2012)
Porphyrinoids		ESI, APCI, APPI	+/-	Direct infusion	None, toluene	(Świder et al. 2013)
Nivalenol and deoxynivalenol toxins	Wheat	APPI	+/-	LC	Aetone	(Tanaka et al. 2009)
Mycotoxins	Cereal	APPI	+/-	LC	Acetone	(Capriotti et al. 2010)
Patulin	Apple products	APPI	-	LC	Toluene, acetone, anisole, chlorobenzene, bromobenzene	(Zhang et al. 2014a)

their esters (Cai & Syage, 2006; Cai et al., 2007). APPI was typically more sensitive than APCI and ESI, and provided a 4–5 orders of magnitude dynamic range. ESI sensitivity could be greatly enhanced with modifiers such as ammonium formate, however addition of buffer severely limited the linear dynamic range. More recently, the use of APPI for a wide range of lipid classes, such as terpenes, triacylglycerols, sterols and oxysterols, phospholipids, ceramides, galactocerebrosides, sulfatides, and sphingomyelin in positive- and negative-ion modes was studied (Gaudin et al., 2012). APPI ionized all lipid classes in both polarities, and thus was more universal for lipid detection than ESI. Fragmentation in the intermediate vacuum stages between the source and the mass analyzer gave added value for the structural analysis of lipids, providing detailed characterization of both the polar head and the nonpolar moiety of most lipid classes. The same group also compared ESI, APCI, and APPI in the LC-MS analysis of lipids from *Leishmania donovani* promastigotes (Imbert et al., 2012). APPI gave higher response than ESI or APCI for low-polarity lipids, but the lowest signal for polar lipids, as shown in Figure 9. APPI and APCI suffered from uncontrolled fragmentation in the intermediate vacuum area, whereas ESI showed more intact molecular species of the analytes. APPI and ESI in connection with NP-LC were recommended as complementary methods to gather as much information as possible from lipids of a wide polarity range. ESI and APPI have been used to fingerprint Iberian ham (González-Dominguez, Garcia-Barrera, & Gómez-Ariza, 2012). Ham intramuscular fat extracts were analyzed with direct infusion, and lipid profiles from pigs with different feed were compared. Different profiles were recorded with ESI and APPI: ESI showed ammonium adducts of mono- di- and triacylglycerols and free fatty acids, whereas APPI showed $[M+H]^+$ and more fragments than ESI. Both techniques showed different profiles for the pigs at different diets and good potential to control the quality of ham and fraud prevention. NP-LC-APPI-MS has been used for the structural elucidation of antifungal hydroxy fatty acids produced by select strains of lactobacilli (Black et al., 2013). NP-LC was efficient to separate mono-, di-, and trihydroxy fatty acids and unhydroxylated compounds, and APPI was chosen as the ionization method due to its compatibility with the NP-LC solvents. Hexane and isopropanol with IEs below 10.6 eV were present in the mobile phase, and therefore additional dopant was not necessary.

Different lipid classes have been analyzed in a comparative study with DAPPI and DESI (Suni et al., 2012). DAPPI provided efficient desorption and ionization for neutral, less-polar and ionic lipids, but caused extensive fragmentation for larger and more-labile compounds, because of the thermal-desorption process. DESI was more suitable for the larger lipids, but its ionization efficiency for less-polar lipids was poor. Both methods were successfully applied to the direct analysis of lipids from pharmaceutical and food products.

LC-APPI-MS has been used to measure vitamin D and its metabolites from serum (Adamec et al., 2011). Sensitivities of APPI and APCI were compared, and APPI gave 4–27 times higher signals than APCI, depending on the compound and the monitored MS/MS transition. UHPLC-APPI-MS has been used for the analysis of oxysterols and vitamin D metabolites from mouse brain and cell line samples to study the role of oxidation of cholesterol in neurodegenerative diseases (Ahonen et al., 2014). The APPI ionization efficiency for the compounds was high, and laborious derivatization procedures needed in ESI were unnecessary. DAPPI has been coupled to travelling-wave ion mobility (TWIMS) MS to screen compounds from surfaces of food products and multivitamin tablets (Räsänen et al., 2014). The DAPPI spectra from the multivitamin tablet showed seven out of thirteen vitamins reported by the product manufacturer, such as nicotinamide, pyridoxine, α-tocopherol, thiamine, biotin, and cholecalcipherol. α-Tocopherol was also detected in direct analysis of an almond surface.

Although ESI is usually the method of choice to analyze large biomolecules, also APPI has some applications in this area. Although proteins and peptides tend to fragment in APPI, the fragments can be used for top-down sequencing. Intensive

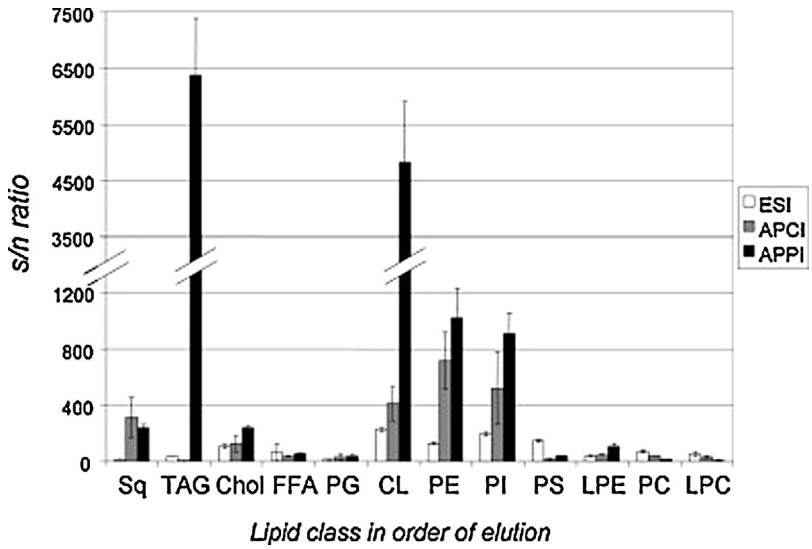

FIGURE 9. Comparison of the signal-to-noise ratios of lipid ion peaks from ESI, APCI, and APPI analyses of a *Leishmania donovani* strain resistant to Amphotericin B ($n = 3$). Reprinted with permission from Imbert et al. (2012), Copyright 2012 [Elsevier].

fragmentation of peptides in the positive- and negative-ion APPI has been reported, mainly ascribed to c-sequence ions along with less-abundant a- and b-type ions (Bagag, Giuliani, & Laprévote, 2011). Later, APPI was used to study the palmitoylation of peptides that originated from plasma-membrane proteolipids (Bagag et al., 2012). The APPI experiments were done with synchrotron radiation (SR-APPI) with a tunable UV source. Intense fragment ions that corresponded to a, b, c, and y ions with conserved palmitoyl modifications were observed in the APPI spectra, and could thus be used for structural characterization of the palmitoylated peptides, similar to results of MS/MS studies. ESI and APPI were compared to characterize peptides from highly hydrophobic membrane tetraspanin CD9 and multidrug transporter BmrA membrane proteins (Bagag et al., 2013). The most-hydrophobic peptides were hardly ionized with ESI, whereas all peptides were easily ionized with APPI. The APPI mass spectrum revealed a-, b-, c-, and y-fragment ions, which allowed unambiguous structural characterization of the transmembrane domain. The results by Bagag et al. inspired the development of a novel source for studying peptides: multiply-charged peptides were created by an electropneumatic-heated nebulizer, and photoelectrons from APPI induced in-source fragmentation (Robb et al., 2010). Readily interpretable spectra of peptide fragments were acquired from a 100 fmol sample on a chromatographic timescale.

Rhourri-Frih and co-workers compared ESI, APCI, and APPI for LC-MS analysis of pentacyclic triterpenes (Rhourri-Frih et al., 2009). APPI was the most-sensitive technique in positive-ion mode, and APCI the most-sensitive in negative-ion mode. LC-APPI-MS was used for the analysis of tree extracts that showed high amounts of betulinic acid, betulinic aldehyde, and betulinic aldehyde acetate. For LC-MS of carotenoids, APCI was a more-powerful technique than ESI and APPI (Rivera, Vilaró, & Canela, 2011). Negative-ion APPI has been used for the LC-MS analysis of phytoestrogenic isoflavones and lignans, which are secondary plant metabolites commonly encountered in the diet, from urine (Parker, Rybak, & Pfeiffer, 2012). In a comparison of ESI, APCI, and APPI in the analysis of porphyrinoids and their metal complexes, ESI was the most-sensitive technique for free-base porphyrins and corroles, and APPI for metalloporphyrins and copper complexes (Świder et al., 2013). For silver and chromium complexes APCI and ESI, respectively, were the best.

APPI has been used as the ion source for the LC-MS analysis of mycotoxins, which are fungal metabolites produced in cereals and other crops during drying or storage (Capriotti et al., 2010). Mycotoxins are highly toxic at very low concentrations, and their monitoring in food products is highly important. Good analytical performance with LOQs at limits set by EU policy was achieved with LC-APPI-MS. Higher sensitivity was reported with APPI than ESI, together with reduced matrix effects. LC-APPI-MS has also been used for the analysis of toxic patulin mycotoxin in apple juice and other apple-based products (Zhang et al., 2014a).

D. Environmental

Many environmentally relevant compounds are neutral or nonpolar, and challenging analytes for ESI. As a consequence, APPI has been widely used in environmental monitoring applications (Table 5). PAHs are nonpolar compounds, and many of them are carcinogenic or toxic. PAHs are mostly formed during incomplete combustion, and they are ubiquitous contaminants in the environment. In APPI, PAHs can be ionized with direct photoionization or charge-exchange, and they typically form intense molecular ions. A fast, 3.5 min UPLC-MS/MS method for PAHs from the EPA priority pollutant's list has been developed (Cai et al., 2009). LC-APPI-MS has been used to analyze PAHs from a variety of sample types, such as shrimp, oysters and diesel soots (Smoker, Tran, & Smith, 2010; Hutzler, Luch, & Filser, 2011; Cai, Stevens, & Syage, 2012). GC-MS and APPI with Fourier transform ion cyclotron resonance (FTICR) have been used to characterize PAHs from ambient aerosols (Jiang et al., 2014). About 27 wt% of the compounds in aromatic fractions could not be eluted from the GC column, and some of the high molecular weight PAHs were not detected with GC-MS. Instead, APPI-FTICR could detect also the large molecular species. Finally, APPI-FTICR was successfully used to characterize an aromatic sample from Beijing urban aerosols. LC-APPI-MS has also been used to analyze azaaranes – a subclass of polycyclic aromatic nitrogen heterocycles (PANHs) – from atmospheric particulates (Lintelmann et al., 2010). Unlike traditional PAHs that only contain C and H, azaaranes also contain N and can form protonated molecules in ESI. However, ESI often suffers from high matrix suppression, and therefore APPI was chosen. Significant signal improvement was achieved when compared to a similar APCI method. Besides azaaranes, PAHs and azaarones (hydroxyl-PANHs) from river sediments have been analyzed by LC-APPI (Brulik, Simek, & de Voogt, 2013). PAHs are also extensively analyzed from petroleum samples, which are discussed more in detail below.

Fullerenes are spherical, completely nonpolar compounds, which are important in nanomaterial technology. Development of analysis methods for fullerenes from complex biological or environmental matrices has become increasingly important in their risk assessment. Negative-ion APPI has been applied for the analysis of fullerenes with better performance than ESI or APCI (Li et al., 2012). Fullerenes have positive EAs and form efficiently negative molecular ions by electron capture. Because fullerenes are likely to end up terminally in the environment, they have been analyzed from environmentally relevant matrices, such as municipal influent and effluent, industrial wastewater, and surface waters (Chen & Ding, 2012; Núñez et al., 2012).

Halogenated flame retardants are commonly added to consumer products, such as furniture and textiles to reduce their flammability. They accumulate in nature, animals, and humans, and many have toxic effects. Sensitive and reliable analysis methods are needed to study the bioaccumulation and health effects of this compound class. Several reports, where APPI has been used to analyze halogenated flame retardants, have been published (Table 5). Halogenated compounds often have positive EAs, and in APPI they are typically analyzed in the negative-ion mode. A variety of ions, such as negative molecular ions, deprotonated molecules, fragments (typically loss of halogen), oxidation products (e.g., $[M - X + O]^-$), and adducts ($[M + X]^-$) can be formed to make identification of unknown compounds challenging. The ions can be similar to those formed in negative-ion APCI, as shown for dichloranes (Zhou et al., 2011). Adduct formation can sometimes be used for sensitivity enhancement, as shown by inclusion of brominated reagents

TABLE 5. APPI in environmental analysis.

Analytes/purpose of the study	Sample matrix	Ionization techniques	Polarity	Sample introduction	Dopant in APPI	Reference
Polycyclic aromatic hydrocarbons (PAHs)						
PAHs		APPI	+	UPLC	Chlorobenzene	(Cai et al. 2009)
PAHs		APPI	+	LC		(Itoh et al. 2009a)
PAHs	Schrimps	APPI	+	LC	Toluene	(Smoker, Tran, & Smith 2010)
PAHs	Diesel soots	ESI, APCI, APPI	+/-	LC	Toluene	(Hutzler, Luch, & Filser 2011)
PAHs	Oyster	APPI	+	UPLC	Chlorobenzene	(Cai, Stevens, & Syage 2012)
PAHs		APPI	+	LC	Ethanol/bromobenzene/chlorobenzene/anisole (98.975/0.1/0.9/0.025)	(Amad & Sioud 2012)
PAHs		APPI	+	UHPLC	Ethanol/chlorobenzene/bromobenzene/anisole (98.975/0.1/0.9/0.025)	(Sioud, Amad, & Al-Talla 2012)
PAHs, oxy-PAHs	Environmental and petroleum samples	ESI, APCI, APPI	+	Direct infusion	Hexane (solvent)	(Ghislain, Faure, & Michels 2012)
Parent and alkylated PAHs	Environmental waters	APPI	+	LC	Chlorobenzene	(Ramirez, Wang, & Gardinali 2014)
Benzo[a]pyrene	Cigarette filter	APPI	+	LC	Toluene	(Zhang et al. 2014b)
PAHs	Atmospheric aerosols	APPI-FTICR	+	Direct infusion	Toluene (solvent)	(Jiang et al. 2014)
Azaarenes	Atmospheric particulate matter	APPI	+	LC	Toluene	(Lintelmann et al. 2010)
Azaaranes, azaarones	River sediments	APPI	+	LC	Toluene	(Brulik, Simek, & de Voogt 2013)
Fullerenes						
Fullerene aggregates	Environmental waters	ESI, APCI, APPI	-	LC	Toluene (solvent), acetone, isooctane, heptanes, THF, benzene, pyridine,anisole	(Chen & Ding 2012)
Fullerenes		APPI	-	LC	Toluene (solvent)	(Núñez et al. 2012)
Fullerene C_{60}-derivatives, pristine fullerenes	Sediment, pond water	APPI	-	UHPLC	Toluene (solvent)	(Astefanei, Nunez, & Galceran 2014)
Halogenated flame retardants						
PBDEs	House dust	APPI	-	LC	Toluene	(Lagalante & Oswald 2008)
PBDEs	House dust	APPI	-	LC	Toluene	(Abdallah, Harrad, & Covaci 2009)
Brominated flame retardants	Environmental water, industrial effluents	APPI	-	LC	Acetone (solvent)	(Bacaloni et al. 2009)
Brominated flame retardants	Sewage sludge	ESI, APCI, APPI	-	UPLC	Toluene	(Mascolo, Locaputo, & Mininni 2010)
Tetrabromobisphenol-A derivative flame retardants	Great lakes herring gull eggs	APPI	-	LC	Acetone	(Letcher & Chu 2010)
Hexabromocyclododecane enantiomers	Sediment	ESI, APCI, APPI, anion attachment APPI	+/-	LC	Toluene, 1,4-dibromobutane/toluene	(Ross & Wong 2010)
Halogenated flame retardants	Fish	APPI	-	LC	Toluene, acetone	(Zhou et al. 2010)
Dechloranes (halogenated norbornene flame retardants)	Surface water, fish, sediments	ESI, APCI, APPI	-	LC	Acetone	(Zhou et al. 2011)
Brominated flame retardants	Seepage and sewage waste water, sewage sludge,sediments	APPI	-	LC	Acetone	(Nyholm et al. 2013)
Brominated and organophosphorus flame retardants, resorcinol bis(biphenylphosphate), bisphenol A	Plastic products, electronic waste, car interiors, consumer products	DP-APPI, ASAP		Desorption	None, toluene	(Ballesteros-Gomez et al. 2014)

Emerging contaminants						
Pharmaceuticals: bezfibrate, cyclophosphamide, enalapril, methotrexate, orlistat	Municipal wastewater	ESI, APCI, APPI	+/-	LC	Toluene	(Garcia-Ac et al. 2011)
Synthetic musks	Air	APPI	+/-	UPLC	Toluene/anisole (95.5/0.5%) bromobenzene/2,4-difluoroanisole (95.5/0.5%), chlorobenzene/2,4-difluoroanisole (95.5/0.5%)	(Lung & Liu 2011)
Endocrine disrupting compounds (e.g. bisphenol A)	River water	APPI	+	LC	Anisole	(Matějíček 2012)
PPCP	Aqueous matrices	Heated ESI, APCI, APPI	+/-	LC	Toluene, acetone, anisole, chlorobenzene	(Wang & Gardinali 2012)
PPCP, pesticides, biocides, additives, corrosion inhibitors, musk fragrances, UV light stabilizers, industrial chemicals	Lake sediments	ESI, APPI	+/-	LC	Toluene/anisole (95/5%)	(Chiaia-Hernandez, Krauss, & Hollender 2013)
Other persistent contaminants						
Fluorotelomer alcohols, perfluorinated sulfonamides	Biota samples	APPI	-	LC	Toluene	(Chu & Letcher 2008)
Achiral and chiral methylsulfonyl PCB metabolites	Animal tissue extracts	APPI	-	LC	Toluene	(Cooper et al. 2012)
PCBs	Surface water, tap water, treated wastewater	APPI	-	LC	Toluene	(Moukas, Thomaidis, & Calokerinos 2014)
Pesticides and food adulteration						
Sudan dyes	Tomato sauce, chili powder	APPI	+	NP-LC	None, toluene, acetone, anisole	(Murty et al. 2009)
Pesticides	Unpolished rice	APPI	+/-	LC	Acetone	(Itoh et al. 2009b)
Hexachlorobenzene, pentachlorophenol		APCI, APPI	-	LC	Toluene	(Osaka et al. 2009)
Chlorothalonil	Aqueous environment and food samples	APPI	-	LC	Toluene	(Yamamoto et al. 2009)
Fungicides o-phenylphenol , diphenyl, thiabendazole, imazalil and metabolites	Citrus fruits	APPI	+/-	LC	None	(Yoshioka et al. 2010)
Carbamate pesticides	Tomato	µAPPI	+	capLC	Toluene, acetone, anisole	(Kruve et al. 2011)
Neonicotinoids	River water	APPI	+	LC	Toluene	(Yamamoto et al. 2012)
Neonicotinoids	Plant leaves and flowers	DAPPI	+	Desorption	Acetone	(Vaikkinen et al. 2015)
Atmospheric compounds						
Aliphatic and aromatic amines	Atmospheric particles	ESI, APCI, APPI	+	LC	n.a.	(Ruiz-Jiménez et al. 2012)
Aldehydes	Atmospheric particles	ESI, APCI,APPI	-	LC	Anisole/toluene (1/1)	(Ruiz-Jiménez et al. 2013)
Marine compounds						
Characterization of organic matter	Lake water	ESI-, APPI-FTIR	+/-	Direct infusion	Toluene	(Hockaday et al. 2009)
Marine dissolved organic matter	Weddell surface and deep-sea water	ESI-, APPI-FTICR	-	n.a.	Toluene (in sample)	(D'Andrilli et al. 2010)
Dissolved organic nitrogen	Deep-sea marine, combusted biomass, river water	ESI-, APPI-FTICR	+/-	n.a.	Toluene	(Podgorski et al. 2012b)
Characterization of reactive and refractory dissolved organic nitrogen compounds	River water	APPI-FTICR	+/-	Direct infusion	Toluene (in sample)	(Osborne et al. 2013)

into the dopant flow for analysis of brominated compounds (Ross & Wong, 2010). LC-APPI-MS reliability in the analysis of polybrominated diphenylethers (PBDEs) from house dust was studied by comparing to well-established GC-EI/MS and GC-ECNI/MS methods; similar quantitative data were obtained with all methods (Abdallah, Harrad, & Covaci, 2009). However, although negative-ion APPI ionized all studied PBDEs, in GC-MS two different ionization methods were required. Further advantage achieved with the APPI method was that thermal degradation, which is typically observed in GC-MS for PBDEs, was not observed. A comprehensive high-throughput LC-APPI-MS method for 36 halogenated flame retardants of different compound classes has been reported and applied for fish samples (Zhou et al., 2010). Other matrices, from which halogenated flame retardants have been analyzed with APPI are, e.g., bird eggs, environmental waters, sediment, and industrial effluents (Table 5).

Emerging contaminants are compounds whose potential harmful nature has only recently been recognized. These compounds originate from human or animal medication or consumption products, and end up in the environment. This group includes pharmaceuticals and personal care products, steroids, and bisphenol A. Many of these compounds have endocrine-disrupting effects on water organisms, and their monitoring is highly important. LC-MS with ESI and APPI has been used to screen over 180 pharmaceuticals, personal care products, pesticides, biocides, additives, corrosion inhibitors, musk fragrances, UV light stabilizers, and industrial chemicals from sediments (Chiaia-Hernandez, Krauss, & Hollender, 2013). The high number of detectable compounds was made possible by the complimentary nature of the ionization methods, and the use of both polarities in ESI. Other sample types, where emerging contaminants have been analyzed with LC-MS with APPI include natural waters and air (Table 5).

Pesticides are a highly diverse group with different physical and chemical structures, and their quantitative analysis with one method is challenging. LC-MS has the advantage that it can be used also for nonvolatile compounds, unlike GC-MS. APPI, on the other hand, has been chosen in several cases due to its ability to ionize polar and nonpolar compounds, unlike ESI and APCI. Itoh and co-workers used LC-APPI-MS to quantitate highly diverse pesticides from dithiolane, organophosphorus organochlorine and pyrethroid groups in unpolished rice (Itoh et al., 2009b). Capillary-LC-μAPPI-MS, on the other hand, has been used for the quantitative analysis of carbamate pesticides (oxamyl, methomyl, aldicarb, carbofuran, pirimicarb, thiocarb, and ditalimfos) from tomato (Kruve et al., 2011). LODs below the maximum residue limits for the analyzed pesticides in fruits and pesticides were achieved.

LC-MS is an efficient method to measure the chemical composition of atmospheric aerosols, and study the influence of different factors at reactions in the atmosphere and climate. Ruiz-Jimenez et al. compared ESI, APCI, and APPI for the determination of aliphatic and aromatic amines and aldehydes in atmospheric particles (Ruiz-Jiménez et al., 2012, 2013). ESI was superior to APCI and APPI in the analysis of amines, whereas APPI gave the highest analytical performance for aldehydes. The amines and aldehydes were detected as their dansyl chloride and 2,4-dinitrophenylhydrazine derivatives, respectively.

ESI and APPI-FTICR have been used to characterize dissolved organic nitrogen (DON), such as urea, amino acids, and humic and fulvic acids, from various aquatic environments (Podgorski et al., 2012b). Negative-ion ESI and positive-ion APPI were used as complimentary techniques for a more-comprehensive characterization of the DON than negative ESI alone. As a single ionization technique, positive APPI was superior to ESI, because the APPI spectra reflected the actual DON content of the dissolved organic matter in the samples. ESI and APPI have also been used as complimentary ionization methods to characterize marine dissolved organic matter (DOM) from Antarctica (D'Andrilli et al., 2010). APPI ionized compounds with higher numbers of carbon double bonds than ESI, whereas ESI generated ions of more-oxygenated species. Moreover, many polar sulfur-containing compounds were efficiently ionized with ESI but not detected with APPI. Because of the different selectivities, both techniques were necessary for the complete description of the DOM.

E. Petroleomics

The area where highest activity has been seen in APPI-related publications in 2008–2014, is petroleomics (Table 6). Petroleomics studies, e.g., the chemical composition of crude oil for classification purposes, and the effect of different refining steps to the oil quality. Oil samples are highly complex, and can contain thousands or tens of thousands of components with highly different properties, such as completely nonpolar PAHs, polar acids and bases, or metal complexes. Rather than targeted analysis, the aim in petroleomics is often to characterize different compound classes and their proportions. The characterization is typically done based on exact masses from ultra-high resolution FTICR-MS, which can derive double-bond equivalences, and identities and numbers of heteroatoms (McKenna et al., 2010a, b, 2013a; Kekäläinen et al., 2013; McKenna, Marshall, & Rodgers, 2013; Podgorski et al., 2013). Promising results for structural elucidation of crude-oil components have also been achieved with ion-mobility spectrometry (IMS) and theoretical collision cross-section calculations (Ahmed et al., 2014). In most studies, direct infusion has been used; but in some cases, LC or GC analysis has been performed prior to MS. Another form of separation prior to the FTICR-MS analysis is fractionation of the oil to saturates, aromatics, resins, and asphaltenes (SARA) based on different solubilities and polarities of the components (Cho et al., 2012; Islam et al., 2013).

Due to oil sample complexity, the most-comprehensive characterization of petroleum compounds is achieved when several ionization techniques (and sometimes both polarities) are combined (Barrow et al., 2010; Kekäläinen et al., 2013; Chiaberge et al., 2014; Headley et al., 2014; Lababidi & Schrader, 2014; Ruddy et al., 2014). For example, NPLC-FTICR-MS was used to characterize de-asphalted crude oil with ESI, APCI, APPI, and APLI as ionization techniques (Lababidi & Schrader, 2014). ESI detected only nitrogen-containing compounds, whereas hydrocarbons and sulfur-containing compounds were not detected. APPI showed the widest selection of compound classes and unique compound assignments, including nonpolar compounds, and was especially effective to detect oxygen-containing compounds. APCI showed a high number of protonated hydrocarbons and sulfur species,

TABLE 6. APPI in petroleomics.

Analytes/purpose of the study	Sample matrix	Ionization techniques	Polarity	Sample introduction	Dopant in APPI	Reference
Vanadylporphyrins	Heavy crude oil, raw asphaltene	APPI-FTICR	+	Direct infusion	Toluene (solvent)	(McKenna et al. 2009)
Molecular speciation	Petroleum	μAPPI-FTICR	+	Direct infusion	Toluene (solvent)	(Haapala et al. 2009)
Molecular characterization	Oil sands processed water	ESI-, APPI-FTICR	+/-	Direct infusion	Toluene (solvent)	(Barrow et al. 2010)
Nickel porphyrins	Petroleum asphaltene	APPI-FTICR	+	Direct infusion	Toluene (solvent)	(Qian et al. 2010)
Compositional analysis	Athabasca bitumen heavy vacuum gas oildistillates	APPI-, ESI-FTICR	+/-	Direct infusion	Toluene (solvent)	(McKenna et al. 2010b)
Compositional analysis	Middle distillate range of heavy crude oil	APPI-FTICR	+	Direct infusion	Toluene (solvent)	(McKenna et al. 2010a)
	Maltene saturated oil, aromatic fraction in bitumen	APPI	+	Direct infusion	Toluene	(Tachon et al. 2011)
SARA-fractionation: saturates, aromatics, resins, asphaltenes	Crude oil	APPI-FTICR	+	Direct infusion	Toluene (solvent)	(Cho et al. 2012)
Classification + statistical analysis	Crude oil	APPI-FTICR	+	Direct infusion	Toluene (solvent)	(Chiaberge et al. 2013)
Compositional analysis	Oil residues	ESI-, APPI-FTICR	+/-	Direct infusion	Toluene (solvent)	(Kekäläinen et al. 2013)
Characterization of asphaltenes	Asphaltene fraction of heavy petroleum distillates	APPI-FTICR ,-TOF	+	Direct infusion	Toluene (solvent)	(McKenna et al. 2013a)
Molecular characterization of asphaltenes	Maltene and asphaltene fractions of heavy petroleum	APPI-FTICR, -IT	+	Direct infusion	Toluene (solvent)	(McKenna, Marshall, & Rodgers 2013)
Compositional analysis	Heavy petroleum distillate cut HPLC fractions	APPI-, AP/LIAD-CI-FTICR	+	Direct infusion	Toluene (solvent)	(Podgorski et al. 2013)
Oil spill characterization	Native and weathered crude oil samples					(McKenna et al. 2013b)
Characterization of SARA fractions	Weathered and artificially photo-degraded oil	APPI-FTICR	+	Direct infusion	Toluene (solvent)	(Islam et al. 2013)
Characterization	Waste-originating bio-oil	ESI, APCI, APPI-FTICR	+	Direct infusion	Toluene (solvent)	(Chiaberge et al. 2014)
Asphaltenes	Crude oil	APPI-FTICR	+/-	Direct infusion	Toluene (solvent)	(Pereira et al. 2014a)
Asphaltenes, fullerenes	Crude oil	ESI-, APCI-, APPI-, MALDI-, LDI-FTICR	+/-	Direct infusion	Toluene (solvent)	(Pereira et al. 2014b)
Oxygen-containing transformation products of petrogenic contaminants	Macondo well oil, oil sands after Deepwater Horizon oil spill	ESI, APPI	+/-	GCxGC, direct infusion	n.a.	(Ruddy et al. 2014)
Characterization	Crude oil	ESI, APCI, APPI, APLI-FTICR		NP-LC	None	(Lababidi& Schrader 2014)
Characterization	Crude oil	APPI-IMS-QTOF	+	Direct infusion	Toluene (solvent)	(Ahmed et al. 2014)
Vanadyl and nickel porphyrins	Natural petroleum seep	APPI-FTICR	+	Direct infusion	Toluene (solvent)	(McKenna et al. 2014)
Characterization	Sunlight-exposed crude oil	APPI-FTICR ESI-FTICR	+ +/-	Direct infusion	Toluene (solvent)	(Griffiths et al. 2014)
Characterization of naphthenic acid fraction components	Oil sands processed water	APPI	+/-	Direct infusion	Toluene (solvent)	(Headley et al. 2014)
Oil weathering	Oil spill samples	APPI-FTICR	-	Direct infusion	n.a.	(Lemkau et al. 2014)
Characterization	Crude oil	ESI-FTICR APPI-FTICR	+/- +	Direct infusion	Toluene (solvent)	(Oldenburg et al. 2014)
Characterization	Pyrogenic black carbon	DAPPI-FTICR	-	Desorption	Toluene	(Podgorski et al. 2012a)
Esterified oxidation products of coal species	Subbituminous coal	ESI, APPI	+	LC	Toluene, toluene/anisole (95/5%)	(Zheng et al. 2014a)
Esterified oxidation products of coal species	Bituminous coal	ESI, APPI	+	LC	Toluene, toluene/anisole (95/5%)	(Zheng et al. 2014b)

and APLI aromatic species. All the techniques showed a high number of unique compound assignments, which were not detected with other methods. Thus, the use of four different ionization techniques allowed a more-detailed characterization of the sample than with one technique only. However, in most cases sufficient information has been obtained with APPI and ESI.

Besides the studies of industrial interest, petroleomics analysis methods can prove useful in cases where oil or other harmful substances have come in contact with nature, such as in case of oil spills. In several studies, APPI-FTICR has been used to study the molecular changes in oil components due to bio- or photodegradation, for fundamental understanding of the impact of oil spills on the environment, and to devise methods for the recovery of natural environments damaged by oil spills (Qian et al., 2012; Islam et al., 2013; McKenna et al., 2013b; Griffiths et al., 2014; Lemkau et al., 2014; Ruddy et al., 2014). For example, the compounds formed by oil weathering after the Deepwater Horizon oil spill have been investigated with ESI- and APPI-FTICR (McKenna et al., 2013b; Ruddy et al., 2014). The weathered oil displayed greater than two-fold higher molecular complexity than the original Macondo well oil, especially with respect to oxygenated species (Ruddy et al., 2014). APPI provided added compositional coverage of highly oxygenated, acidic species. Combined, APPI and ESI results identified thousands of alkane, cycloalkane, and aromatic oxygenated species (positive-ion mode) and thousands of additional acidic alkane, cycloalkane, and aromatic oxygenated transformed species (negative-ion mode). An even higher number of compounds was reported by McKenna et al.: more than 30,000 acidic, basic, and nonpolar unique neutral elemental compositions were characterized to provide an archive for future chemical analyses of the environmental consequences of the oil spill (McKenna et al., 2013b). ESI- and APPI-FTICR in the positive- and negative-ion modes have also been used for the

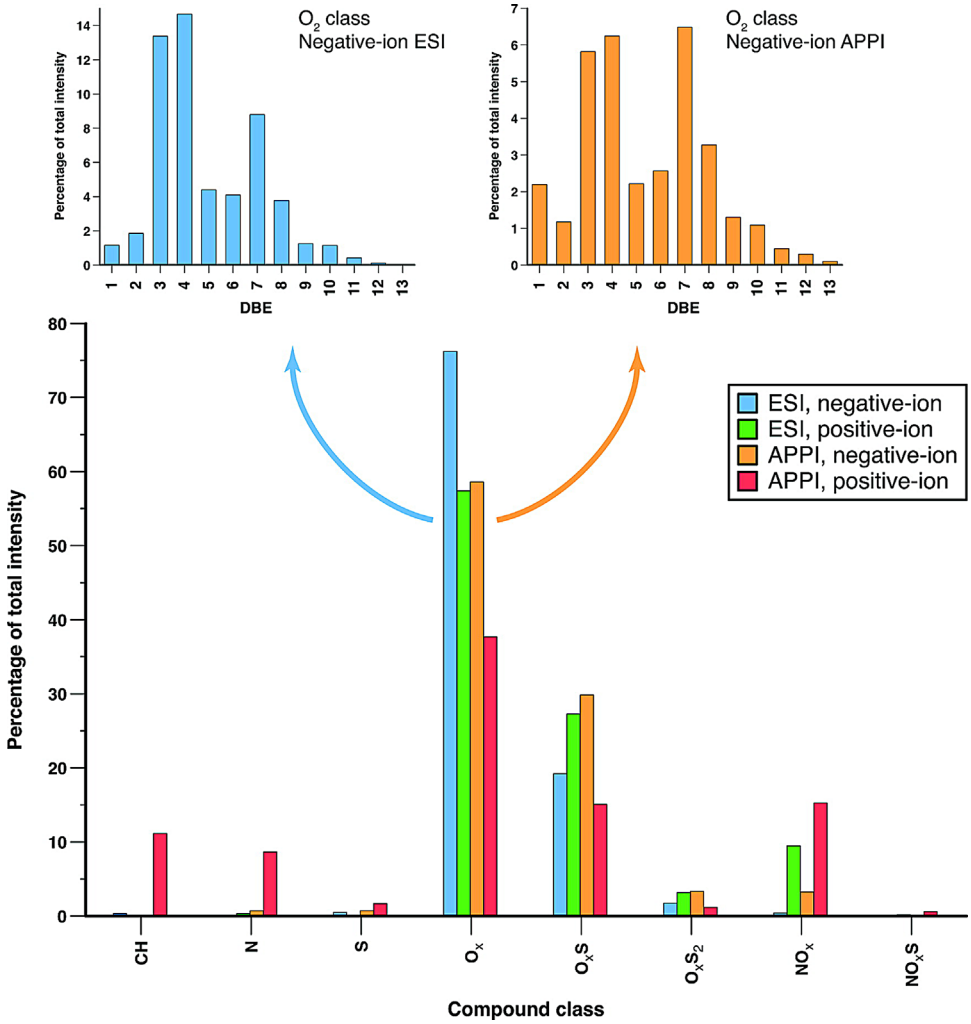

FIGURE 10. Plot of compound classes within the Athabasca oil sands process water sample, as observed with the ESI and APPI sources in both positive-ion and negative-ion modes. APPI generally provided accessibility to a greater range of compounds. As an example of a further breakdown of the data, the insets highlight the range of double bond equivalents (calculated for the neutral state) associated with the O_2 species observed within the negative-ion mode ESI and APPI data. Reprinted with permission from Barrow, Witt, Headley, and Peru (2010) Copyright 2010 [American Chemical Society].

molecular characterization of Athabasca oil sands process water to evaluate its toxicity and environmental impact (Barrow et al., 2010). Positive-ion APPI led to the observation of the greatest number of components, as shown in Figure 10. As observed with both ESI and APPI, the predominant components of the oil sands process water sample were oxygenated species, including naphthenic acids, known for their toxicity toward aquatic organisms.

F. Other Applications

Other interesting APPI applications that were difficult to classify to the groups presented above, and which therefore are not included in Tables 2–6, include analysis of explosives and samples from polymer industry, the analysis of indigo-type compounds in natural dyes for studies of historical objects, and characterization of the organic residue in meteorite extracts (Duderstadt & Fischer, 2008; Papanastasiou et al., 2008, 2012; Himmelsbach, Buchberger, & Reingruber, 2009; Song & Bartmess, 2009; Reingruber et al., 2010; Callahan et al., 2013; Reisinger, Beissmann, & Buchberger, 2013).

VI. CONCLUSIONS

APPI is a vibrant field of study and constitutes a valuable tool in the LC-MS analysis toolbox. Its applications extend to a wide range of compound classes. The last few years have seen particular emphasis in petroleomics, and steroid and pesticide analysis. For these areas, APPI is frequently chosen as the ionization method over ESI or APCI because of its better suitability to non-polar analytes. Other reasons to choose APPI include its wider linear dynamic range, and better tolerance of matrix components, which in ESI cause signal suppression. The latter benefit is very important, because it allows simpler matrix-cleaning methods, reduces labor costs, and improves the recovery of compounds from matrices that can be compromised by more-aggressive cleaning procedures. When a variety of compound groups has been compared in profiling or characterization purposes, APPI has repeatedly been the technique that can ionize the largest number of compounds from different groups. Of course, not even APPI is universal, and complementary use of APPI and ESI, and sometimes both polarities, leads to the most comprehensive and reliable results.

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ABBREVIATIONS

AAS	anabolic androgenic steroid
APCI	atmospheric pressure chemical ionization
API	atmospheric pressure ionization
AP/LIAD-CI	atmospheric pressure laser-induced acoustic desorption chemical ionization
APLI	atmospheric pressure laser ionization
APPI	atmospheric pressure photoionization
ASAP	atmospheric solids analysis probe
CE	capillary electrophoresis
CE-MS	capillary electrophoresis-mass spectrometry
cAPPI	capillary atmospheric pressure photoionization
capLC	capillary liquid chromatography
CPI	capillary photoionization
CI	chemical ionization
DAPPI	desorption atmospheric pressure photoionization
DESI	desorption electrospray ionization
DART	direct analysis in real time
DP-APPI	direct probe atmospheric pressure photoionization
DOM	dissolved organic matter
DON	dissolved organic nitrogen
EI	electron ionization
EA	electron affinity
ECD	electron capture dissociation
ECNI	electron capture negative ionization
ESI	electrospray ionization
EPA	environmental protection agency
EU	European Union
FIA	flow injection analysis
FTICR	fourier transform ion cyclotron resonance
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
IMS	ion mobility spectrometry
IE	ionization energy
LAAPPI	laser ablation atmospheric pressure photoionization
LDI	laser desorption ionization
LC	liquid chromatography
LC-MS	liquid chromatography-mass spectrometry
LOD	limit of detection
LOQ	limit of quantification
MS	mass spectrometry, mass spectrometer
MALDI	matrix-assisted laser desorption ionization
μAPPI	microchip atmospheric pressure photoionization
MEKC	micellar electrokinetic chromatography
MEEKC	microemulsion electrokinetic chromatography
$M^{+\cdot}$	molecular ion
$M^{-\cdot}$	negative molecular ion
NP-LC	normal phase liquid chromatography
PPCP	pharmaceuticals and personal care products
PBDE	polybrominated diphenylether
PCB	polychlorinated biphenyl
PAH	polycyclic aromatic hydrocarbon
PANH	polycyclic aromatic nitrogen heterocycle
PA	proton affinity
$[M+H]^+$	protonated molecule
RP-LC	reversed phase liquid chromatography
RR-LC	rapid resolution liquid chromatography
SARA	saturates, aromatics, resins and asphaltenes
SR	synchrotron radiation
S/N	signal-to-noise ratio
MS/MS	tandem mass spectrometry
THF	tetrahydrofuran
TSI	thermospray ionization
TOF	time-of-flight
TWIMS	travelling wave ion mobility spectrometry
TMS	trimethylsilyl
2D-LC	two-dimensional liquid chromatography
UHPLC	ultra-high performance liquid chromatography

UPLC	ultra performance liquid chromatography
UV	ultraviolet
VUV	vacuum ultraviolet
EE_2	17α-ethinylestradiol

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