Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Chromatography A, 1050 (2004) 45–62
JOURNAL OF CHROMATOGRAPHY A
www.elsevier.com/locate/chroma

Review

State-of-the art of selective detection and identification of I-, Br-, Cl-, and F-containing compounds in gas chromatography and liquid chromatography

Cato Brede [a], Stig Pedersen-Bjergaard [b,*]

[a] *Department of Chemistry, University of Oslo, P.O. Box 1033, Blindern, Oslo 0315, Norway*
[b] *School of Pharmacy, University of Oslo, P.O. Box 1068, Blindern, Oslo 0316, Norway*

Available online 25 June 2004

Abstract

This review article presents an overview of halogen-specific detection in gas chromatography (GC) and liquid chromatography (LC). Attention is primarily focused on the use of plasma emission spectroscopy and plasma mass spectrometry as detectors, but other halogen-selective detection principles are also mentioned. Different instrumental configurations are discussed both with respect to technical set-up and performance, the principal reasons for halogen-selective detection are highlighted, and recent applications are reviewed from areas such as environmental chemistry, petroleum characterization, and drug analysis.

Keywords: Reviews; Detection, GC; Plasma emission spectroscopy; Plasma mass spectrometry; Halogen-selective detection; Element-selective detection

Contents

1. Introduction 46
2. Detection by plasma emission spectroscopy 46
2.1. Principle 46
2.2. Gas chromatography and atomic emission detection 46
2.2.1. Instrumental configurations and performance of GC–AED 46
2.2.2. Advantages and limitations of GC–AED 47
2.2.3. Applications of F-, Cl-, Br-, and I-selective GC–AED 49
2.3. Liquid chromatography and plasma emission spectrometry (LC–AES) 50
3. Detection by plasma mass spectrometry 50
3.1. Principle 50
3.1.1. Instrumentation 50
3.1.2. Positive ion detection 52
3.1.3. Negative ion detection 53
3.2. Gas chromatography and plasma mass spectrometry 53
3.2.1. ICP-MS 53
3.2.2. Low pressure ICP-MS 55
3.2.3. MIP-MS 56
3.2.4. Microwave plasma torch (MPT) 56
3.2.5. Microplasma (MP) 56
3.2.6. Glow discharge plasma 57

* Corresponding author. Tel.: +47-2285-6576; fax: +47-2285-4402.
E-mail address: stig.pedersen-bjergaard@farmasi.uio.no (S. Pedersen-Bjergaard).

0021-9673/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.chroma.2004.04.082

3.3. Liquid chromatography and plasma mass spectrometry 58
4. Others techniques for halogen-selective detection 59
5. Conclusions 60
References 60

1. Introduction

Halogenated compounds play an important role in many areas of analytical chemistry, and they are frequently separated by gas chromatography (GC) or liquid chromatography (LC). In many cases, halogenated compounds are detected in complex samples, and in spite of the resolving power of both GC and LC, some type of selective detection is required in order to obtain chromatographic peaks free of interferences from underlying components. Mass spectrometric (MS) detection is very popular and provides excellent selectivity based on molecular masses. Thus, halogenated compounds may be detected selectively as long as their molecular masses are known in a complicated matrix of other components. In some cases however, a halogen-selective detector may be an advantage, responding selectively to compounds containing the halogens, and differentiating between F, Cl, Br, and I.

In this review article, we present an overview of halogen-specific detection in gas chromatography and liquid chromatography. Attention is primarily focused on the use of plasma emission spectroscopy and plasma mass spectrometry as GC and LC detectors, since we consider these techniques as the most important F-, Cl-, Br-, and I-selective detectors. However, some other halogen-selective detection principles are also included to clarify that there are also other solutions to halogen-selective detection. Different instrumental configurations will be discussed both with respect to technical set-up and performance, the principal reasons for halogen-selective detection will be highlighted, and recent applications are reviewed from areas like environmental chemistry, petroleum characterization, and drug analysis.

2. Detection by plasma emission spectroscopy

2.1. Principle

When gas or liquid chromatography is coupled with atomic emission spectroscopy (AES), high separation power and simultaneous multielemental detectability are combined into an attractive (hyphenated) analytical technique. Different compounds are separated in the chromatographic system, and subsequently introduced into a helium (or argon) plasma placed in continuation of the chromatographic column. This is illustrated in Fig. 1 for gas chromatography, and this coupling is normally termed gas chromatography–atomic emission detection (GC–AED). The high temperature of the plasma (3000–10000 K) results in atomization of each of the separated compounds followed by excitation of the constituent atoms to higher electronic states. Light of wavelengths characteristic of the elements introduced is emitted by the excited atoms as they undergo transitions to lower energy levels. With an optical spectrometer, emission light for the elements of interest (F, Cl, Br, I) is selected and measured continuously resulting in element-selective chromatograms. Since atomic lines are narrow and often intense, chromatography coupled with AES provides high elemental selectivity and acceptable sensitivity. Theoretically, every element from the periodic table (except helium or argon) may be detected by a simple change of the wavelength, and since all emission lines are present in the plasma simultaneously, either single- or multichannel detection is possible. Below, attention will be focused on detection of F, Cl, Br, and I.

2.2. Gas chromatography and atomic emission detection

2.2.1. Instrumental configurations and performance of GC–AED

In GC–AED, the capillary column is normally extended from the GC oven through a heated transfer line and directly into the plasma. The heated transfer line serves to avoid analyte condensation prior to detection. In modern instrumentation, the plasmas are sustained in helium, and the carrier gas used in the GC is also helium. The GC effluent is highly compatible with the plasma because the flow rate of carrier gas normally is low, the carrier gas is the same gas as used as plasma gas, and because the analytes are introduced in their gaseous state into the plasma. Actually, introduction through a GC system is the perfect way of introducing an analyte to a plasma.

The attractive features of GC–AED were reported for the first time in 1965 by McCormick et al. [1] with an

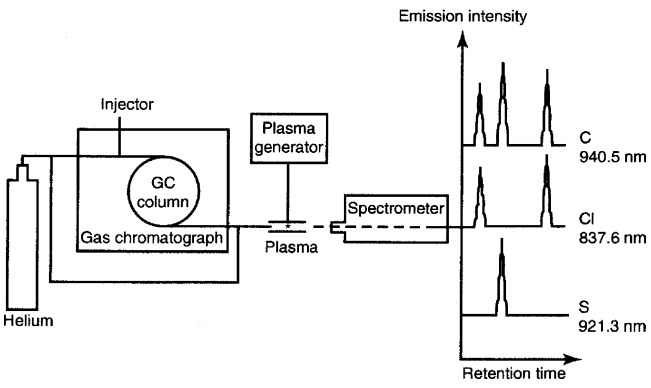

Fig. 1. Schematic principle of GC–AED.

atmospheric pressure argon microwave-induced plasma (MIP) coupled to packed column GC. From this first report and until 1989, a significant number of research papers emerged with different approaches to GC–AED. Different plasma sources were tested in home-built systems, including a 25 kHz helium after-glow device [2], a 350 kHz radio frequency helium plasma [3,4], a 60 Hz alternating current helium plasma [5], a 27.18 MHz capacitively coupled helium plasma [6], and a 27.12 MHz stabilized capacitively coupled helium plasma [7]. In general, the systems utilized helium as the plasma gas, because helium has a higher excitation potential than argon. Thus, while argon provides poor excitation conditions for several important non-metallic elements like the halogens, helium plasmas cover F, Cl, Br, and I. Most of the systems utilized small plasma sources with low gas consumption (typically 10–100 ml min^{-1}), which is an important issue in gas chromatographic detection where systems are operated continuously for long periods of time. In addition to the above mentioned helium plasmas, both direct current plasmas (DCPs) [8] and inductively coupled plasmas [9] sustained in argon have been evaluated for gas chromatographic detection. However, both plasma systems suffered from poor excitation characteristics and from a large consumption of high-purity argon. Thus, in spite of the commercial availability and the widespread use of ICP atomic emission spectroscopy, this plasma source is very little in use for element-selective detection in GC.

In 1989, the first commercial GC–AED system was introduced by Hewlett-Packard. This utilized an atmospheric pressure helium MIP for analyte excitation and a photodiode array for the monitoring of atomic emission [10,11]. The photodiode array, which covered the wavelength range 160–800 nm in 25 nm portions, provided simultaneous multielement detection, multipoint spectral background correction, and elemental confirmation by atomic spectra. From the same company (which later changed its name to Agilent), an improved version was introduced in 1996 as a less expensive second generation instrument with enhanced sensitivity. This instrument is now manufactured by Joint Analytical Systems in Germany.

In addition to Hewlett-Packard, a few small companies tried to commercialize alternative GC–AED systems, but to the best of our knowledge, their systems are not on the market any longer. Because of this, and because there seems to be very little interest in connecting traditional atomic emission spectrometers like the ICP to GC, the remaining discussion on GC–AED will mainly be focused on results obtained with the instruments from Hewlett-Packard/Agilent/Joint Analytical Systems.

2.2.2. Advantages and limitations of GC–AED

As atomic emission lines are very narrow, overlap from different elements is normally not a problem in GC–AED. However, emission spectra from helium plasmas also contain molecular bands originating from incomplete atomization or from atomic recombinations. These are generally relatively broad, and may interfere with the atomic lines causing false signals (interferences) or negative baseline excursions. Therefore, in order to realize the full potential of the narrow atomic emission lines and to ensure high elemental selectivity, spectral background correction is of great importance in GC–AED [12]. With the commercial GC–AED, this is accomplished utilizing a photodiode array for the optical measurements, where continuous multipoint data correction results in very high selectivity. This is illustrated in Table 1, where the selectivity for F, Cl, Br, and I has been determined relative to carbon. For practical work, the high elemental selectivity obtained for the halogens by GC–AED is obviously a major advantage. Compounds containing F, Cl, Br, or I may be selectively detected even in very complicated samples where the resolving power of the GC is insufficient. This is illustrated in Fig. 2, where GC–AED was utilized for the detection of polychlorinated biphenyls (PCBs) in a highly contaminated marine sediment [13]. In spite of the high background from a complicated crude oil matrix, the PCBs emerged as distinct peaks in the highly selective Cl-chromatogram. Thus, with help from the Cl-chromatogram, the PCBs were easily located and quantified. The highly contaminated sediment sample was also exposed to analysis by GC–MS, but this technique suffered from serious interferences when operated both in the low- and high-resolution modes (Fig. 2). Thus, for reliable quantification by GC–MS, the sample required more complex sample preparation to remove interfering components.

In addition to selectivity considerations, detection limits of GC–AED are of great importance. As illustrated in Table 1 for the commercial system, detection limits of GC–AED are generally at the low picogram per second level. Values for the different elements vary substantially depending on several factors like atomic line intensity, excitation potential, and spectral background. For F, Cl, and Br, the values are relatively high. This may limit the applicability of the technique in some cases or may call for extensive analyte preconcentration in order to match low analyte concentrations to the sensitivity of the instrumentation. As discussed in more details below, detection limits of GC–AED may be

Table 1
Selectivities and detection limits for the second generation of the commercial GC–AED from Hewlett-Packard/Agilent/Joint Analytical Systems [163]

Element	Wavelength (nm)	Selectivity[a]	Detection limit[b] (pg s^{-1})
C	193	–	0.6
F	690	166,000	10.7
Cl	479	13,000	14.3
Br	478	14,000	18.3
I	206	10,200	2.1

[a] Selectivities were defined as the ratio of the response per nanogram of element to the response per nanogram of carbon.

[b] Detection limits were defined as the amount of element required to produce a peak twice the noise level, divided by the full-width at half-height of the peak in seconds.

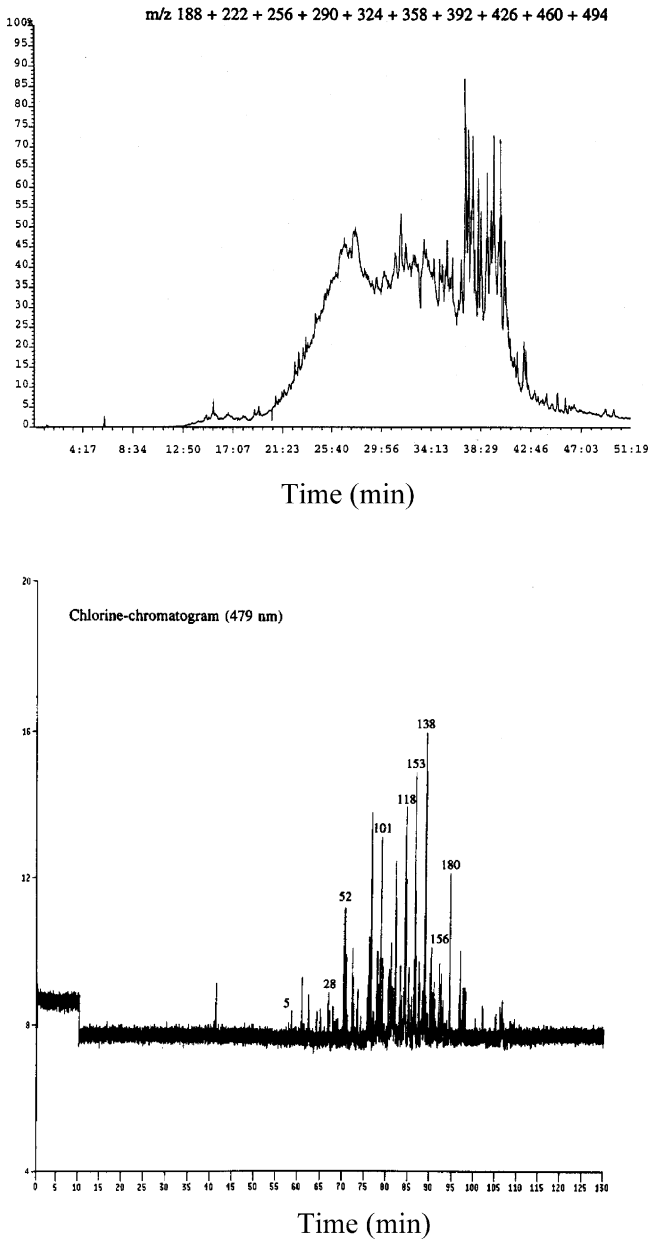

Fig. 2. GC analysis of an extract of a highly contaminated marine sediment. Upper chromatogram: GC–MS summarized molecular ions of PCBs. Lower chromatogram: GC–AED in Cl-selective mode. Identified PCB congeners numbered in the lower chromatogram. Reprinted with permission [13].

substantially higher than for GC with electron capture detection (ECD) and for GC–MS.

During detection, the compounds separated by GC are atomized within the plasma and emission is measured from excited atoms. Therefore, in theory, the detector response per element (area counts per nanogram of element) should be independent of the molecular structure from which it originated. For quantitative purposes, this should enable universal calibration (or compound independent calibration) where a large number of different compounds are quantified based on a single elemental calibration curve (for F, Cl, Br, or I) obtained for a randomly selected reference compound. A relatively large number of research papers have discussed compound independent calibration, and some of them have pointed out practical limitations to this approach due to discrimination during GC injection and due to chemical reactions/spectral interferences occurring in the plasma. One example on this is illustrated in Table 2, where variations observed in the response factor for Cl are shown for some PCBs [13]. Nevertheless, for applications where reference substances are not available or in cases where very high accuracy is not required, analysis by GC–AED and universal calibration (or compound independent calibration) may be a very fast, simple, and interesting concept to obtain quantitative data [14–17].

With GC–AED operated in the multielement selective mode, where several different elements are monitored simultaneously, the resulting element-selective chromatograms directly give qualitative information about the constituent elements for each of the separated compounds. With peak no. 5 in Fig. 3 as an example, where halogenated alkylbenzenes were detected in nickel refinery waste water, the element-selective chromatograms proved that both C, H, and Cl were present in the compound, while Br was not a constituent of this particular compound. In addition to this, since elemental responses are almost independent of molecular structures (as discussed above), the element-selective chromatograms also contains quantitative information about the elemental composition of the separated compounds. Thus, based on simple calibration and multielemental detection, empirical or molecular formulas may be calculated based on GC–AED. Also, this approach has been investigated in a large number of research papers, and the different authors have concluded somewhat differently concerning the practical utility. Nevertheless, an example is illustrated in Table 3, where the molecular formula was calculated for several halogenated alkylbenzenes present in nickel refinery waste water (Fig. 3) based on dichlorobenzene as reference [18]. Although deviations up to 30% from correct values were observed in some cases, the approximate empirical formulas were utilized to support rapid analyte identification. For target compound analysis, where analyte identification principally is based on retention time data obtained with standard solutions of the components of interest, empirical formulas calculated by GC–AED may significantly improve

Table 2
GC–AED responses in Cl-selective mode for selected PCBs

PCB no.	GC–AED response (normalized)
87	1.09
101	1.11
104	1.18
105	1.03
114	1.00
118	1.09
126	1.08

All values normalized against PCB no. 114 [13].

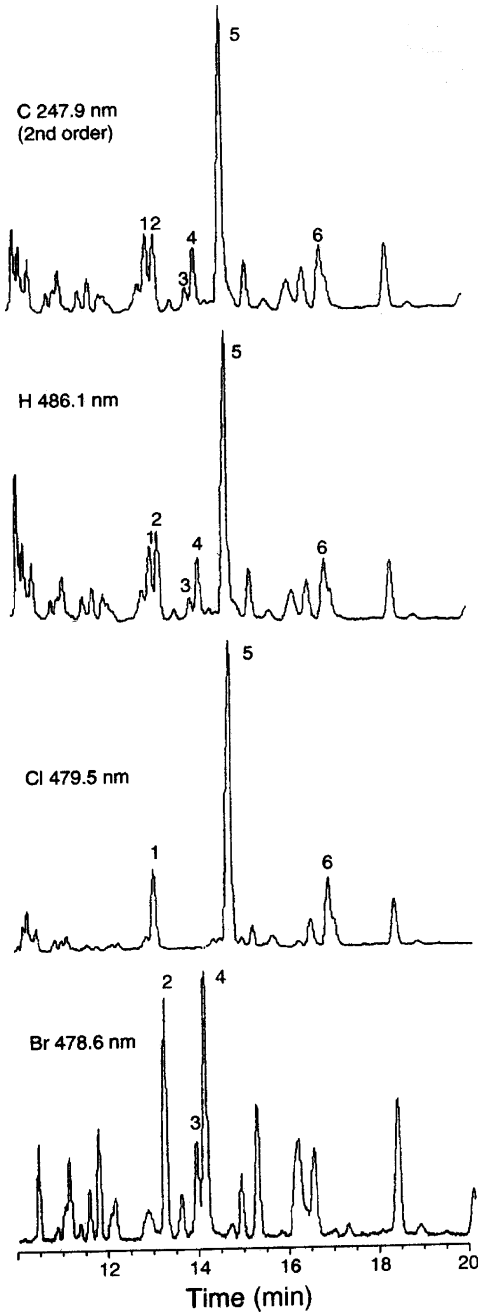

Fig. 3. GC–AED analysis of an extract of nickel refinery waste water in the C-, H-, Cl-, and Br-selective modes. Peak identification: 1 = $C_9H_9Cl_3$, 2 = $C_9H_{10}Br_2$, 3 = $C_9H_{10}Br_2$, 4 = $C_9H_{10}Br_2$, 5 = $C_9H_9Cl_3$ and 6 = $C_9H_9Cl_3$. Reprinted with permission [18].

the reliability of analyte identifications. For nontarget purposes however, where retention time information normally is not available, identification based solely on GC–AED is not possible, and GC–MS is required [19,20]. Although nontarget identification is based principally on GC–MS, GC–AED results may be of great interest to complement mass spectral data [19–24]. This is illustrated in Fig. 4, for an unknown peak found in influent water of a sewage treatment plant [24]. In this case, the GC effluent was split providing parallel AED and MS detection. Peak no. 5, which

Table 3
Molecular formulas determined by GC–AED for six halogenated alkylbenzenes present in nickel refinery waste water [18].

Peak no.	Correct formula	Formula determined by GC–AED
1	$C_9H_9Cl_3$	$C_{8.8}H_{8.3}Cl_3$
2	$C_9H_{10}Br_2$	$C_{11.3}H_{13.2}Br_2$
3	$C_9H_{10}Br_2$	$C_{8.1}H_{7.9}Br_2$
4	$C_9H_{10}Br_2$	$C_{7.3}H_{7.2}Br_2$
5	$C_9H_9Cl_3$	$C_{9.0}H_{8.6}Cl_3$
6	$C_9H_9Cl_3$	$C_{8.2}H_{7.9}Cl_3$

was an unknown nontarget compound, was totally obscured in the full scan chromatogram from GC–MS, and without the GC–AED system, this peak most probably would have been ignored. However, the GC–AED system proved the presence of a chlorinated compound, and the GC–AED results also demonstrated that the compound contained P. With this knowledge in mind, extensive background correction was performed on the GC–MS results, and a search in the MS library suggested this compound to be the flame retardant tris(2-chloroethyl) phosphate. Although the MS hit (match) quality was rather low, the additional data on the elemental composition (Cl and P) from GC–AED helped to confirm the correctness of the identification.

Based on the discussion above, the strong sides of GC–AED are related to the excellent elemental selectivity and to the possibilities of simplifying calibration. The former advantage may be utilized: (1) to easily discover and locate nontarget compounds containing I, Br, Cl and F (and other heteroatoms), and (2) for determinations of halogen-containing compounds in very complex and dirty samples. The calibration advantage of GC–AED may be utilized in cases: (1) where reference substances are not available (nontarget applications) or (2) to simplify the calibration procedure.

2.2.3. Applications of F-, Cl-, Br-, and I-selective GC–AED

Most of the applications of F-, Cl-, Br-, and I-selective detection in GC–AED have been focused on environmental

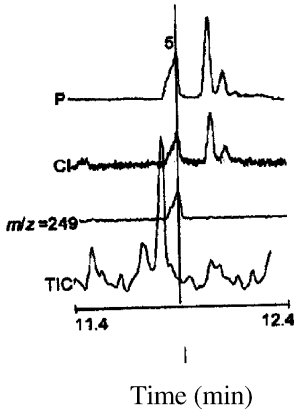

Fig. 4. Enlargement of GC–MS (TIC and $m/z = 249$) and GC–AED (Cl- and P-selective) chromatograms of influent water of a sewage plant. Reprinted with permission [24].

analysis, and this will also be the main focus of this section reviewing some recent publications. In addition, some interest has also been reported in the fields of petroleum, drug, and chemical warfare agent analysis.

Within the area of environmental analysis, most GC–AED attention has been focused on pesticides. This broad class of compounds, which are produced industrially as agricultural chemicals, are particular good candidates for GC–AED analysis since they are rich in heteroatoms like F, Cl, and Br. Thus, pesticides have been detected in different vegetables [25–31], soil [32–34], and in water [33,35–40] utilizing halogen-selective detection by GC–AED. An example is illustrated in Fig. 5, where several pesticides were detected in soil at the low ng/g level. Excellent selectivity has been reported in the Cl-selective mode for different pesticides present in agricultural products, while the established ECD and electrolytic conductivity detectors (ELCDs) suffered from matrix-related interferences [27,28]. Based on this, a GC–AED screening method has been approved by the US Environmental Protection Agency (EPA Method 8085), where a broad range of pesticides are identified based on empirical formulas, and where they are quantified by compound independent calibration. Unfortunately, the pesticide detection limit in the Cl-selective mode is substantially higher than for GC–ECD [41]. Thus, extensive analyte preconcentration was required to detect organochlorine pesticides by GC–AED at the 0.01 ppm level in agricultural matrices [28].

In addition to pesticides, some efforts have been reported on the GC–AED investigations of polychlorinated biphenyls [42–45], chlorophenols [46,47], chlorobenzenes [48], volatile organic compounds in drinking water with both Br- and Cl-detection [49], and brominated flame retardants [50]. The strong potential of GC–AED to get a quick overview of the occurrence of chlorinated compounds was demonstrated for the analysis of rain and snow [51,52], where chlorinated acetic acids, alkyl phosphates, and benzenes were among the most abundant components. In addition, in several papers, different high molecular weight matter from the environment was characterized with respect to chlorine-containing structural elements using pyrolysis or oxidative degradation and GC–AED in the Cl-selective mode [53–56].

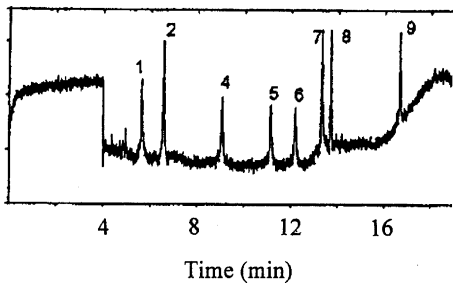

Fig. 5. GC–AED analysis (Cl-selective) of soil fortified with a standard mixture of pesticides. Peak identification: 1 = chlorpropham (55 ng/g), 2 = lindane (15 ng/g), 4 = chlorpyriphos (30 ng/g), 5 = α-endosulfan (15 ng/g), 6 = *p,p′*-DDE (20 ng/g), 7 = *p,p′*-DDD (20 ng/g), 8 = *p,p′*-DDT (20 ng/g) and 9 = permethrin (45 ng/g). Reprinted with permission [34].

GC–AED has also been used extensively within the field of petroleum analysis, but most attention has been focused on S-selective detection. One interesting application in this field utilizing Br-selective detection was reported, where alkenes in complex hydrocarbon mixtures were selectively and quantitatively brominated, and where the formed dibromoalkanes were analyzed by GC–AED in the Br-selective mode [57]. A few recent papers have also been published within the field of drug analysis [58,59], where F- and Cl-selective GC–AED were utilized in combination with GC-FTIR, GC–MS, and NMR-spectroscopy to identify impurities in drug substances. Also, GC–AED in the Br-selective mode has recently been used for the analysis of flame retardants in thermoplastics [60], in the Cl-selective mode for analysis of triclosan in human dental plaque [61], and in the Cl- and F-selective modes for the identification of chemical warfare-related material [62].

2.3. Liquid chromatography and plasma emission spectrometry (LC–AES)

Although ICP may be easily connected to liquid chromatography, this system provides insufficient excitation conditions for the atomic emission spectroscopic detection of the halogens. On the other hand, microwave-induced plasmas sustained in helium are more interesting for halogen-selective detection in LC, because helium plasmas provide a higher excitation potential. Unfortunately, the coupling of LC and MIP is seriously complicated by the LC effluent, which quenches the plasma and may produce substantial amounts of carbon deposits degrading the performance of the whole system. In the literature, there have been only a limited number of reports on the successful combination of LC and MIP for halogen-selective detection [63–66]. Early research focused on the use of a moving band interface to evaporate the LC effluent prior to detection [63,64], but detection limits for Cl were generally a factor 10 higher than typical values reported in GC. Thus, the systems gained very little popularity. Recently, research papers on the use of LC–MIP with a membrane desolvator have emerged [65,66], but also in this case detection limits were substantially higher than reported for GC. Thus, it was concluded that more investigations have to be done in this field in order to build systems with the sensitivity required for trace halogen-selective detection.

3. Detection by plasma mass spectrometry

3.1. Principle

3.1.1. Instrumentation

Plasma mass spectrometry (MS) has traditionally been utilized mainly for inorganic analysis. However, plasma-MS

also provides an exciting and powerful approach to element-selective detection in gas and liquid chromatography [67–70]. Compared with the AED, plasma-MS instruments have usually been associated with lower detection limits, although this is not necessarily the case for F-, Cl-, Br-, and I-selective detection. In plasma-MS, the plasma is the ion source, typically a helium or an argon discharge, in which atomic ions are produced. The atomic ions are separated and detected by a mass analyser and an ion detector respectively. In this way, MS detection is applied for element-selective detection on basis of the atomic or even the isotopic constituents of the chromatographically separated substances. Most work with plasma-MS has been performed with external plasma ion sources and with a pressure-reducing interface to separate the atmospheric or low-pressure plasma from the high vacuum area of the MS. The interface consists of a sampler orifice, onto which the plasma is directed. This results in a plasma jet downstream of the orifice, which then expands into a chamber where the pressure is reduced by pumping. By placing a skimming orifice near the so-called Mach disk of the plasma spray, a high ion sampling efficiency can be obtained [71] due to feasible gas dynamics of the interface [72,73]. However, the main duty of the sampler/skimmer interface is simply to allow the use of external plasma ion sources with a wide span of gas flow rates, and still maintain a high vacuum within the MS.

Today, several manufacturers are offering instrumentation for inductively coupled plasma mass spectrometry (ICP-MS). The mass analysers that have been implemented in commercial ICP-MS instrumentation include quadrupole, time-of-flight and double focusing magnetic sector field. Because of availability and maturity, ICP-MS is the most obvious choice for plasma-MS detection in chromatography. Nevertheless, many papers have reported instrumental and operational modifications to the ICP ion source, and there has also been a steady development of alternative plasma ion sources for mass spectrometry, including the microwave-induced plasma. An excellent treatment of ICP and MIP plasma sources for mass spectrometry has been published [74].

Coupling of liquid chromatography with ICP-MS is straightforward, because traditional ICP-MS instrumentation is operated with a nebulization device for introducing a liquid flow as an aerosol into the plasma [75]. The flow rate from a conventional bore LC column (4.6 mm i.d.) is similar to the flow rate of ICP-MS operation for analysis of liquid samples (1 ml min^{-1}). One concern may arise from the use of high content of organic solvent in the LC mobile phase, e.g. in reversed-phase LC applications. The organic solvent can lead to carbon deposit on the sampler cone of the ICP or may even extinguish the plasma [76]. Some manufacturers are offering accessory devices for introducing oxygen to the plasma in order to prevent carbon deposit when analysing organic liquid samples. Otherwise, a certain content of water in the effluent will usually provide enough oxygen for obtaining the same effect. Another solution to this problem is to use small bore LC columns.

Severe memory effects may be encountered for the halogens when liquid sample introduction systems based on nebuliser and spray chamber are used in ICP-MS [77]. Such memory effects have been associated with the volatility of the halogen species and with the introduction of samples in acidic solution [78–80]. Acid promotes the formation of volatile hydrogen halides, which may be delayed in the spray chamber and thereby cause memory effects. It has been described how memory effects can be minimised for the four halogens in a microconcentric nebuliser equipped with a spray chamber, by avoiding the use of acidic solution, and most efficiently by using a 5% ammonium hydroxide solution [81]. There are also papers describing the utilisation of alternative nebulisers, e.g. the direct injection nebuliser (DIN), which is suited for low flow introduction to the ICP. Unlike conventional nebulisers that are operated with a spray chamber, the DIN did not exhibit unwanted memory effects for elements such as Hg and I [82]. In fact, the rinse-out time for I was reduced from 10 min to 15 s by using the DIN, and the detection limit found for I with 20 μl flow injection to the DIN coupled with ICP-MS was 0.06 μg l^{-1} (1 pg absolute). It was a 10 times improvement in detectability as compared to using a pneumatic nebulizer with the same instrument.

The gas effluent from a gas chromatography column can be introduced directly to the plasma, without the need for any nebulization and spray chamber device. The most straightforward GC–plasma-MS set-up implies the utilisation of commercially available instrumentation, i.e. the argon ICP-MS. In GC, attention must be paid to substances of low volatility, which may condense and be lost at cool spots in the line between the GC and the plasma ion source. The transfer line must therefore be temperature-controlled and heated to a suitable temperature in order to avoid condensation. The GC effluent is usually mixed with an additional gas flow, in order to puncture the plasma, which is required for successful detection of the analytes [83]. Introduction of oxygen may also be necessary in order to avoid carbon deposition from the analytes on the sampler cone. A complete GC–ICP-MS instrument can now be purchased, e.g. as offered by Agilent Technologies (Fig. 6).

Atmospheric pressure ICP-MS consumes large amounts of plasma gas (approximately 15 l min^{-1} of argon), and is therefore considered to be a rather expensive detector for chromatography, especially with run times as long as 15–60 min. This is a valid reason for speeding up the chromatography by coupling fast GC or fast LC with ICP-MS. Today, several techniques are available for fast GC–ICP-MS, including the use of small-bore capillary GC columns (100 μm i.d. or less) or multicapillary columns. Especially fast GC may impose some requirements on the instrumentation, concerning the scanning speed of the mass analyser [84]. In comparison with other mass analysers, the time-of-flight analyser is regarded as superior for fast scanning.

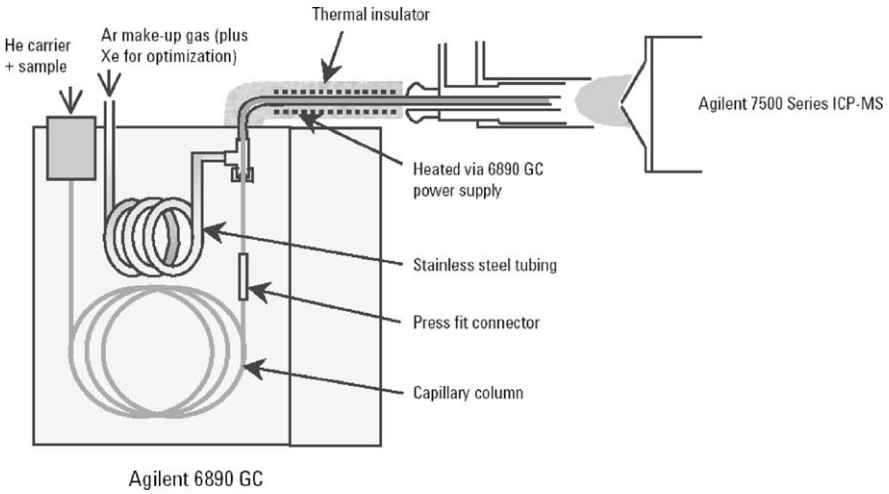

Fig. 6. Schematic of commercially available GC–ICP-MS instrument. Reprinted with permission.

3.1.2. Positive ion detection

Positive ion detection is the common operation modus of plasma mass spectrometry. Argon, which is generally used as plasma gas in ICP-MS, has relatively low 1st ionization energy (15.8 eV) when compared to the high ionization energies (10.5–17.4 eV) required for ionization of the halogen elements (Table 4). While Br and I have acceptable high degrees of ionization in argon plasma, the situation is more severe for Cl and F. Especially, F has a remarkably low degree of ionization, only 9×10^{-4}%, which makes F-selective detection with argon ICP-MS considerably less sensitive compared to detection of other halogens. In comparison, many metals have ionization energies below 7 eV, giving them near 100% ionization efficiency in argon plasma. The low degree of ionization for F is said to be the main reason why the sensitivity of F is about 2 million times lower than that of fully ionized Na [81].

Helium can be used as plasma gas instead of argon. The advantage of using He as plasma gas for F-, Cl-, Br-, and I-selective detection by plasma-MS is that He has substantially higher 1st ionization energy (24.6 eV) than argon, and will therefore provide a higher degree of ionization of the

Table 4
Ionization potentials, degree of ionization, isotope masses, and possible interference relevant for halogen detection by plasma mass spectrometry

Element	1st ionization energy (eV) [164]	Degree of ionization (%) in argon plasma at an ionization temperature of 7500 K [75]	Isotope masses and natural abundance	Interference in argon plasma in the positive ion detection mode [81]	Interference in helium plasma in the positive ion detection mode [93]
F	17.423	9×10^{-4}	18.9984 (100%)	$^{38}Ar^{2+}$ $^{1}H^{18}O^{+}$ $^{1}H_{3}{}^{16}O^{+}$ $^{1}H_{2}{}^{17}O^{+}$ $^{16}O^{1}H_{3}{}^{+}$	$^{16}O^{1}H_{3}{}^{+}$
Cl	12.968	0.9	34.9689 (75.77%) 36.9659 (24.23%)	$^{18}O^{16}O^{1}H^{+}$ $^{36}Ar^{1}H^{+}$	
Br	11.814	5	78.9183 (50.69 %) 80.9163 (49.31 %)	$^{40}Ar^{38}Ar^{1}H^{+}$ $^{40}Ar^{40}Ar^{1}H^{+}$	
I	10.451	29	126.9045 (100%)		
He	24.587		3.01603 (0.0001 %) 4.0026 (99.9998 %)		
Ar	15.759	0.04	35.9676 (0.34 %) 37.9627 (0.07 %) 39.9624 (99.59 %)		
O	13.618	0.1	15.9949 (99.76 %) 16.9991 (0.04 %) 17.9992 (0.20 %)		
H	13.598	0.1	1.0078 (99.985 %) 2.0141 (0.015 %)		

halogens. Hence, the main reason for using He as plasma gas is the prospect of reaching low detection limits for the halogens. This fact was clearly confirmed by the first successful coupling of an atmospheric pressure He ICP to a commercial ICP-MS system [85]. Mixtures of He and Ar as plasma gas in ICP-MS resulted in an improvement of 2 orders of magnitude in the detection limits for non-metals in comparison with Ar ICP-MS [86]. Highest signal-to-noise ratios for the halides were obtained with a 30% He plasma.

Ignition of a He ICP is said to be easier at reduced pressure, and special ICP ion sources have been designed for this purpose [87–89]. Halogen detection by analysis of aqueous samples introduced to a low-pressure (LP) He ICP-MS system resulted in detection limits of 23, 2.4, 0.13, and 0.05 ng ml^{-1} for F^+, Cl^+, Br^+, and I^+, respectively [90]. These numbers represented a significant improvement when compared to performance of Ar ICP-MS both at atmospheric and reduced pressure.

The utilization of a helium microwave-induced plasma as an ion source enabled a sensitive detection of the halogens [91,92]. Detection limits for Br^+, Cl^+, and I^+ were found to be at or below the picogram level. It must be emphasised that He is considerably more expensive than Ar, and the quest for reduced-flow plasma sources is therefore of some importance for the propagation of He plasma-MS in general.

Another advantage of using helium as plasma gas compared to argon is less interference. Interference in argon plasma may occur due to simple species produced by the plasma gas and other elements present, e.g. H and O derived from introduction of water. F^+, Cl^+ and Br^+ may all suffer due to interference from different argon species, while I^+ has sufficiently high mass to avoid interference from any background species (Table 4). Br^+ has no H/O interference, while chlorine has an insignificant H/O interference due to $^{18}O^{16}O^1H^+$. On the other hand, F^+ encounters interference due to $^1H_2{}^{16}O^1H^+$. The only relevant interference for halogen-selective detection with He plasma-MS seems to be interference by $^{16}O^1H_3{}^+$, appearing at the only isotope mass that is available for F-selective detection [93,94].

Using a mass analyzer capable of high mass resolution can circumvent problems of interference in argon plasma-MS. Determination of halogens in organic compounds was performed by using Ar ICP-MS equipped with a double focusing magnetic sector field mass analyser [81]. Liquid samples were introduced to the ICP by nebulization, and detection limits for ^{19}F, ^{35}Cl, ^{37}Cl, ^{79}Br, ^{81}Br, and ^{127}I were 8530, 3.25, 4.18, 0.08, 0.10, and 0.05 ng ml^{-1}, respectively, when recording at high-resolution ($m/\Delta m = 10^4$).

3.1.3. Negative ion detection

Due to the limited ionization energy of argon ICP, halogen-selective detection is less sensitive than the detection of more easily ionized elements, in the positive mode. However, the halogens are known to have strong electron affinities, leading to an abundance of negatively charged halogen ions in the plasma. Detection in the negative ion mode is therefore an interesting solution to achieve increased sensitivity for halogen-containing compounds.

The first report of negative ion detection in plasma-MS was by Douglas and French [95], with an argon MIP-MS set-up. Introduction of a 10 mg l^{-1} solution of NaBr in water enabled the recording of the isotopic pattern for Br in the negative ion mass spectrum. A high sensitivity was found, and the authors expressed their optimism on future work with detection of halogens by plasma-MS in the negative ion mode.

Detection of negative ions by argon ICP-MS has been reported [96]. It was found that the only elemental species that could be detected with reasonable sensitivity as negative ions were the halogens. The negative ion background mass spectrum comprised of considerably fewer interfering ions than in the positive mode. Solutions containing halides as well as associated cations and the anionic species of the analytes were introduced by nebulization. The instrument was operated in the negative ion detection mode with just a few operational adjustments, including reversal of potentials in the MS. Detection limits for $^{19}F^-$, $^{35}Cl^-$, $^{79}Br^-$, and $^{127}I^-$ were 400, 80, 10, and 70 ng ml^{-1}, respectively. Somewhat higher detection limits for F and Cl were due to background signals, probably originating from low levels of the elements in the blank solutions. With corrections, detection limits for F and Cl were estimated to 30 and 20 ng ml^{-1}, respectively. Linear calibration curves were obtained over at least 4 orders of magnitude. Isotope ratio measurements for Cl and Br showed excellent matches with the literature. There were no matrix effects on the signal, either by associated cations or when introducing the halogens in different anionic species.

The possibility of coupling microwave-induced plasma with an ion trap mass analyser has been shown [97]. Configuring the lens assembly to transmit negative ions was readily accomplished. CCl_4 vapour was swept into the microwave-induced plasma in a flow of He, resulting in the observation of the distinctive isotopic pattern of Cl at 35 and 37 amu.

Despite the favourable characteristics of halogen detection in the negative mode, only a few papers, if any, have reported its utilisation for real sample analysis. The authors of this paper have yet to find a reasonable explanation for such a noticeable lack of work on detection of halogens by negative ion plasma-MS. Positive ion detection has been used in most of the work reviewed below, except where clearly stated otherwise.

3.2. Gas chromatography and plasma mass spectrometry

3.2.1. ICP-MS

The state-of-the-art GC–ICP-MS has recently been reviewed [98], and it was concluded that the technique has reached maturity for speciation of organometallic compounds in a variety of sample matrices. On the other hand, there are relatively few papers describing the application of

GC–ICP-MS for selective detection and characterisation of F-, Cl-, Br-, and I-containing compounds.

An early report by Chong and Houk [99] discusses the application of GC–ICP-MS for elemental and isotope ratio determination. Element-selective detection was obtained for H, C, N, O, S, Cl, Br, I, P, B, and Si. Furthermore, C-detection was suggested as a convenient universal detection of organic compounds. Detection limits varied greatly, from the high ng s^{-1} to the low pg s^{-1} level, and these variations were explained by differences in the ionization energies of the non-metals.

Coupling of GC with ICP-MS was achieved by a specially designed interface that allowed easy switching, with no instrumental reconfiguration, between liquid sample introduction and gas chromatography [100]. Dichloromethane, 1,1,1-trichloroethane and trichloroethylene were separated by gas chromatography and detected by $^{35}Cl^{+}$ monitoring, with detection limits of 2.6, 2.2 and 2.6 ng, respectively.

Volatile metal(loid) species, including I-species, like hydrides, methylated hydrides and other alkylated compounds were determined by GC–ICP-MS equipped with a joint unit which allowed calibration by introduction of aqueous solution of the elements [101]. Low temperature GC (LTGC) was coupled with the ICP-MS set-up and was found to provide highly sensitive detection of volatile species in soil and soil gas samples [102]. Another paper describes the detection of volatile species of As, Sb, Sr and I in gases over hot springs in British Columbia, by utilizing LTGC–ICP-MS [103]. Furthermore, by coupling hydride generation (HG) with LTGC–ICP-MS, the technique was applied for analysis of soil samples from municipal waste deposits in Germany [104]. In the I-selective chromatogram, iodomethane is shown in addition to other unidentified I-species (Fig. 7).

Brominated flame retardants are persistent substances appearing in the environment, mainly due to their use for fire protection of plastics, with subsequent release by direct emission or product disposal. GC–ICP-MS was recently shown as a viable method for their determination in environmental samples [105]. Advantages mentioned in comparison with electron capture detection and molecular MS were high detection sensitivity for Br and excellent selectivity in presence of other compounds containing sulphur or oxygen. The method was demonstrated by analysis of standard mixtures of polybrominated diphenyl ethers (PBDPEs) and sewage sludge samples obtained from three local wastewater treatment plants (Fig. 8). Increased sensitivity was obtained by adding He to the Ar-plasma, resulting in instrumental detection limits in the low $\mu g\,l^{-1}$ range.

Biogenic halogenated volatile organic compounds (HVOCs) may be transferred from the surface of the earth to the atmosphere, and their concentration levels in different environmental samples are monitored in order to explore their sources. Recently, GC coupled with combined detection by ECD and ICP-MS in series was found to provide excellent halogen-selective detectability for HVOC in aquatic and air samples [106]. Stir bar sorption extraction (SBSE) technique was used for sampling, followed by thermodesorption for sample introduction to the two-dimensional GC–ECD/ICP-MS system. An advantage of using ECD was lower detection limits for brominated

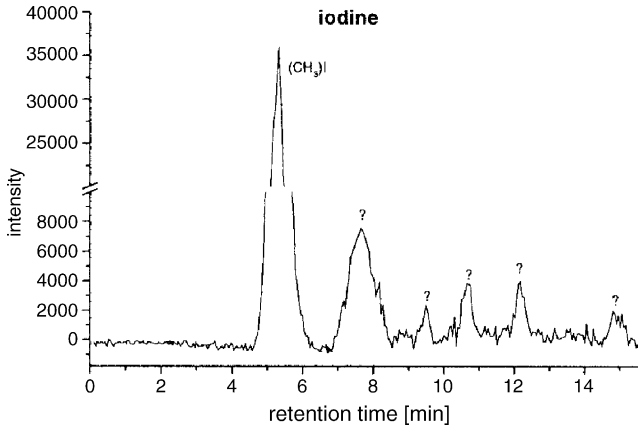

Fig. 7. ^{127}I-selective chromatogram of species found in soil samples from municipal waste by analysis with HG-LTGC–ICP-MS. Reprinted with permission [104].

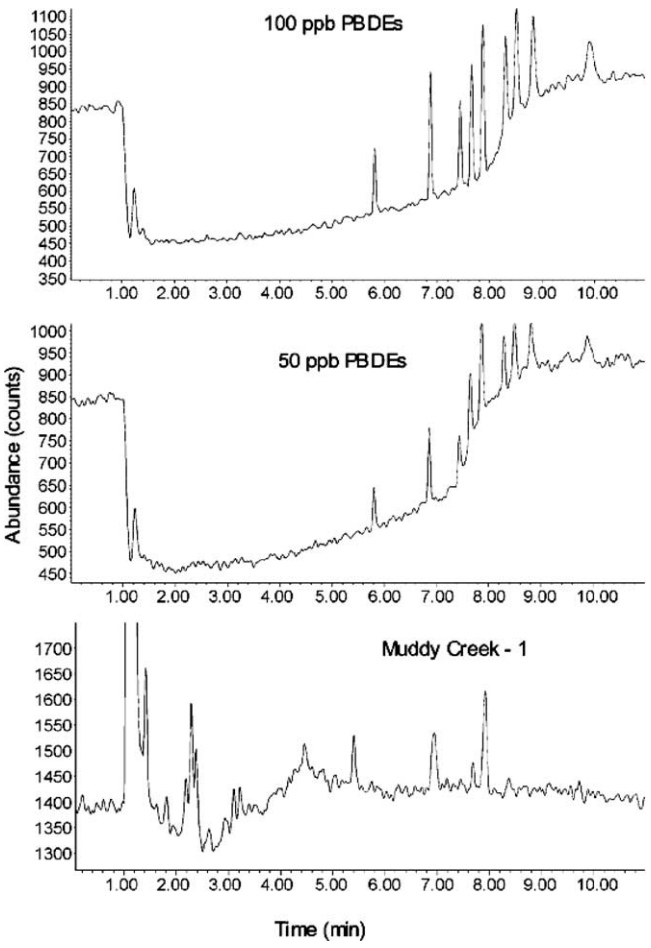

Fig. 8. Chromatogram obtained from the analysis of a sample taken from the Muddy Creek treatment plant and accompanying low level polybrominated diphenyl ether standards. Reprinted with permission [105].

and especially for chlorinated compounds, while iodinated compounds mainly exhibited lower detection limits by ICP-MS. An advantage of using ICP-MS was the achievement of element-selectivity. In addition to giving information on elemental composition of the species, ICP-MS was helpful in overcoming problems of co-elution not resolved by ECD detection. Compound dependent calibration is encountered with ECD, while ICP-MS provides an almost compound independent response for the halogens. A further comparison of the GC–ECD/ICP-MS system with EI-MS and MIP-AED detection revealed improved detectability by ICP-MS compared with MIP-AED for brominated and iodinated compounds, by a factor of 6 and 80, respectively. Although EI-MS in the selected ion monitoring (SIM) mode generally provides excellent detection limits, the detectability of iodinated compounds was found to be superior by ICP-MS. Chromatograms obtained by analysis of a seawater sample with the GC–ECD/ICP-MS set-up are presented in Fig. 9, which clearly demonstrate the advantage by using I- and Br-selective detection, e.g. to resolve peaks 2 and 3.

The high sensitivity for I-detection by GC–ICP-MS was recently taken advantage of for the determination of iodinated phenol species at parts-per-trillion levels in water samples [107]. Solid-phase microextraction (SPME) was used for sample concentration and introduction to the GC. Introduction of 9% oxygen to the Ar-plasma gas flow was required to reach detection limits at the low ng l^{-1} level for all the compounds. Interesting results were obtained by analysis of tap, river and bottled water. Several iodinated compounds were revealed, including 2-iodophenol, 4-iodophenol and 2,4,6-triiodophenol. Three unidentified I-compounds, likely to be disinfection by-products, were found in tap water. Several unidentified I-compounds appeared in the river water, and had probably been generated from naturally occurring organic matter. These results clearly demonstrate the power of GC–ICP-MS for environmental screening.

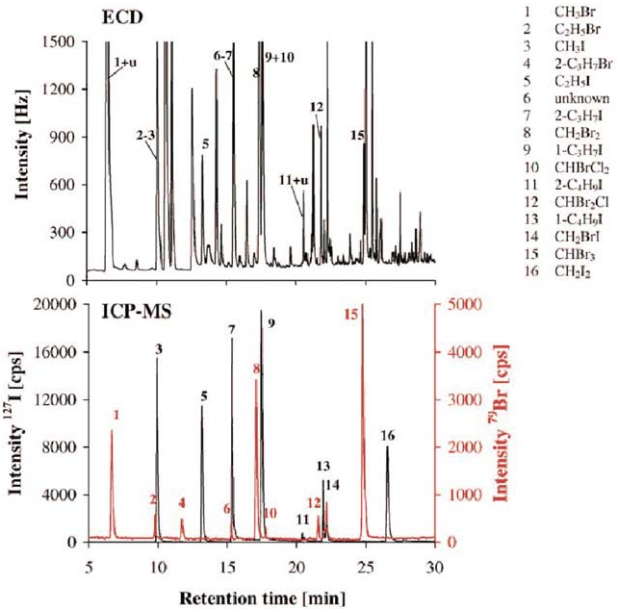

Fig. 9. Simultaneous ECD and ICP-MS chromatograms of a seawater sample for the determination of brominated and iodinated volatile organic compounds (result of the first extraction step by the Twister® SBSE). Reprinted with permission [106].

3.2.2. Low pressure ICP-MS

A low-pressure ICP-MS setup was introduced for coupling with GC. The argon plasma was sustained in a water-cooled low-pressure torch, and was combined with an interface for mass spectrometric sampling [108]. It has been suggested that a high kinetic energy electron collision ionization mechanism may be important in the halogen ionization at reduced pressure, because the signal intensity increases with decreased plasma pressure [109]. Other contributing factors may be a more efficient ion sampling and a reduced electron-ion recombination rate. The LP-ICP-MS set-up was capable of sustaining a helium plasma at a plasma gas flow of 0.5 l min^{-1} and 100 W forward power [87], which enabled a sensitive element-selective detection of halogenated compounds, including pesticides. Detection limits of 25 and 15 pg were reported for chlorobenzene and hexachlorobenzene, respectively.

Further development of the LP-ICP-MS set-up (Fig. 10) presented the possibility of obtaining both atomic and molecular ions [110], by using a combination of helium and argon as plasma gases, and by adjusting the plasma gas flow and forward power. Hence, LP-ICP-MS was shown to have tunable capabilities, i.e. to be used either for elemental or molecular MS. By decreasing the power and plasma gas flow, it was possible to sustain a He plasma using only the carrier gas from the GC (3 ml min^{-1}), and mass spectra were obtained for chlorobenzene, bromobenzene, and iodobenzene that were similar to those obtained using an electron impact (EI) ionization source. Ten ng of chlorobenzene injected on-column was required to observe the molecular ion. In the element-selective mode, when feeding 1 l min^{-1} of Ar to the plasma in addition to the 3.5 ml min^{-1} of He carrier gas, the detection limits for chlorobenzene, bromobenzene, and iodobenzene were 500, 50, and 25 pg, respectively.

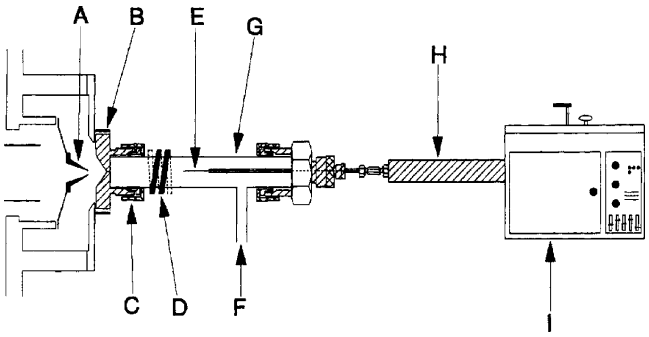

Fig. 10. GC-LP-ICP-MS instrumentation. A, skimmer; B, low-pressure sampler; C, vacuum fitting; D, ICP load coil; E, tip of GC column; F, plasma gas; G, quartz torch; H, heated transfer line; I, gas chromatograph. Reprinted with permission [110].

A specially designed instrument was assembled in order to further investigate the LP–ICP as a tunable ion source [88]. Unfortunately, previous work with LP-ICP-MS revealed a non-linear relationship between analyte concentration and molecular ion signal when operating in the molecular MS mode. The effect of adding reagent gases was therefore studied, in order to address some of these problems [111].

A modified LP-ICP-MS setup was described [89], which was based on an alternative radio frequency (rf) plasma generator. The He plasma could be sustained at low power (12–15 W) with a reduced pressure (1.0–1.4 mbar) and a plasma gas flow of 625–790 ml min^{-1} [112]. Limits of detection for bromobenzene, 1-bromoheptane, and benzyl bromide were 11, 6 and 4 pg, respectively. In addition to element-selective detection, the system provided mass spectra with characteristic fragmentation patterns and molecular ions for the analytes.

3.2.3. MIP-MS

Compared with ICP, it is interesting to note that microwave-induced plasma in some cases has been generated with a 10-fold decrease in plasma gas flow rate, e.g. 0.4 l min^{-1} of argon [95], which can make MIP attractive as an MS ion source for chromatography, in order to save operational costs.

Argon plasmas are associated with more interference due to background species and have lower ionization energy than helium plasmas. Therefore, several alternative plasma ion sources, such as the MIP, have been explored, in order to sustain helium plasmas. In some early studies, MIP-MS enabled halogen detection of organic compounds introduced in the gas phase [91,92]. When coupling GC to helium MIP-MS, detection limits for chlorinated compounds ranged from 9.2 to 21 pg, while the detection limits for brominated and iodinated compounds ranged from 0.92 to 1.05 pg [113]. In this time, another paper also reported the speciation of halogenated compounds, with detection limits in the pg level for Br and I [114]. However, some background interference at *m*/*z* 35 precluded the sensitive detection of Cl, which led to the development of a reduced pressure interface for MIP-MS operation. With the low-pressure MIP-MS set-up, a reduction of the background signals was observed, probably due to hindered air entrainment. This later enabled the successful application of GC–LP-MIP-MS for detection of elements like Cl, Br, I, P, and S. After optimization with respect to microwave power and the first-stage pressure of the mass spectrometer, detection limits for I, Br, and Cl were 0.1, 3.5, and 24 pg respectively [115]. The linear range for detection of iodobenzene was three orders of magnitude, starting at 1 pg. A GC–LP-ICP-MS setup, using a water-cooled plasma torch, was used for analysis of a mixture of seven components [116]. Simultaneous element-selective detection was obtained for Cl (*m*/*z* 35 and *m*/*z* 37), P (*m*/*z* 31), S (*m*/*z* 32), Br (*m*/*z* 79 and *m*/*z* 81), and I (*m*/*z* 127), with detection limits below the ng level for all elements.

Only few reported real sample applications of GC–MIP-MS can be found, with respect to F-, Cl-, Br-, and I-selective detection. One paper found the technique to be a useful multielement analytical tool for organic geochemistry [117]. More recently, three low-pressure plasma ion sources were coupled to GC and mass spectrometry and were evaluated for the analysis of volatile organic compounds in food, including some chlorinated compounds [118]. The sources were low-pressure helium MIP, and low-pressure helium and argon ICP. A flow of 0.7 l min^{-1} of He was found to be the optimal plasma gas flow in the LP-MIP-MS set-up, because an increased flow gave lower $^{35}Cl^{+}$ signal and a decreased flow produced an unstable plasma that extinguished when the solvent eluted from the GC column. The power was set to 60 W. Detection limits for Cl-selective detection (*m*/*z* 35) of some chlorinated compounds were in the range 0.031–0.301 ng on-column. Detectability of carbon was poor, due to a high background signal. A total of 6 ml min^{-1} of He (including 3 ml min^{-1} of GC carrier gas) was found to be optimal for Cl-selective detection by He LP-ICP-MS, which also exhibited poor C-detectability. The power was set to 6 W. Detection limits for Cl-selective detection (*m*/*z* 35) of some chlorinated compounds were in the range 0.072–4 ng on-column. Optimal conditions for the Ar LP-ICP-MS were 0.45 l min^{-1} of Ar plasma gas and 100 W of forward power. Detection limits for Cl-selective detection (*m*/*z* 35) of some chlorinated compounds were in the range 0.0001–0.206 ng on-column. Detectability of carbon was somewhat improved with the Ar LP-ICP-MS set-up, enabling detection limits for C-selective detection at or slightly below the ng level. Hence, best overall performance was found for the Ar LP-ICP-MS set-up, which was subsequently applied for analysis of spiked olive oil samples by headspace GC-LP-ICP-MS.

3.2.4. Microwave plasma torch (MPT)

A microwave plasma torch was modified [119] and utilized as an ion source for time-of-flight mass spectrometry (TOF-MS) [120]. Cl, Br, and I were detected at the 74–254 fg level. Additionally, the rapid scanning of the TOF-MS was found advantageous for detection of fast eluting compounds and to avoid mass-dependent errors that might be encountered with quadrupole MS instrumentation. Thus, empirical formulas could be estimated with a high correlation coefficient (0.999).

3.2.5. Microplasma (MP)

A microplasma ion source based on a capacitively coupled radio frequency He plasma sustained in a volume of a few μl has been reported [121]. The plasma was sustained inside the last 3.5 cm of the GC capillary column, at a forward power of 2 W and by using 25 ml min^{-1} of He as plasma gas. One special feature of the microplasma ion source was the location inside the MS high vacuum, enabling direct transfer of atomic ions without the need for a sampler and a skimmer interface. Further work, by implementing a narrowing at the microplasma ion source orifice, enabled the

plasma to be sustained at a low plasma gas flow rate, using only the GC carrier gas (2.25 ml min^{-1} of He) [122]. Hence, the microplasma ion source was made compatible with ordinary bench-top GC–MS instrumentation. Simultaneous detection of F, Cl, Br, and I was achieved in the positive ion detection mode [94] and in the negative ion detection mode [123]. A comparison of GC–MP-MS (positive ion detection) and GC–AED of a real sample extract from a nickel refinery shows a similarity in the halogen-selective detection (Fig. 11). Detection limits for the halogens were at the pg s^{-1} level.

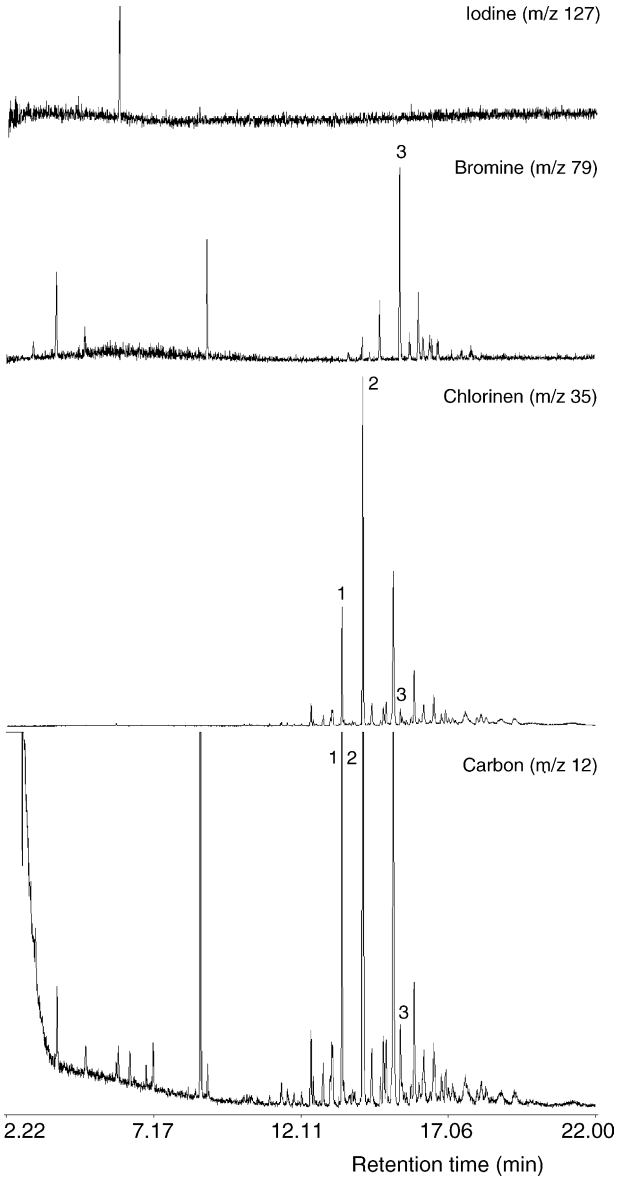

Fig. 11. I-, Br-, Cl- and C-selective chromatograms obtained by GC–microplasma-MS (positive ion detection) of a Soxhlet extract of a deposited sludge from a nickel refinery. This was exactly the same sample as analysed by GC–AED, shown in Fig. 3 Peak identification: 1 = $C_9H_9Cl_3$, 2 = $C_9H_9Cl_3$ and 3 = $C_9H_{10}BrCl_2$. Reprinted with permission [94].

3.2.6. Glow discharge plasma

A direct current gas sampling glow discharge (GSGD) ionization source for time-of-flight mass spectrometry has been developed [124]. With He as plasma gas for atomic MS, detection limits for the halogens were in the 20–90 pg s^{-1} range. The GSGD ion source consumed less than 1 l min^{-1} of plasma gas, and was hence seen as a cost-efficient alternative to sources such as ICP and MIP. By using Ar as plasma gas, it was also possible to obtain molecular fragmentation mass spectra. Further development of GSGD-MS showed that it is possible to switch between atomic and molecular MS mode by changing the polarity of voltage applied to the sample introduction plate [125]. Switching rates up to 100 Hz were investigated. The simultaneously recorded mass spectra of bromoform in both atomic and molecular MS mode are shown in Fig. 12. The atomic detection limits for Cl and Br were in the 3–110 pg s^{-1} range, and the molecular MS detection limits in the 15–250 pg s^{-1} range. Introduction of several chlorinated hydrocarbons allowed the differentiation of the compounds based on their $^{35}Cl/^{12}C$ elemental ratios. GC coupled with GSGD-MS operated in the dynamic mode (switched) has opened the world of halogen-selective detection and EI-like MS detection using only one MS detection device [126].

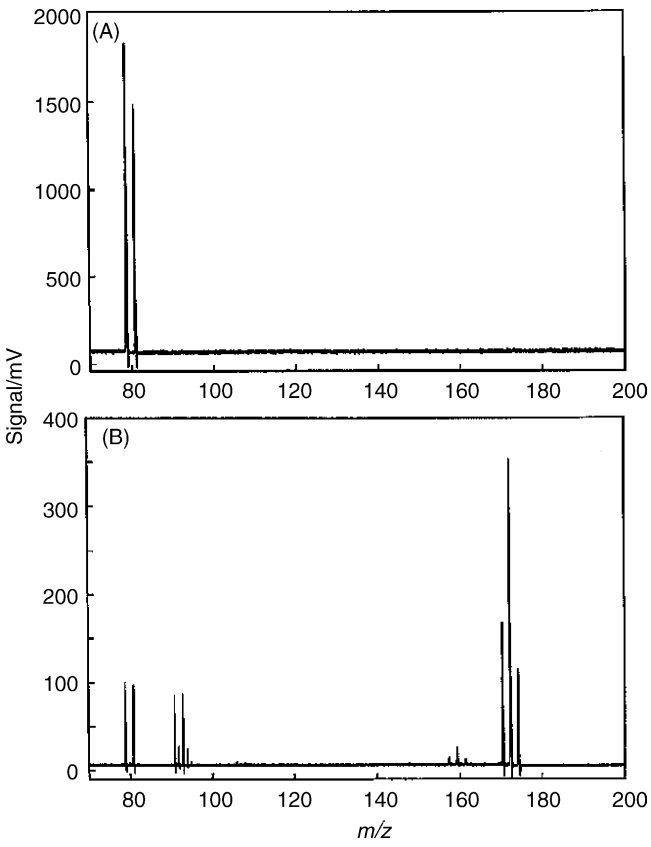

Fig. 12. Atomic (A) and molecular (B) mass spectra for bromoform vapour swept into the GSGD while the plasma was modulated at 10 Hz. Reprinted with permission [125].

A microsecond pulsed glow discharge (μs-pulsed GD) ion source for TOF-MS was used for elemental, structural and molecular analysis [127]. The plasma was generated repeatedly at 100 Hz with a 1 kV electrical pulse lasting 20 μs. By coupling GC to the set-up, aromatic and chlorinated hydrocarbons were determined by recording the complete mass spectrum at three different time regimes occurring during the glow discharge pulse cycle, aiming to obtain information on elemental constituents, chemical structure and molecular weight [128,129].

3.3. Liquid chromatography and plasma mass spectrometry

A comprehensive review of ICP-MS for detection in chromatography, including liquid chromatography has been published [70]. Some applications of halogen speciation can be found, especially with Br- and I-selective detection, but when compared to metal speciation, the reports are rather few in number. It is fair to say that this trend has not changed in recent years.

Depending on the sources, methamphetamine may contain several inorganic impurities. Various elements, including I and Br, were detected in seized samples by ion chromatography (IC) coupled to ICP-MS [130]. The technique was seen to have a potential in forensic studies for distinguishing between different methamphetamines by their inorganic element content.

LC has been coupled with Ar-ICP-MS for the determination of inorganic halogen species [131]. Absolute detection limits for Cl, Br and I were 36, 0.8 and 25 pg, respectively. Size-exclusion LC was used for the separation, which facilitated the separation of I^- from IO_3^-, Br^- from BrO_3^- and Cl^- from ClO_3^-. The chemical form of the elements had no influence on the ICP-MS response. IO_3^- was the only I-species determined in drinking water samples, and was likely to be present there as a disinfection by-product.

Ion chromatography coupled with Br-selective detection by ICP-MS was explored as a selective method for bromate determination in drinking water [132]. When evaluating three different anion exchange columns, detection limits were found to be in the 1–2 $\mu g\,l^{-1}$ range by direct analysis. The detection limit was further reduced, to the 0.1–0.2 $\mu g\,l^{-1}$ range, by using a Dionex AG10 column for preconcentration of 1.8 ml samples. Selectivity and recovery were excellent, even when analysing samples spiked with a high content of potential interference, such as chloride, sulphate and nitrate.

Isotope dilution mass spectrometry (IDMS) [133] offers the possibility of achieving high accuracy in the LC–ICP-MS determination of iodinated species [134,135]. Several organic I-species were identified at concentrations in the 0.4–1.7 $\mu g\,l^{-1}$ range in environmental water samples, by using reversed phase LC coupled with ICP-MS. By using size exclusion chromatography (SEC), even high molecular iodinated species were identified in surface water samples. SEC–ICP-MS was also helpful for characterization of halogenated species in relation to humic substances (HS) of different origin [136]. Problems of interference were encountered with the application of IDMS for Cl and Br-selective detection. I-selective detection was performed with a continuous spiking solution, allowing the mass flow of I ($pg\,s^{-1}$) to be plotted directly in the chromatogram, instead of signal intensity that otherwise require external calibration. The SEC–ICP-IDMS technique was successfully applied for the study of ageing of dissolved humic substances and the effect of microbiological activity on this process [137]. In contrast to chlorinated and brominated species with HS, a substantial transformation of the HS/iodine species was confirmed. Furthermore, a strong microbiological influence on the transformation of HS/iodine species was found, which is shown in Fig. 13.

Takatera and Watanabe [138] used reversed-phase LC–ICP-MS with I-selective detection, for the determination of iodide ion (I^-) and five iodo amino acids (monoiodotyrosine, diiodotyrosine, 3,3′,5- and 3,3′,5′-triiodothyronine and thyroxine) commonly found in thyroglobulin. For clinical diagnosis of thyroid diseases, including hyperthyroidism, it is important to have analytical methods for determination of these amino acids in plasma and urine. Detection limits

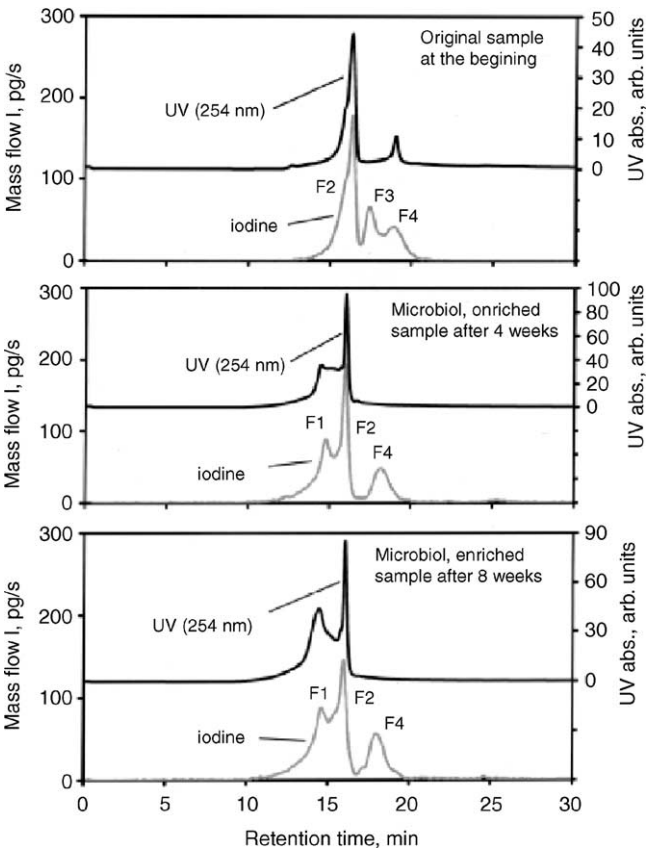

Fig. 13. SEC–ICP-IDMS chromatogram of iodine for a microbiologically enriched sewage water sample after 4 and 8 weeks of ageing in comparison with the original sample at the beginning. Reprinted with permission [137].

were in the range of 35–130 pg as iodine. Thyroglobulin was digested by Pronase, which is a preparation of several proteolytic enzymes. By using I-selective detection, sample preparation was easy, with no need to extract the iodo amino acids with organic solvents, in order to separate hydrophilic amino acids. Only ultrafiltration was required, for the removal of residual proteins. This was seen as a major advantage of ICP-MS in comparison with UV-detection.

Reversed phase LC was coupled with I-selective ICP-MS detection for simultaneous quantification of iodine, in addition to active hormones (T4 and T3), as well as (inactive) reverse T3, and the synthetic precursors of TH, monoiodotyrosine (MIT) and diiodotyrosine [139,140]. The method was even put to use for the analysis of whole-body homogenates of adult male and female zebrafish (*Danio rerio*) and tadpoles of the African clawed frog (*Xenopus laevis*) at two different developmental stages [141].

In recent years, there have been some exciting uses of LC–ICP-MS for analysis of biomedical samples. Br-selective detection was found to be a viable tool for screening of metabolites in biological fluid samples following the administration of drugs [142]. At least 16 metabolites of 4-bromoaniline were distinguished in rat urine. Br-selective detection also enabled the identification of metabolites of 2-Bromo-4-trifluoromethyl-[^{13}C]-acetanilide in rat urine [143]. The effluent from the reversed phase LC column was split and directed to both the ICP-MS and to an orthogonal acceleration TOF-MS. In this way, molecular structure information was obtained simultaneously with the halogen-selective screening of metabolites in the biological samples. The method was applied successfully for studies of the metabolites of 4-bromoaniline in rat urine [144], bromine labelled bradykinin metabolism in human and rat plasma [145], and for profiling the metabolites produced in the earthworm Eisenia veneta by exposure to 2-fluoro-4-iodoaniline [146].

4. Others techniques for halogen-selective detection

Halogen-selective detection may be obtained by means other than atomic emission spectroscopy and plasma mass spectrometry. For instance, halogen-specific detector signals are obtained by use of flame photometric detection (FPD), where heteroatom-containing compounds are burned in a hydrogen-rich flame to produce chemiluminescent species that emit light at specific wavelengths. Indium is added for the detection of halogens. For example, Cl-selective detection may be achieved by measuring emission from indium (I) chloride at 360 nm. Although FPD is typically used with GC, coupling with LC is possible by use of microbore LC columns with reduced flow [147].

Chemical reaction interface mass spectrometry (CRIMS) is a relatively new technique, where a microwave-induced plasma is used as a reaction chamber for introduction of compounds separated by GC or LC. Reagent gas is added to the plasma, and all molecules are decomposed to atoms. When leaving the plasma, the atoms recombine to produce small and volatile compounds with the halogens, e.g. HBr and HCl. These are transferred on-line to a mass spectrometer for detection. One advantage of CRIMS is the possibility to operate also in normal organic MS mode, by simply turning off the plasma interface. SO_2 was found to be a highly efficient as reagent gas for selective detection of Cl and Br by GC–CRIMS [148,149]. Cl-selective detection was obtained by recording the signal for $H^{35}Cl$, or the signal for $H^{37}Cl$ in cases of complex samples that exhibited interference at *m/z* 36. Diazepam could be determined to the 50 pg level, with a linear range covering four orders of magnitude. The method was further explored for drug metabolism studies by analysis of urine spiked with four chlorine-containing drugs (Fig. 14) and for the study of triclopyr herbicide uptake in plants [150]. Also other reagent gases may be suitable for CRIMS, for instance NF_3, which performed well for detection of P, ^{2}H, Cl and S by utilizing a production of fluorinated species [151]. By solvent removal with a Vestec Universal Interface, it is possible to couple LC with CRIMS [152].

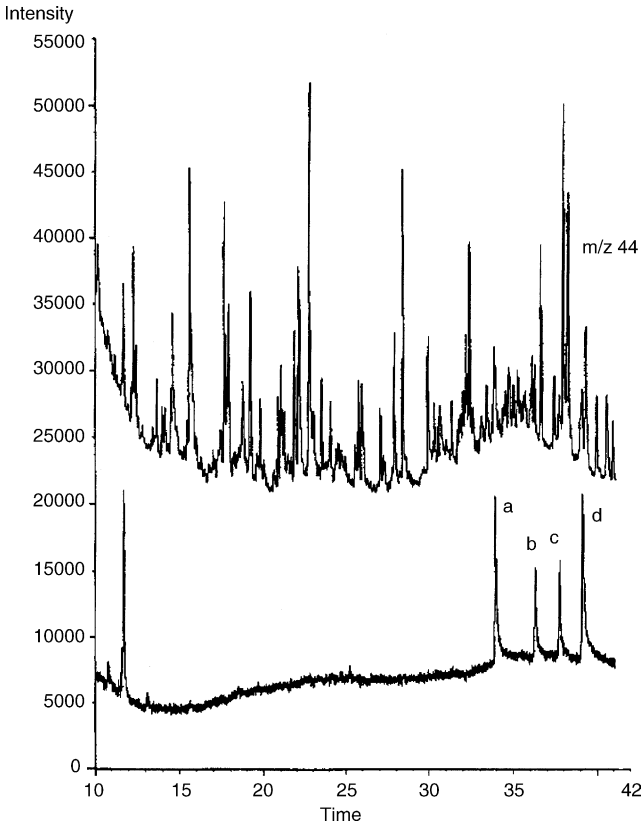

Fig. 14. GC–CRIMS analysis of urine spiked with four benzodiazepines: (a) desmethyl-diazepam; (b) oxazepam; (c) diazepam; and (d) lorazepam. The C-selective (upper) and I-selective (lower) chromatograms were recorded at *m/z* 44 (CO_2) and *m/z* 36 (HCl), respectively, by using SO_2 as reagent gas. Peak identification: a = diazepam, b = desmethyldiazepam, c = oxazepam, and d = lorazepam. Reprinted with permission [149].

Although not covered in the present review, it must be mentioned that organic MS detection can be operated in various modes for halogen-selective detection. High-resolution mass spectrometry offers the prospect of obtaining the molecular formula, including information on halogen content of the analyte. Another methodology is GC–MS with negative ion chemical ionization (NICI), preferably when optimized for dissociative electron attachment (DEA), i.e. in order to obtain Cl-selective detection by monitoring the $^{35}Cl^-$ signal [153]. An early report found that NICI may be a valuable technique for detection of brominated compounds by monitoring the Br^- signal [154]. The paper described, for the first time, the successful application of GC–NICI-MS for detection of brominated flame-retardants, such as PBDPEs, by monitoring the highly abundant $^{79}Br^-$ and $^{81}Br^-$ signals. Detection limits below the 0.1 pg level were achieved. Today, GC–NICI-MS is a well-established analytical technique for monitoring the emerging environmental problem of brominated flame retardants [155–161]. A similar dissociative approach has also been explored for LC, with electrospray ionization operated in the negative ion mode with an induced in-source fragmentation [162]. Iodinated organic compounds were determined even in complex samples, by recording of the I^- signal.

5. Conclusions

Substantial research has been directed into the field of halogen-selective detection in GC and LC as reviewed in the present paper, and most of this work has been based on either plasma emission spectroscopy or plasma mass spectrometry. The advantages of halogen-selective detection are clear as demonstrated by the substantial amount of excellent applications published in the literature. Halogen-selective detection is a very strong tool for the location of halogenated compounds, and for their identification. In addition, halogen-selective detection by plasma emission spectroscopy or plasma mass spectrometry provides an interesting tool for quantitative purposes, for instance enabling compound independent calibration. In some areas of analytical chemistry, halogen-selective detection has gained acceptance in routine laboratories. However, it appears that halogen-selective detection is still far from realizing its full potential in many areas, and this is from our point of view related to limited detectability and lack of commercial instrumentation. Thus, in order to increase the impact of halogen-selective detection in GC and LC in the future, systems providing similar detection limits as GC–MS and LC–MS should be developed and introduced commercially. Most probably, these systems should be based on miniaturized ion-sources compatible with conventional mass spectrometric instrumentation.

References

[1] A.J. McCormick, S.C. Tong, W.D. Cooke, Anal. Chem. 37 (1965) 1470.
[2] G.W. Rice, A.P. D'Silva, V.A. Fassel, Spectrochim. Acta Part B 40 (1985) 1573.
[3] R.J. Skelton, K.E. Markides, P.B. Farnsworth, M.L. Lee, J. High Resolut. Chromatogr. 11 (1988) 75.
[4] S. Pedersen-Bjergaard, T. Greibrokk, Anal. Chem. 65 (1993) 1998.
[5] R.B. Constanzo, E.F. Barry, Anal. Chem. 60 (1988) 826.
[6] D. Huang, D.C. Liang, M.W. Blades, J. Anal. Atom. Spectrom. 4 (1989) 789.
[7] G. Knapp, E. Leitner, M. Michaelis, B. Platzer, A. Schalk, Int. J. Environ. Anal. Chem. 38 (1990) 369.
[8] R.J. Loyd, R.M. Barnes, P.C. Uden, W.G. Elliott, Anal. Chem. 50 (1978) 2025.
[9] D.L. Windsor, M.B. Denton, Appl. Spectrosc. 32 (1978) 366.
[10] B.D. Quimby, J.J. Sullivan, Anal. Chem. 62 (1990) 1027.
[11] J.J. Sullivan, B.D. Quimby, Anal. Chem. 62 (1990) 1034.
[12] S. Pedersen-Bjergaard, T. Greibrokk, J. High. Resolut. Chromatogr. 18 (1995) 9.
[13] S. Pedersen-Bjergaard, S.I. Semb, J. Vedde, E.M. Brevik, T. Greibrokk, Chromatographia 43 (1996) 44.
[14] N. Kovacic, T.L. Ramus, J. Anal. Atom. Spectrom. 7 (1992) 999.
[15] M. Mazurek, Z. Witkiewicz, S. Popiel, M. Sliwakowski, J. Chromatogr. A 919 (2001) 133.
[16] D.F. Gurka, S. Pyle, R. Titus, Anal. Chem. 69 (1997) 2411.
[17] K. Janak, A. Colmsjo, C. Oestman, J. Chromatogr. Sci. 33 (1995) 611.
[18] S. Pedersen-Bjergaard, T.N. Asp, J. Vedde, T. Greibrokk, J. Microcolumn Sep. 4 (1992) 163.
[19] S. Pedersen-Bjergaard, T.N. Asp, J. Vedde, G.E. Carlberg, T. Greibrokk, Chromatographia 35 (1993) 193.
[20] S. Pedersen-Bjergaard, S.I. Semb, J. Vedde, E.M. Brevik, T. Greibrokk, Chemosphere 32 (1996) 1103.
[21] T. Hankemeier, J. Rozenbrand, M. Abhadur, J.J. Vreuls, U.A.T. Brinkman, Chromatographia 48 (1998) 273.
[22] H.G.J. Mol, T. Hankemeier, U.A.Th. Brinkman, LC–GC Int. 17 (1999) 544.
[23] L.L.P. van Stee, P.E.G. Leonards, W.M.G.M. van Loon, A.J. Hendriks, J.L. Maas, J. Struijs, U.A.Th. Brinkman, Water Res. 36 (2002) 4455.
[24] L.L.P. van Stee, P.E.G. Leonards, R.J.J. Vreuls, U.A.Th. Brinkman, Analyst 124 (1999) 1547.
[25] J. Cook, M. Engel, P.L. Wylie, B.D. Quimby, J. AOAC Int. 82 (1999) 313.
[26] H.-J. Stan, M. Linkerhagner, J. Chromatogr. A 750 (1996) 369.
[27] S. Mark Lee, P.L. Wylie, J. Agric. Food Chem. 39 (1991) 2192.
[28] H.-J. Stan, M. Linkerhagner, J. High Resolut. Chromatogr. 16 (1993) 539.
[29] K.-C. Ting, P. Kho, J. Assoc. Off. Anal. Chem. 74 (1991) 991.
[30] P.L. Wylie, R. Oguchi, J. Chromatogr. 517 (1990) 131.
[31] Z.V. Skopec, R. Clark, P.M.A. Harvey, R.J. Wells, J. Chromatogr. Sci. 31 (1993) 445.
[32] J.L. Bernal, M.J. Del Nozal, M.T. Martin, J.J. Jimènez, J. Chromatogr. A 754 (1996) 245.
[33] N.L. Olson, R. Carrell, R.K. Cummings, R. Rieck, LC–GC Int. 12 (1994) 142.
[34] P. Vinas, N. Campillo, I. Lopez-Garcia, N. Aguinaga, M. Hernandez-Cordoba, J. Agric. Food Chem. 51 (2003) 3704.
[35] E.C. Goosens, D. De Jong, G.J. De Jong, F.D. Rinkema, U.A.Th. Brinkman, J. High Resolut. Chromatogr. 18 (1995) 38.
[36] T. Hankemeier, A.J.H. Louter, F.D. Rinkema, U.A.Th. Brinkman, Chromatographia 40 (1995) 119.
[37] F.D. Rinkema, A.J.H. Louter, U.A.Th. Brinkman, J. Chromatogr. A 678 (1994) 289.

[38] R. Eisert, K. Levsen, G. Wunsch, J. Chromatogr. A 683 (1994) 175.
[39] P. Vinas, N. Campillo, I. Lopez-Garcia, N. Aguinaga, M. Hernandez-Cordoba, J. Chromatogr. A 978 (2002) 249.
[40] A. Wenner, M. Wortberg, J. High Resolut. Chromatogr. 21 (1998) 661.
[41] R. Eisert, K. Levsen, G. Wunsch, Int. J. Environ. Anal. Chem. 58 (1994) 103.
[42] S. Pedersen-Bjergaard, S.I. Semb, E.M. Brevik, T. Greibrokk, J. Chromatogr. A 723 (1996) 337.
[43] J. Hajslova, P. Cuhra, M. Kempny, J. Poustka, K. Holadova, V. Kocourek, J. Chromatogr. A 699 (1995) 231.
[44] K. Janak, E. Grimvall, C. Ostman, A. Colmsjo, J. Microcolumn Sep. 6 (1994) 605.
[45] K. Janak, G. Becker, A. Colmsjo, C. Oestman, M. Athanasiadou, K. Valters, Å. Bergman, Organohalogen Compd. 39 (1998) 35.
[46] I. Rodriguez, M.I. Turnes, M.C. Mejuto, R. Cela, J. Chromatogr. A 721 (1996) 297.
[47] M.I. Turnes, I. Rodriguez, M.C. Mejuto, R. Cela, J. Chromatogr. A 683 (1994) 21.
[48] P. Mussmann, R. Eisert, K. Levsen, G. Wunsch, Acta Hydrochim. Hydrobiol. 23 (1995) 13.
[49] I. Silgoner, E. Rosenberg, M. Grasserbauer, J. Chromatogr. A 768 (1997) 259.
[50] A. Johnson, N.L. Olson, Arch. Environ. Contam. Toxicol. 41 (2001) 339.
[51] K. Laniewski, H. Boren, A. Grimvall, Chemosphere 38 (1998) 393.
[52] K. Laniewski, H. Boren, A. Grimvall, Environ. Sci. Technol. 32 (1998) 3935.
[53] K. Laniewski, H. Boren, A. Grimvall, J. Chromatogr. A 826 (1998) 201.
[54] C. Johansson, I. Pavasars, H. Boren, A. Grimvall, O. Dahlmann, R. Moerck, A. Reimann, Environ. Int. 20 (1994) 103.
[55] C. Flodin, E. Johansson, H. Boren, A. Grimvall, O. Dahlmann, R. Moerck, Environ. Sci. Technol. 31 (1997) 2464.
[56] C. Flodin, M. Ekelund, H. Boren, A. Grimvall, Chemosphere 34 (1997) 2319.
[57] N.R. Hardas, R. Adam, P.C. Uden, J. Chromatogr. A 844 (1999) 249.
[58] K. Laniewski, T. Wannman, G. Hagman, J. Chromatogr. A 985 (2003) 275.
[59] K. Laniewski, M. Vagero, E. Forsberg, T. Forngren, G. Hagman, J. Chromatogr. A 1027 (2004) 93.
[60] F.C.-Y. Wang, Anal. Chem. 71 (1999) 2037.
[61] H.T. Rasmussen, R. McDonough, R.J. Gargiullo, B.P. McPherson, J. High Resolut. Chromatogr. 19 (1996) 359.
[62] J.R. Stuff, W.R. Creasy, A.A. Rodriguez, H.D. Durst, J. Microcolumn Sep. 11 (1999) 644.
[63] P.B. Mason, L. Zhang, J.W. Carnahan, R.E. Winas, Anal. Chem. 65 (1993) 2596.
[64] L. Zhang, J.W. Carnahan, R.E. Winas, P.H. Neill, Anal. Chem. 61 (1989) 895.
[65] D. Das, J.W. Carnahan, Anal. Chim. Acta 444 (2001) 229.
[66] O.T. Akinbo, J.W. Carnahan, Anal. Chim. Acta 390 (1999) 217.
[67] J.A. Caruso, D. Heitkemper, H. Suyani, J. Creed, T. Davidson, Abstr. Pap. Am. Chem. Soc. 195 (1988) 182.
[68] J.A. Caruso, A. Alrashdan, J. Creed, C. Story, D. Heitkemper, H. Suyani, Abstr. Pap. Am. Chem. Soc. 199 (1990) 179.
[69] L.K. Olson, D.T. Heitkemper, J.A. Caruso, ACS Symp. Ser. 479 (1992) 288.
[70] K. Sutton, R.M.C. Sutton, J.A. Caruso, J. Chromatogr. A 789 (1997) 85.
[71] J.A. Olivares, R.S. Houk, Anal. Chem. 57 (1985) 2674.
[72] D.J. Douglas, J.B. French, J. Anal. At. Spectrom. 3 (1988) 743.
[73] T.N. Olney, W. Chen, D.J. Douglas, J. Anal. At. Spectrom. 14 (1999) 9.
[74] E.H. Evans, J.J. Giglio, T.M. Castillano, J.A. Caruso, Inductively Coupled and Microwave Induced Plasma Sources for Mass Spectrometry, Royal Society of Chemistry, Cambridge, 1995.
[75] K.E. Jarvis, A.L. Gray, R.S. Houk, Handbook of Inductively Coupled Plasma Mass Spectrometry, Blackie, Glasgow, 1992.
[76] R.S. Lobinski, I.R. Pereiro, H. Chassaigne, A. Wasik, J. Szpunar, J. Anal. At. Spectrom. 13 (1998) 859.
[77] W. Kerl, J.S. Becker, H.J. Dietze, W. Dannecker, J. Anal. At. Spectrom. 11 (1996) 723.
[78] E.H. Larsen, M.B. Ludwigsen, J. Anal. At. Spectrom. 12 (1997) 435.
[79] B. Li, H.L. He, S.Y. Shi, X.R. Ma, H.L. Wen, C.F. Lu, J. Anal. At. Spectrom. 17 (2002) 371.
[80] S. Sturup, A. Buchert, Fresenius J. Anal. Chem. 354 (1996) 323.
[81] X. Bu, T. Wang, G. Hall, J. Anal. At. Spectrom. 18 (2003) 1443.
[82] D.R. Wiederin, F.G. Smith, R.S. Houk, Anal. Chem. 63 (1991) 219.
[83] A.W. Kim, M.E. Foulkes, L. Ebdon, S.J. Hill, R.L. Patience, A.G. Barwise, S.J. Rowland, J. Anal. At. Spectrom. 7 (1992) 1147.
[84] K. Mastovska, S.J. Lehotay, J. Chromatogr. A 1000 (2003) 153.
[85] A. Montaser, S.K. Chan, D.W. Koppenaal, Anal. Chem. 59 (1987) 1240.
[86] B.S. Sheppard, W.L. Shen, T.M. Davidson, J.A. Caruso, J. Anal. At. Spectrom. 5 (1990) 697.
[87] T.M. Castillano, J.J. Giglio, E.H. Evans, J.A. Caruso, J. Anal. At. Spectrom. 9 (1994) 1335.
[88] G. O'Connor, L. Ebdon, E.H. Evans, H. Ding, L.K. Olson, J.A. Caruso, J. Anal. At. Spectrom. 11 (1996) 1151.
[89] J.W. Waggoner, M. Belkin, K.L. Sutton, J.A. Caruso, H.B. Fannin, J. Anal. At. Spectrom. 13 (1998) 879.
[90] H. Hayashi, Y. Hara, T. Tanaka, M. Hiraide, Bunseki Kagaku 52 (2003) 275.
[91] R.D. Satzger, F.L. Fricke, P.G. Brown, J.A. Caruso, Spectrochim. Acta Part B: At. Spectrosc. 42B (1987) 705.
[92] P.G. Brown, T.M. Davidson, J.A. Caruso, J. Anal. At. Spectrom. 3 (1988) 763.
[93] S.H. Nam, W.R.L. Masamba, A. Montaser, Anal. Chem. 65 (1993) 2784.
[94] C. Brede, E. Lundanes, Y. Greibrokk, S. Pedersen-Bjergaard, J. High Resolut. Chromatogr. 21 (1998) 633.
[95] D.J. Douglas, J.B. French, Anal. Chem. 53 (1981) 37.
[96] G.H. Vickers, D.A. Wilson, G.M. Hieftje, Anal. Chem. 60 (1988) 1808.
[97] M.E. Cisper, A.W. Garrett, Y.X.X. Duan, J.A. Olivares, P.H. Hemberger, Int. J. Mass Spectrom. 178 (1998) 121.
[98] B. Bouyssiere, J. Szpunar, R. Lobinski, Spectrochim. Acta Part B: At. Spectrosc. 57 (2002) 805.
[99] N.S. Chong, R.S. Houk, Appl. Spectrosc. 41 (1987) 66.
[100] G.R. Peters, D. Beauchemin, J. Anal. At. Spectrom. 7 (1992) 965.
[101] J. Feldmann, J. Anal. At. Spectrom. 12 (1997) 1069.
[102] A.V. Hirner, E. Krupp, F. Schulz, M. Koziol, W. Hofmeister, J. Geochem. Explor. 64 (1998) 133.
[103] A.V. Hirner, J. Feldmann, E. Krupp, R. Grumping, R. Goguel, W.R. Cullen, Org. Geochem. 29 (1998) 1765.
[104] U.M. Gruter, J. Kresimon, A.V. Hirner, Fresenius J. Anal. Chem. 368 (2000) 67.
[105] A.P. Vonderheide, M. Montes-Bayon, J.A. Caruso, J. Anal. At. Spectrom. 17 (2002) 1480.
[106] A. Schwarz, K.G. Heumann, Anal. Bioanal. Chem. 374 (2002) 212.
[107] R.G. Wuilloud, J.C.A. de Wuilloud, A.P. Vonderheide, J.A. Caruso, J. Anal. At. Spectrom. 18 (2003) 1119.
[108] E.H. Evans, J.A. Caruso, J. Anal. At. Spectrom. 8 (1993) 427.
[109] X. Yan, T. Tanaka, H. Kawaguchi, Spectrochim. Acta Part B: At. Spectrosc. 51B (1996) 1345.
[110] E.H. Evans, W. Pretorius, L. Ebdon, S. Rowland, Anal. Chem. 66 (1994) 3400.
[111] G. O'Connor, L. Ebdon, E.H. Evans, J. Anal. At. Spectrom. 12 (1997) 1263.

[112] J.W. Waggoner, L.S. Milstein, M. Belkin, K.L. Sutton, J.A. Caruso, H.B. Fannin, J. Anal. At. Spectrom. 15 (2000) 13.
[113] A.H. Mohamad, J.T. Creed, T.M. Davidson, J.A. Caruso, Appl. Spectrosc. 43 (1989) 1127.
[114] J.T. Creed, A.H. Mohamad, T.M. Davidson, G. Ataman, J.A. Caruso, J. Anal. At. Spectrom. 3 (1988) 923.
[115] J.T. Creed, T.M. Davidson, W.L. Shen, J.A. Caruso, J. Anal. At. Spectrom. 5 (1990) 109.
[116] W.C. Story, J.A. Caruso, J. Anal. At. Spectrom. 8 (1993) 571.
[117] P. Read, H. Beere, L. Ebdon, M. Leizers, M. Hetheridge, S. Rowland, Org. Geochem. 26 (1997) 11.
[118] G. O'Connor, S.J. Rowland, E.H. Evans, J. Sep. Sci. 25 (2002) 839.
[119] B.W. Pack, G.M. Hieftje, Spectrochim. Acta Part B: At. Spectrosc. 52 (1997) 2163.
[120] B.W. Pack, J.A.C. Broekaert, J.P. Guzowski, J. Poehlman, G.M. Hieftje, Anal. Chem. 70 (1998) 3957.
[121] C. Brede, S. Pedersen-Bjergaard, E. Lundanes, T. Greibrokk, Anal. Chem. 70 (1998) 513.
[122] C. Brede, E. Lundanes, T. Greibrokk, S. Pedersen-Bjergaard, J. High Resolut. Chromatogr. 21 (1998) 282.
[123] C. Brede, S. Pedersen-Bjergaard, E. Lundanes, T. Greibrokk, J. Anal. At. Spectrom. 15 (2000) 55.
[124] J.P. Guzowski, J.A.C. Broekaert, S.J. Ray, G.M. Hieftje, J. Anal. At. Spectrom. 14 (1999) 1121.
[125] J.P. Guzowski, G.M. Hieftje, J. Anal. At. Spectrom. 15 (2000) 27.
[126] J.P. Guzowski, G.M. Hieftje, Anal. Chem. 72 (2000) 3812.
[127] V. Majidi, M. Moser, C. Lewis, W. Hang, F.L. King, J. Anal. At. Spectrom. 15 (2000) 19.
[128] C.L. Lewis, M.A. Moser, W. Hang, D.E. Dale, D.C. Hassell, V. Majidi, J. Anal. At. Spectrom. 18 (2003) 629.
[129] C.L. Lewis, M.A. Moser, D.E. Dale, W. Hang, C. Hassell, F.L. King, V. Majidi, Anal. Chem. 75 (2003) 1983.
[130] S. Suzuki, H. Tsuchihashi, K. Nakajima, A. Matsushita, T. Nagao, J. Chromatogr. 437 (1988) 322.
[131] V.V. Salov, J. Yoshinaga, Y. Shibata, M. Morita, Anal. Chem. 64 (1992) 2425.
[132] J.T. Creed, M.L. Magnuson, J.D. Pfaff, C. Brockhoff, J. Chromatogr. A 753 (1996) 261.
[133] K.G. Heumann, Int. J. Mass Spectrom. Ion Process. 118 (1992) 575.
[134] K.G. Heumann, L. Rottmann, J. Vogl, J. Anal. At. Spectrom. 9 (1994) 1351.
[135] K.G. Heumann, S.M. Gallus, G. Radlinger, J. Vogl, Spectrochim. Acta Part B: At. Spectrosc. 53 (1998) 273.
[136] G. Radlinger, K.G. Heumann, Fresenius J. Anal. Chem. 359 (1997) 430.
[137] K.G. Heumann, G. Radlinger, M. Erbes, I. Heiber, U. Obst, Z. Filip, H. Claus, Acta Hydrochim. Hydrobiol. 28 (2000) 193.
[138] K. Takatera, T. Watanabe, Anal. Chem. 65 (1993) 759.
[139] B. Michalke, P. Schramel, H. Witte, Biol. Trace Elem. Res. 78 (2000) 67.
[140] B. Michalke, P. Schramel, H. Witte, Biol. Trace Elem. Res. 78 (2000) 81.
[141] R. Simon, J.E. Tietge, B. Michalke, S. Degitz, K.W. Schramm, Anal. Bioanal. Chem. 372 (2002) 481.
[142] J.K. Nicholson, J.C. Lindon, G. Scarfe, I.D. Wilson, F. Abou-Shakra, J. Castro-Perez, A. Eaton, S. Preece, Analyst 125 (2000) 235.
[143] J.K. Nicholson, J.C. Lindon, G.B. Scarfe, I.D. Wilson, F. Abou-Shakra, A.B. Sage, J. Castro-Perez, Anal. Chem. 73 (2001) 1491.
[144] F.R. Abou-Shakra, A.B. Sage, J. Castro-Perez, J.K. Nicholson, J.C. Lindon, G.B. Scarfe, I.D. Wilson, Chromatographia 55 (2002) S9.
[145] P. Marshall, O. Heudi, S. Mckeown, A. Amour, F. Abou-Shakra, Rapid Commun. Mass Spectrom. 16 (2002) 220.
[146] C.J. Duckett, I.D. Wilson, H. Walker, F. Abou-Shakra, J.C. Lindon, J.K. Nicholson, Rapid Commun. Mass Spectrom. 17 (2003) 1855.
[147] S. Folestad, B. Josefsson, P. Marstorp, Anal. Chem. 59 (1987) 334.
[148] J.T. Morre, M. Moini, Biol. Mass Spectrom. 21 (1992) 693.
[149] H. Song, F.P. Abramson, Anal. Chem. 65 (1993) 447.
[150] D.J. Morre, J.T. Morre, J. Lawrence, M. Moini, J. Plant Growth Regul. 17 (1998) 125.
[151] H. Song, F. Abramson, J. Am. Soc. Mass Spectrom. 6 (1995) 421.
[152] M. McLean, M.L. Vestal, Y. Teffera, F.P. Abramson, J. Chromatogr. A 732 (1996) 189.
[153] J.M. Curtis, R.K. Boyd, Int. J. Mass Spectrom. 165 (1997) 625.
[154] H.R. Buser, Anal. Chem. 58 (1986) 2913.
[155] U. Sellstrom, A. Kierkegaard, C. de Wit, B. Jansson, Environ. Toxicol. Chem. 17 (1998) 1065.
[156] A. Sjodin, E. Jakobsson, A. Kierkegaard, G. Marsh, U. Sellstrom, J. Chromatogr. A 822 (1998) 83.
[157] A. Sjodin, H. Carlsson, K. Thuresson, S. Sjolin, A. Bergman, C. Ostman, Environ. Sci. Technol. 35 (2001) 448.
[158] E. Eljarrat, S. Lacorte, D. Barcelo, J. Mass Spectrom. 37 (2002) 76.
[159] U. Sellstrom, A. Bignert, A. Kierkegaard, L. Haggberg, C.A. De Wit, M. Olsson, B. Jansson, Environ. Sci. Technol. 37 (2003) 5496.
[160] G. Marsh, M. Athanasiadou, A. Bergman, L. Asplund, Environ. Sci. Technol. 38 (2004) 10.
[161] T. Hyotylainen, K. Hartonen, Trends in Anal. Chem. 21 (2002) 13.
[162] A. Putschew, M. Jekel, Rapid Commun. Mass Spectrom. 17 (2003) 2279.
[163] B.D. Quimby, P.A. Larson, P.C. Dryden, Application Note 228–363, Hewlett-Packard Company, Wilmington, DE, USA 1996.
[164] NIST, in, National Institute of Standards and Technology, USA, 2003.