ELSEVIER

Journal of Chromatography A, 703 (1995) 81–121

JOURNAL OF CHROMATOGRAPHY A

Review

Column liquid chromatography–mass spectrometry: selected techniques in environmental applications for polar pesticides and related compounds

J. Slobodník[a,*], B.L.M. van Baar[b], U.A.Th. Brinkman[a]

[a]*Department of Analytical Chemistry, Free University, De Boelelaan 1083, 1081 HV Amsterdam, Netherlands*

[b]*Department of Organic Chemistry, Free University, De Boelelaan 1083, 1081 HV Amsterdam, Netherlands*

Abstract

A review covering the field of environmental applications of liquid chromatography–mass spectrometry (LC–MS) is presented. Recent developments and advances are discussed with emphasis on the presently popular thermospray, particle beam and atmospheric pressure ionisation interfaces. Each interface is described separately covering the principle of operation, typical detection limits and characteristics of the mass spectra. All reviewed interfacing techniques provide useful data for identification/confirmation of analytes with various chemical properties. The application-oriented part of the review primarily deals with polar pesticides and related compounds. However, generally speaking the conclusions which are drawn also hold true for other classes of micro-contaminants. LC–MS obviously is complementary to 'routine' GC–MS and it extends the boundaries of the 'analytical window' of mass spectrometry to polar, non-volatile and/or thermolabile compounds. LC–MS is a powerful tool in environmental analysis and especially when it is combined with appropriate sample-treatment procedures it allows one to obtain detection limits adequate for trace-level analysis.

Contents

* Corresponding author. On leave from the Environmental Institute, Dlhá 44/46, 971 01 Prievidza, Slovak Republic.

0021-9673/95/$09.50
SSDI 0021-9673(95)00129-8

1. Introduction

The broad spectrum of well established gas chromatography–mass spectrometry (GC–MS) techniques available today allows the identification and determination of hundreds of toxic organic micro-contaminants in a variety of environmental samples [1]. Frequently, however, compounds are not amenable to analysis by GC without time-consuming derivatisation procedures being employed. For such compounds, liquid chromatography (LC) generally is the most appropriate separation method, and direct LC–MS analysis is an effective way to obtain both qualitative and quantitative information.

Modern pesticides, together with their degradation products, can be considered as typical candidates for LC separation, because of their medium to high polarity, and their thermolability and/or low volatility (for a review, see Ref. [2]). As even low concentrations of these compounds can cause a serious threat to life, they have to be monitored at trace levels of, typically, 0.1 μg/l for tap water, 1 μg/l for surface water, and 1 mg/kg for foodstuffs. Most LC-based methods use common ultraviolet (UV), fluorescence or electrochemical detection, which is occasionally combined with post-column treatment, e.g. derivatisation. However, MS often has the advantage over these conventional detectors because it can provide information for confirmation or unambiguous identification.

Although the first coupling of LC to MS was reported over 20 years ago, and several LC–MS interfaces were described in the course of time (see, e.g. Refs. [1–6]), the technical difficulties involved in interfacing a liquid flow of up to several ml/min with the high vacuum of a mass spectrometer source prevented the widespread use of LC–MS in method development until about seven years ago. LC–MS is now widely applied in biomedical and biochemical research, often for qualitative purposes. The development of LC–MS procedures for environmental analysis directed to quantitative analysis of target compounds, is gaining attention, as is demonstrated by several reviews on the subject [6–16].

In the present review, recent developments in the application of LC–MS in environmental analysis, particularly the determination of polar pesticides and related compounds, will be outlined for three interfacing techniques: thermospray (TSP), particle beam (PB), and atmospheric pressure ionisation (API: electrospray, ESP; ionspray, ISP; and atmospheric pressure chemical ionisation, APCI). Only very few studies have recently been published on direct liquid introduction [6,17] and on the moving belt interfacing [18,19]; these techniques will therefore not be discussed. Continuous-flow fast atom bombardment (CF-FAB) will not be discussed separately, because pesticide analysis is only rarely performed using this method. From the vast number of pesticides presently in use, attention will be focused on phenylurea herbicides, triazines, carbamates, organophosphorus pesticides, chlorinated phenoxyacetic acids, quaternary ammonium salts and chlorophenols. Most of these compound classes can not be easily analyzed by means of GC and, moreover, all of them have successfully been analyzed by LC with a variety of detectors. Analyte detectability and the possibility of obtaining structural information for the identification of target and non-target analytes will be included in the discussion.

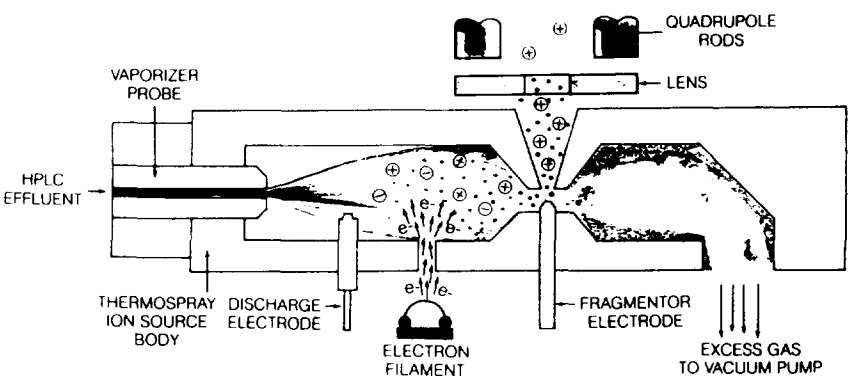
2. LC–MS interfaces

2.1. Thermospray

The thermospray interface, as it was originally developed by Vestal and co-workers [20], used heated nebulisation of the LC column effluent and extra pump capacity for effective desolvation. The TSP interface, which is schematically

depicted in Fig. 1A, consists of a resistively heated capillary (the 'vaporiser') which generates an aerosol from the effluent. The aerosol is sprayed into a desolvation chamber, which is maintained at fore-vacuum pressure by a high-capacity pump. The aerosol spray is directed perpendicular to the mass spectrometer entrance; the desolvation chamber and the mass spectrometer are separated by one or more skimmers and they are differentially pumped. Any ions in the aerosol may be forced into the mass spectrometer by a repeller electrode, which is commonly placed opposite the skimmer. The TSP can create sufficient desolvation, i.e., MS pressures can be kept below 10^{-4} Torr (1 Torr = 133.322 Pa) for conventional-size LC.

(A)



(B)

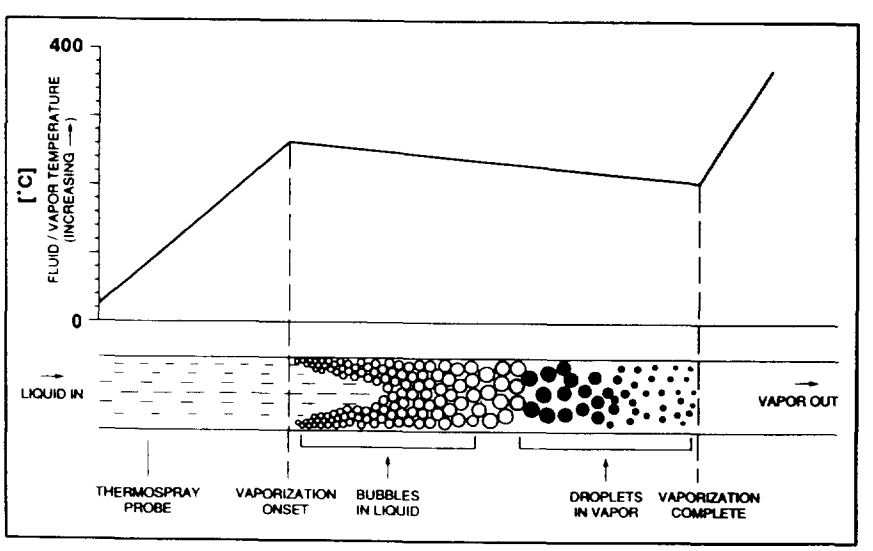


Fig. 1. (A) Schematic diagram of a thermospray interface. (B) Temperature profile over the length of the vaporiser and schematic illustration of the thermospray nebulisation mechanism.

The process of vaporisation is schematically depicted in Fig. 1B. Although the precise mechanism of ion formation is still the subject of some controversy [21], a summarised view is given here. Due to the combined action of heat and low pressure, the column effluent breaks up into large droplets, which in turn evaporate volatile constituents, particularly solvent molecules. Evaporation proceeds inside the desolvation chamber to give fully desolvated analyte molecules and primary ions; these primary ions are formed by ion evaporation [21]. Effectively, ion evaporation is achieved by the addition of a volatile buffer salt, typically ammonium acetate, to the eluent. Ionic analytes, e.g., quaternary ammonium salts, do not always require the addition of a salt, because they may undergo ion evaporation themselves. The primary ions become available for gas phase reactions with the neutral analyte molecules. The mode of ionisation which involves ion evaporation and subsequent gas phase reactions is generally termed 'buffer ionisation' TSP. Alternatively, proton transfer reactions may be stimulated by using a filament or discharge electrode; this is generally termed 'filament assisted TSP' or 'discharge assisted TSP', respectively. Assisted TSP effectively creates chemical ionisation conditions inside the desolvation chamber, with the eluent constituents as the reaction gas. The buffer salt ions, e.g. NH_4^+, produced by buffer ionisation TSP, are generally less reactive than reactants from the eluent produced in either of the other modes, e.g. $CH_3OH_2^+$. The resultant charged constituents of the aerosol may then be transferred to the mass separation system by the combined action of the high vacuum and the repeller electrode.

Ionisation by evaporation or by gas phase reactions, 'soft ionisation', produces ions with a minimum of internal energy and thus leads to a low abundance of ion fragmentation processes. Enlargement of the mean ion kinetic energy through high repeller voltages, may be used to enforce dissociative collisions. This form of collision induced dissociation (CID) is of limited use for structure confirmation in TSP; higher repeller voltages are not compatible with optimal transmission and sensitivity is lost [22]. In general, TSP mass spectra show abundant quasi-molecular ions, $[M+H]^+$, $M^{-\cdot}$ or $[M-H]^-$, of the analytes.

The introduction of the TSP interface brought about a breakthrough in interfacing conventional-size LC with MS. The success is underlined by the facts that TSP is commercially available from several manufacturers and that it is the most widely used LC–MS interface. TSP mass spectra usually yield little structural information and they are, therefore, less useful for the identification of unknown compounds. As the identification capability is often required in environmental analysis, TSP-MS is mainly used for target compound analysis. Recently, there has been a trend to try and obtain more structural information from LC–TSP-MS–MS rather than LC–TSP-MS. The use of tandem MS (MS–MS) provides an elegant means of obtaining structural information, albeit at the cost of an increase in the complexity of the method [23–32]. A schematic representation of a typical triple quadrupole MS–MS operation is shown in Fig. 2. The loss of sensitivity, which is to be expected from a decreased ion transmission in MS–MS, generally appears to be compensated by an enhanced signal-to-noise ratio (selectivity). Actually, only a few authors justify their use of MS–MS quantification by providing quantitative data [23]. The MS–MS approach is also highly useful for the identification of unknown pesticide metabolites formed during degradation processes.

Alternatively, a tentative confirmation of analytes with the help of an exact mass determination can in principle be accomplished by coupling the TSP interface to a magnetic sector mass spectrometer [33–36] or by using a modified quadrupole mass spectrometer [37], but such experiments have not yet been applied to pesticides. It should be noted that exact mass measurement under TSP conditions requires the addition of an internal standard, and elaborate data handling. Also, because of the fact that higher resolution implies less sensitivity, TSP with exact mass determination is not too attractive for routine application.

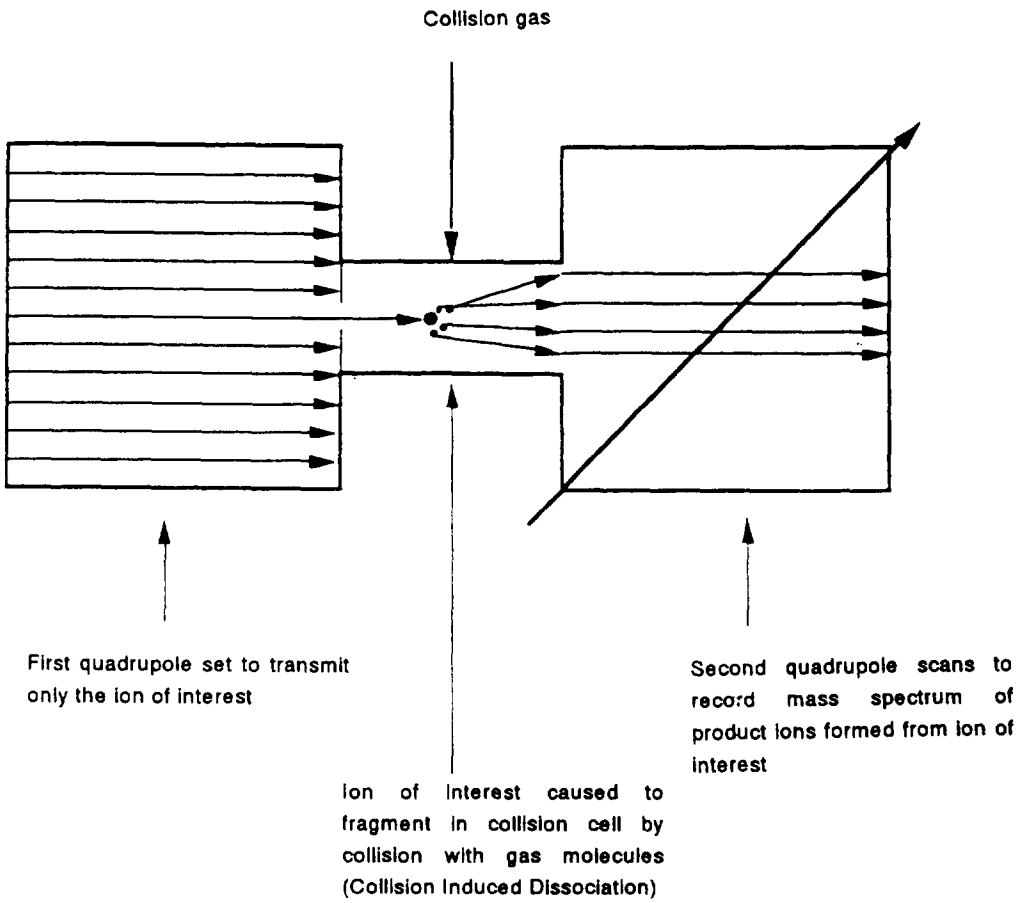


Fig. 2. Schematic diagram of a triple quadrupole mass spectrometer, showing the experimental set-up for obtaining product ion scans. (Adapted from Ref. [12].)

2.2. Particle beam

The introduction of the PB interface, originally known as the 'mono-disperse aerosol generating interface for chromatography' (MAGIC-LC–MS) [38] enables the coupling of a wide range of LC separations to conventional electron ionisation (EI) and chemical ionisation (CI) MS procedures. LC–PB-MS is nowadays mainly used for the identification of non-target compounds in real-world matrices. The interface is commercially available under various names, i.e., 'particle beam' (with concentric pneumatic nebuliser), 'thermabeam' (with thermally assisted pneumatic nebulisation), and 'universal interface' (with thermally assisted pneumatic nebulisation and additional membrane separation). Of all LC–MS interfacing methods, LC–PB-MS comes closest to GC–MS; the PB interface is principally a momentum separator and as such it is derived from the jet-type GC–MS interface (used with packed columns [39]).

A scheme of a PB interface is shown in Fig. 3. Desolvation occurs in steps by leading the column effluent through several differentially pumped chambers. At the exit of the LC column a liquid jet is generated by pumping the effluent through a small (25 μm) orifice into a low vacuum (200 Torr) desolvation chamber. The liquid jet is then dispersed into droplets with a nearly uniform size distribution, by the action of a helium flow. Part of the volatile constituents of

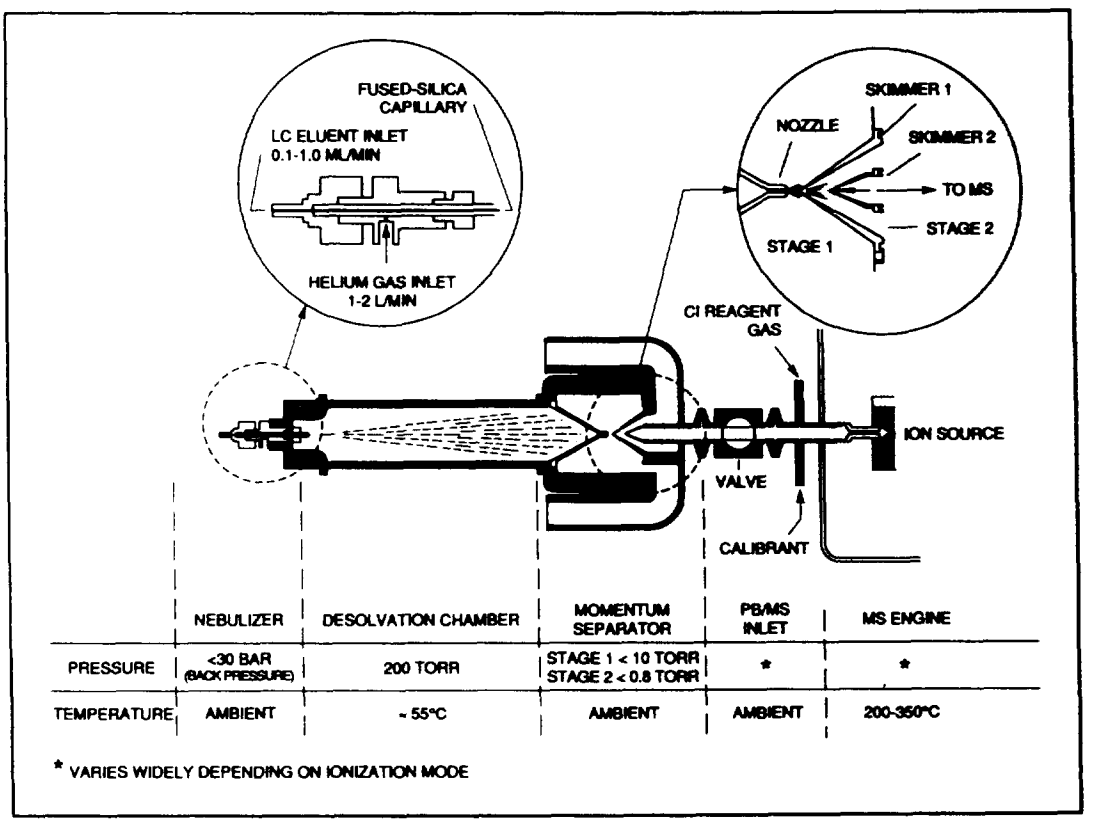


Fig. 3. Schematic diagram of a particle beam interface (Hewlett-Packard 59980B).

the effluent, mainly the solvent, evaporates from the aerosol droplets; this evaporation is supported by heating the desolvation chamber (the pressure allowing heat exchange with the droplets). The aerosol is then forced through a nozzle, into a second vacuum chamber (at about 10 Torr). Both the dimension of the nozzle and the pressure drop result in a supersonic expansion, which is characterised by a laminar flow pattern in which relatively heavy particles move preferentially near the axis. These heavy particles contain more of the analyte than the lighter particles and an enrichment is effected by selectively cutting off the centre of the flow pattern with the help of a skimmer. Another skimmer is used to increase the efficiency of the momentum separation and the resulting particle beam is then led through another vacuum chamber (pressure about 1 Torr) into the mass spectrometer ion source. Inside the source, collision with the source wall breaks up the non-covalent bonds in the particles and the resulting single molecules can be ionised.

The flow-rates that can be accommodated by the PB interface are generally compatible with conventional-size LC; they are between 0.1 and 1.0 ml/min [13], with the maximum attainable flow-rate being lower for higher eluent water content. The limiting values are the result of the flow-rates required to form a stable liquid jet, on both extremes of the flow-rate regime, and the limited capacity to desolvate the aerosol, in the high-flow region. LC–PB-MS mostly yields relevant structural information from the generated EI spectra. The technique is also well suited for thermolabile compounds, because the amount of heat applied during desolvation is usually limited; this even holds for the modified PB interfaces, the 'thermabeam' [40] and the 'universal interface' [41]. A principal advantage of PB over

all other LC–MS interfacing methods is that it can be coupled to any mass spectrometer, without (or with minor) modification.

Two closely related drawbacks of LC–PB-MS are the low sensitivity and the non-linearity of the response. The low sensitivity is due to the low analyte transmission efficiency of the interface [42], typically between 0.5 and 1%. The non-linearity of the signal intensity in LC–PB-MS at low analyte concentrations was first reported by Bellar and co-workers [43]. This phenomenon has been the subject of detailed studies [42,44–46], but so far the results remain inconsistent. The analyte transmission efficiency and the non-linearity of the response are usually thought to be related to the efficiency of the formation of solid particles in the evaporation process [42,46], but there is no compelling evidence to support this. Compounds such as malic acid [47] and ammonium acetate [48] have been added to the LC eluent, to improve particle formation at low analyte concentrations; the rationalisation behind this approach is that a compound-specific or non-specific 'carrier effect' can be achieved. However, such enhancement is not always observed and it appears to differ for each analyte. As an alternative to solvent additives, glow discharge heating in the nebulisation stage of PB was recently tested for the improvement of the transport efficiency [49]. The effect of the discharge on sensitivity is comparable to that of the addition of ammonium acetate, but a combination of additive and glow discharge did not perform better than either of the two separate modifications. In view of the unresolved non-linearity of the response, it was proposed that a calibration method with co-eluting isotopically labelled internal standards is most reliable for real-world environmental samples [45,46].

In spite of the compatibility of PB-MS with conventional-size LC, some studies have recently been published on micro-LC–PB-MS [50,51]. The delivery of micro-LC flows as low as 1 μl/min to a PB interface prompted the development of a modified nebuliser, with the usual PB-MS capabilities at lower vacuum contamination rates [50]. A significant reduction in solvent consumption and better signal response for mobile phases with a higher water content were reported as advantages over 'conventional' PB systems.

The PB interface has also been coupled to an ion trap mass spectrometer (ITMS) [52] and to a magnetic sector instrument [11]. With the ITMS, a third-stage momentum separation was added to the interface to improve desolvation. Despite the fact that an ITMS generally suffers from space charging and ion–molecule reactions at pressures common to most other mass spectrometer sources, the instrument is attractive, because of the MS–MS options and the high sensitivity due to ion storage capabilities. The magnetic sector mass spectrometer was used to aid structural elucidation and confirm molecular formula by high-resolution EI data. The combination of PB and these types of mass spectrometer has not yet been systematically applied to pesticide analysis.

General acceptance of the PB interface in environmental analysis will require considerably improved detection limits; the present values, which typically are in the 10–500 ng range, are often not sufficient. A viable approach to overcome this problem for the analysis of water samples is to use on-line trace enrichment prior to the LC separation, with direct introduction of the LC column effluent into the PB interface (Fig. 4) [53]. As the on-line trace-enrichment

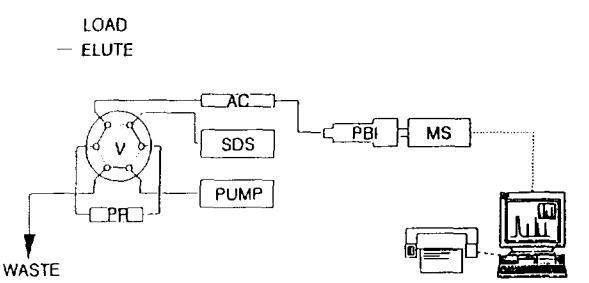


Fig. 4. Experimental set-up for on-line trace enrichment. PR = precolumn; V = six-port switching valve; PUMP = LC pump for delivering aqueous sample and conditioning precolumn; SDS = solvent delivery system of liquid chromatograph; AC = analytical column; PBI = particle beam interface; MS = quadrupole mass spectrometer; computer and printer. 100–250 ml water sample is first enriched on the precolumn packed with specific sorbent and next, after switching the six-port valve into ELUTE position, eluted onto the analytical column by the LC effluent gradient [53].

step is carried out in such a way that it is independent of the LC–MS interfacing, it can be used in essentially all LC–MS procedures involving the analysis of aqueous samples or sample extracts.

Recently, a general review on LC–PB-MS, covering instrumentation, studies on the PB mechanism and selected applications, was published by Creaser and Stygall [13].

2.3. Atmospheric pressure ionisation

In the field of LC–MS coupling, there is much current interest in the use of atmospheric pressure ionisation (API) methods [15,16,54,55]. In an API-MS system (Fig. 5, also see Fig. 7 and 8 below), the ion source region (located outside the mass spectrometer, at ambient pressure) is separated from the high-vacuum mass analyzer region by a small ion sampling orifice. This orifice must be large enough to permit the introduction of a significant proportion of the ions from the atmospheric pressure region into the high-vacuum region. The LC column effluent is sprayed in the vicinity of the orifice, so that free-jet expansion and concomitant adiabatic cooling occur. The formation of a spray is effected by applying heat, a coaxial nebuliser gas stream, an electrostatic potential, ultrasonic vibration of the capillary, or a combination of these. The free-jet cooling contributes to the formation of large clusters of analyte and solvent molecules, which are bound by Van der Waals forces. Desolvation of the clusters is effected by collisions; the collision rate is enhanced either by leading the ions through a gas curtain or by accelerating them through an electric field gradient. Ionisation is effected by applying a high voltage over the spray (electrospray, ESP) or by using a combination of a heated capillary and, e.g., a corona discharge (atmospheric pressure chemical ionisation, APCI). In ESP droplet formation and charging take place simultaneously, while in APCI droplets are formed prior to ionisation. Initially, the main distinction between ESP and APCI was in terms of the eluent flow-rates and the molecular mass ranges that can be handled: low flow-rates (up to 20 μl/min) and a high-molecular-mass range in ESP as compared to high flow-rates (up to 2 ml/min) and a low-molecular-mass range in APCI. Nowadays, ESP can be performed at higher flow-rates, by directing a gas flow into the effluent stream [56] (designated 'pneumatically assisted ESP', 'high-flow ESP' [57], or ionspray, ISP). The fact that also lower molecular mass compounds have already successfully been subjected to analysis by ESP/ISP makes the distinction between ESP/ISP and APCI less pronounced. Generally, all API techniques provide soft ionisation in which little structural information is directly obtained. However, the application of an appropriate voltage difference between two regions of an API source generally induces fragmentation of the primarily formed ions; this mode of operation is termed pre-analyzer CID or cone voltage fragmentation (CVF). A typical example of enhancement of structural information by changing the pre-analyzer CID voltage is shown in Fig. 6A and B.

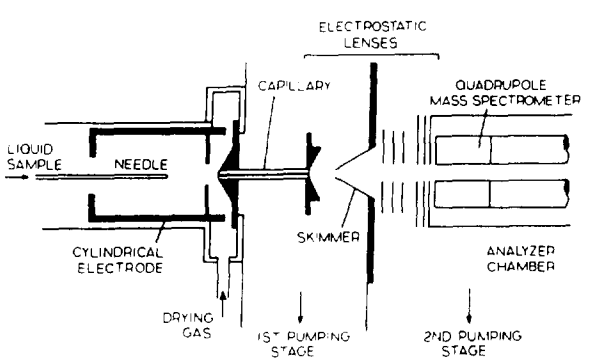


Fig. 5. Schematic diagram of the electrospray interface [58].

In a typical ESP experiment, for which the set-up is shown in Fig. 5, sample solutions enter the spray chamber at a flow-rate of 1–10 μl/min. The liquid is electrosprayed from the tip of a hypodermic needle and the droplets formed are further dispersed by means of a counter current stream of heated nitrogen gas of ca. 150 ml/min. The solvent vapour from the rapidly evaporating droplets is swept away by this so-called bath gas and the ions formed are transported through an orifice or a capillary into a first vacuum chamber, where a supersonic expansion occurs. The core of the expansion is sampled by a skimmer, kept

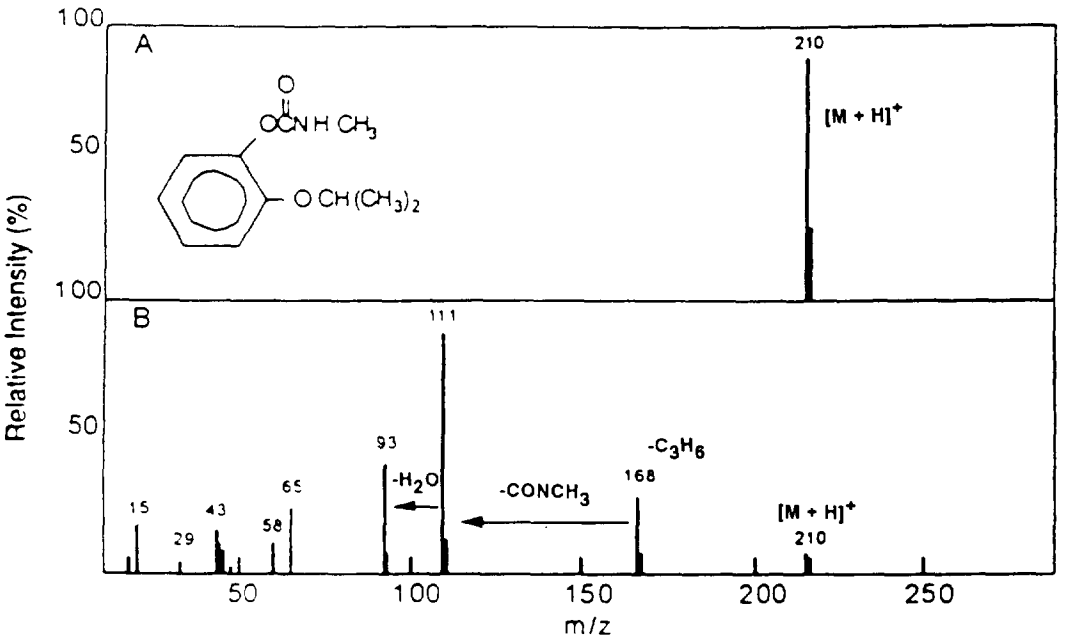


Fig. 6. ESP-MS spectra of propoxur at (A) capillary-skimmer potential difference of 25 V; (B) capillary-skimmer potential difference of 85 V. Spectra were obtained from 2 μg of propoxur in methanol–water at a flow-rate of 2 μl/min. (Adapted from Ref. [145].)

at about −20 V, and transported into the mass analyzer region [58]. Competition between the coulomb repulsion of the charged droplets and the surface tension of the liquid plays a major role in the formation of the ESP aerosol, but the actual mechanism of ESP ionisation is still a matter of discussion [6,59]. The major drawback of LC–ESP-MS is that the maximum allowable flow-rate is in the order of 10 μl/min, with lower flow-rates giving better performance. Regarding the compatibility with conventional size-LC, the ESP interface is often quoted to be a 'concentration-sensitive' device [60]. This would imply that splitting of the LC eluent flow will not cause a loss of sensitivity. Despite the fact that positive ion ESP has been used to study some low-molecular-mass compounds in environmental samples [61–63], only few pesticide studies have been conducted; even less data are available on negative ion ESP of low-molecular-mass compounds in general [62,64].

The ISP interface was originally introduced to enhance the ion evaporation of the ESP. The main advantage of the ISP interface, developed by Bruins et al. [56], over the ESP interface is the tolerance of higher flow-rates. In the ISP interface (Fig. 7), the electrospraying process is assisted by coaxial pneumatic nebulisation of the LC column effluent. ISP has even been coupled successfully to a benchtop-size mass spectrometer [65]. Flow-rates of 40–50 μl/min, which are compatible with 1 mm I.D. LC columns, can be accommodated. ISP shows improved performance over TSP with thermolabile ionic compounds, because ISP operates at room temperature, while heat has to be applied with TSP. The introduction of a 'liquid shield' device, which protects the ion sampling orifice region of the system from droplets formed in the spray process, and heating of the capillary interface allow the use of conventional LC flow-rates of 1–2 ml/min [66].

As the name suggests, APCI involves gas-phase ion–molecule reactions, which cause the

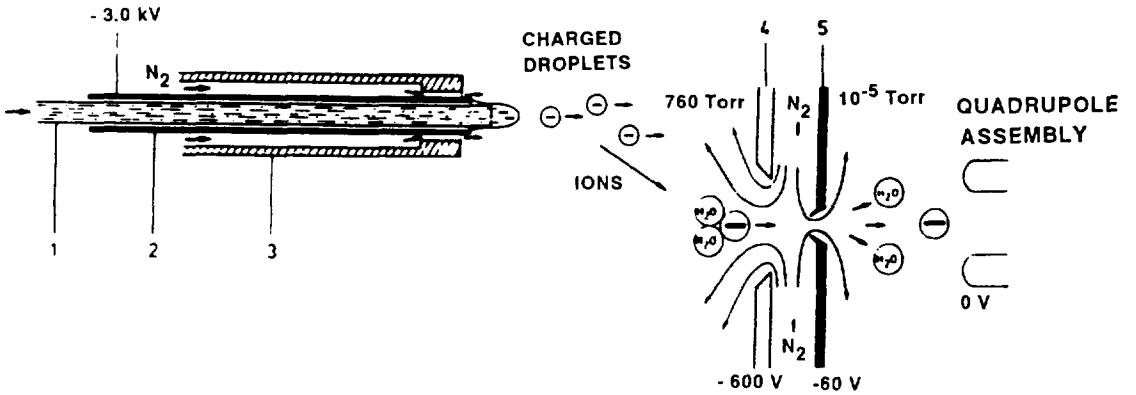


Fig. 7. Schematic diagram of (left) ionspray (ISP) interface and (right) atmospheric pressure ion (API) source (not drawn to scale) with nitrogen gas curtain: 1 = 50 μm I.D. fused-silica capillary; 2 = 0.20 mm I.D. stainless-steel capillary; 3 = 0.8 mm I.D. Teflon tube with narrow bore insert; 4 = ion focusing lens, serving as counter electrode for ion spray; 5 = orifice holding plate with 100 μm I.D. conical orifice [56].

ionisation of analyte molecules under atmospheric pressure conditions. In APCI, both heat and pneumatic nebulisation are applied to evaporate the sample solution and to obtain an effluent spray (Fig. 8) [67]. Under these conditions, reversed-phase LC eluent flows of 0.1–2.0 ml/min can be handled. Reactant ion formation is achieved by the introduction of electrons, either from a corona discharge or from a ^{63}Ni foil. The discharge, established at the tip of a needle which is held at a high voltage (3–6 kV), is routinely used in combination with heated pneumatic nebulisation. In analogy to TSP, ion evaporation can potentially also contribute to reactant ion formation. Both electron mediated ionisation and ion evaporation are very mild ionisation processes which readily provide unfragmented quasi-molecular ions. The molecular mass information and the information obtained from pre-analyzer CID make it possible to use APCI-MS for identification purposes.

In the last few years, API-based methods have been further developed. APCI has been interfaced to MS–MS for the study of complex solids with a pyrolysis module [68,69]. Although API-MS was first developed with quadrupole mass spectrometers, it has now successfully been coupled to an ion trap mass spectrometer [70] and to

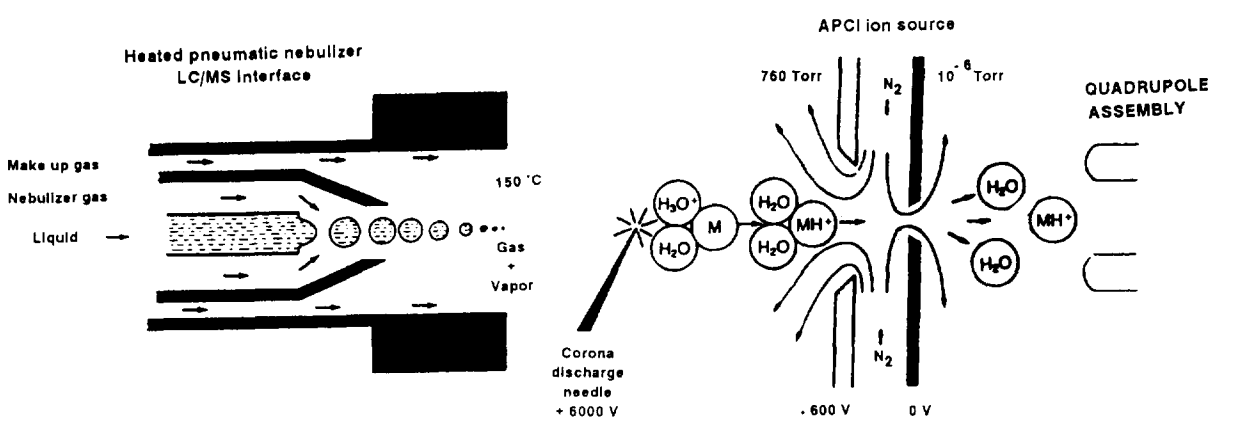


Fig. 8. Schematic diagram of a heated pneumatic nebuliser (APCI) interface [3].

a magnetic sector instrument [71,72]. An atmospheric pressure radio frequency plasma source, which operates with a variety of buffer gases, has been developed as an ionisation method for organic samples introduced into an API-MS instrument by liquid injection [73] and, finally, microwave sources have been used to ionise organic molecules at atmospheric pressure [74].

3. Applications

3.1. Thermospray interface

Nowadays, TSP is the interface most frequently used in LC–MS of pesticides. This is due to its applicability to a wide range of compounds, its compatibility with most MS systems and its ruggedness. Selectivity enhancement has been achieved by adding volatile buffers, organic salts and halogenated organic modifiers to the LC eluent and by using normal-phase LC and post-column extraction. The identification potential has been improved by using TSP-MS–MS. More attention is devoted to overall method development, and to attempts to automate the system and increase the sample throughput.

A wide range of pesticides has already been analyzed using LC–TSP-MS. In general, when using ammonium acetate as an additive with reversed-phase LC, positive ionisation (PI) typically causes protonation (giving $[M + H]^+$ ions) and ammonium adduct formation (giving $[M + NH_4]^+$ ions), while negative ionisation (NI) causes deprotonation (leading to $[M - H]^-$ ions), anion attachment (resulting, e.g., in $[M + MeCO_2]^-$ ions) and electron capture (yielding $[M]^{-\cdot}$ ions). Occasionally, the primary ionisation process leads to fragment ion formation, mostly through the loss of a functional group.

Barceló et al. [75–79] reported on studies of organophosphorus insecticides, chlorophenols, triazines, phenylureas, phenoxyacetic acids and carbamates. A variety of experimental conditions, e.g., employing different solvents, was used to obtain optimal detection. It was found that most of the pesticides investigated can be analyzed straightforwardly by TSP. The selectivity of TSP using NI was demonstrated for several chlorophenols, which show no response in the PI mode (Fig. 9). In general, signal intensities in the PI mode were about three orders of magnitude higher than those in the NI mode; the lowest detectable amounts ranged from 5 to 50 ng.

It has been shown by Voyksner et al. [80] that deterioration of the LC separation of several carbamate and phenylurea compounds by the TSP buffer salt could be prevented by post-column addition of the salt. Employing this, lowest detectable amounts in the PI mode varied from 1 ng for carbofuran to 80 ng for diuron; in the NI mode the sensitivity was 4–5 orders of magnitude lower. Acetic acid (0.1 *M*) was used for eluent acidification in the analysis of several sulfonylureas [81]. As the acidification resulted in a loss of sensitivity, the eluent was neutralised by post-column addition of ammonium hydroxide; this conveniently supplied the ammonium acetate needed for TSP ionisation. The sulfonylurea pesticides were determined in crops at the 50 μg/kg level, using selected ion monitoring (SIM) for quantification [82].

Carbamates, phenoxyacetic acids, chlorinated aliphatic acids, phenylurea herbicides and oxime fungicides were determined in environmental samples with TSP after off-line preconcentration [83]. Concentration was carried out by means of liquid–liquid or liquid–solid extraction for soil and water samples, respectively. The compounds were then separated by gradient elution, with ammonium acetate present in the LC eluent. Under full-scan conditions, the various compounds could be detected in liquid samples at the 0.1–1 μg/l level, with estimated detection limits in the 10 ng/l range. Chlorine-containing analytes, such as carbaryl and linuron, were determined in the NI mode.

Ammonium formate is sometimes preferred as an additive, in order to obtain structural information or to increase the scan range at the low mass end. A thorough study on the applicability of various additives in LC–TSP-MS was carried out by Voyksner and Haney [84]. Ammonium acetate gave the best sensitivity, with detection limits of 20–60 ng for triazines

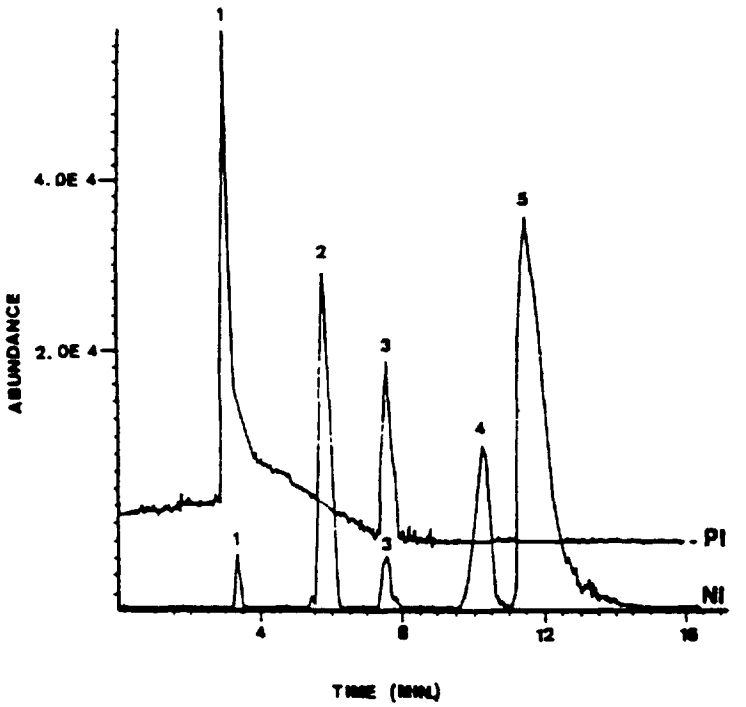


Fig. 9. Reconstructed ion chromatograms from LC–TSP-PI-MS (PI) and LC–TSP-NI-MS (NI) for sample mixture consisting of: 1 = cyanazine; 2 = 2,4-dichlorophenol; 3 = linuron; 4 = 2,4,5-trichlorophenol; 5 = pentachlorophenol. Injection of each component, 100 ng (except compound 5, 300 ng). Carrier stream: methanol–water (70:30) with the addition of 0.1 *M* ammonium acetate and 0.2% acetic acid. Flow-rate; 1.2 ml/min [79].

and 30–300 ng for organophosphorus insecticides. In addition, the adduct ions generated with ammonium formate, from triazines, phenylureas, chlorinated phenoxyacetic acids [85] and carbamates [86], provide complementary structural information which enables unambiguous molecular mass assignment for unknown pesticides. Detection limits (using SIM) for simazine, atrazine and propazine were 5 μg/l while carbamates could be detected at the 50 μg/l level, under full-scan conditions.

The advantage of solvent (i.e., chloroacetonitrile) adduct ion formation was demonstrated for phenoxyacetic acid herbicides [87] and chlorophenols [88] in the NI mode. The addition of 2% chloroacetonitrile to reversed-phase eluents resulted in an $[M + Cl]^-$ base peak, thereby demonstrating abundant chloride attachment. Instrument detection limits for the chlorophenols used as test compounds, in the filament on mode, were in the low ng range. The same authors [89] gave an overview of the use of ammonium formate or acetate, non-polar solvents, or chloroacetonitrile to obtain structural information from TSP mass spectra of a variety of carbamates, chlorinated phenoxyacetic acids, chlorotriazines, organophosphorus insecticides and phenylurea herbicides.

A systematic study of 27 carbamates and their degradation products by flow injection analysis (FIA)–TSP-MS was presented by Honing et al. [90]. It was observed that the addition of ammonium acetate, ammonium formate and nicotinic acid into the LC eluent suppresses fragmentation in spectra and favours adduct ion formation. This led to a, typically ten-fold, increase in sensitivity for PI detection of carbamates, whereas the 'non-carbamate-type' degradation products did not generate adduct ions. In terms of sensitivity, NI detection was found to be

less favourable for all carbamates studied. Thermal degradation of methiocarb and its sulphone were observed by varying the vaporiser temperature.

Effects of various additives in the LC eluent on the sensitivity and selectivity in LC–TSP-MS were studied in detail by Vreeken et al. [91], for 55 pesticides. The use of discharge ionisation was generally preferred over the filament-on mode or buffer ionisation, because of the lower detection limits and increasing structural information in the spectra obtained. Full-scan detection limits for 15 different classes of pesticides, were typically in the range of 20 to 200 ng (Table 1), except for anilines and quaternary ammonium compounds.

The potential of TSP with non-polar, normal-phase LC solvents (*n*-hexane, cyclohexane and dichloromethane) for the analysis of pesticides has been evaluated [92]. In the PI mode, detection limits improved about 10-fold for all test compounds when using a normal-phase instead of a reversed-phase eluent. In the NI mode both types of eluent showed the same sensitivity for several chlorophenols. Using full-scan TSP-MS, detection limits for nine most commonly used groups of pesticides varied between 1 and 200 ng in both PI and NI (Table 1). This is in line with the results of a study on the determination of phenoxyacetic acids and chlorotriazines using cyclohexane as an LC eluent [93]; here, good sensitivity was obtained in the PI mode.

LC separation methods using non-volatile buffers and ion-pair reagents, which can not be introduced into a TSP-MS, can be used if an on-line post-column extraction into a non-polar solvent is carried out, with subsequent phase separation in, e.g., a sandwich-type phase separator. In one study, the procedure was used to determine 2,4-D, 2,4,5-T and silvex in a spiked water sample from Barcelona harbour [92]. Segmented-flow extraction into *n*-heptane

Table 1
Calculated limits of detection (LODs)[a] for various groups of pesticides in LC–TSP-(full-scan)-MS

Class of pesticides	LOD (ng) in					
	PI			NI		
	>200	20–200	<20	>200	20–200	<20
N-substituted amides		+		+		
Anilines	+			+		
Carbamates		+			+	
Thiocarbamates	+					+
Hydroxy-keto-lactones		+				+
Miscellaneous compounds[b]	+				+	
Organophosphorus compounds		+				+
Phenols	+					+
Phenoxy and carboxylic acids	+					+
Pyridine-like compounds		+				+
Quaternary ammonium compounds	+			+		
Thiocyanates		+		+		
Triazines		+			+	
Phenylureas		+				+
Thioureas			+	+		

Carrier stream: water–acetonitrile (50:50, v/v) containing 50 m*M* ammonium acetate (PI) or 25 m*M* tripropylammonium formate (pH 7.5) (NI). Flow-rate, 1 ml/min. Discharge voltage, 1 kV. (Adapted from Ref. [91].)

[a] LOD = amount corresponding to an ion trace of 500 counts multiplied by 10 (in order to compensate additional peak broadening at the change from FIA–TSP-MS to LC–TSP-MS).

[b] Captan, fenaminosulf, sethoxydim, alloxydim and permethrin

was also applied for the LC–TSP-MS determination of organophosphorus insecticides, chlorophenols and phenoxyacetic acids; the organic phase was led through the sample loop of the injection valve of the LC system [94].

Ion-pair reversed-phase LC for the ionic compound difenzoquat and other quaternary ammonium pesticides was combined with post-column extraction (cf. Refs. [92,95]) and TSP-MS; a sulphonate-type counter ion allowed extraction of the analytes into the organic solvent. However, the high detection limits, typically 1–2 μg under full-scan conditions, indicate that the system cannot be used for environmental analysis without substantial improvement of the sensitivity.

Diquat and paraquat were studied by Yoshida et al. [96] who used reversed-phase LC with methanol–water containing 0.1 *M* ammonium acetate as the eluent and SIM; detection limits were about 20 ng. It should be noted that quaternary ammonium compounds are not easily identified as such and that the above LC–TSP-MS methods are applicable for target compound analysis only. Unequivocal identification of quaternary ammonium compounds can be performed by liquid secondary ion mass spectrometry (SIMS), on the basis of NI spectra and adduct ion formation with matrix additives [97]. Such 'MS-only' methods, i.e., without LC separation, may be of help in environmental LC–MS analysis.

An interesting aspect is the variation in mass spectral information obtained when using TSP interfaces from different manufacturers. It is shown [10] that e.g. the Hewlett Packard interface has a higher tendency to form acetate adduct ions than the Finnigan MAT (4500) interface, which appears to be better suited for electron-capture processes [23,88,98,99]. The use of filament off, filament on or discharge ionisation has only a slight influence on the abundance ratios of the quasi-molecular ions on the different instruments.

LC–TSP-MS is often used complementary to GC–MS for the identification or characterisation of degradation products of various pesticides. Barceló et al. [100] studied the photodegradation of fenitrothion and propazine under different photochemical conditions in distilled water, artificial sea water and methanol–water solutions. GC–MS allowed the off-line characterisation of the various photolysis products of fenitrothion. The combined data from LC–UV diode array detection and LC–TSP-MS permitted the identification of four photoalteration products of propazine in different types of water, using direct injection of the photodegradation solutions into the LC systems. The method is rather simple because there is no need for extraction prior to LC–MS characterisation of the breakdown products. The use of LC–TSP-MS, however, provides too little structural information, thus making identification difficult.

Betowski and Jones [26] compared GC–MS and LC–TSP-MS–MS methods for ten analytes from the US EPA, SW-846 Method 8140, Organophosphorus Pesticide Parameters. Limits of detection for the analysis of soil samples using TSP ionisation were quite good and generally better than those attained by GC–MS (Table 2). The degradation of naled to dichlorvos, observed with GC, did not occur with TSP introduction.

LC–TSP-MS was used in an interlaboratory study on the analysis of (nine) carbamate and phenylurea pesticides in the low mg/l range [101]. Results from nine participating laboratories showed an intralaboratory precision of LC–TSP-MS ranging from 6.5 to 33.1% relative standard deviation (R.S.D.), whereas those from the interlaboratory comparison ranged from 29.8 to 98.2% R.S.D. The authors mentioned the day-to-day variations of TSP spectra as the most important parameter responsible for the unsatisfactory results. No real environmental samples were used in the study. A similar validation of TSP-MS and PB-MS methods, is given in Ref. [102].

Niessen et al. [27] explored the possibility to detect and identify minor constituents in benzothiazole-derived compounds by various MS techniques, such as GC–MS, and LC–MS with a moving belt, TSP or PB interface, and LC–TSP-MS–MS. A diode array UV detector was used to trace the peaks. The results, which are summarised in Table 3, demonstrate that more than one

Table 2
Concentration of organophosphorus pesticides in several soil samples [26]

Sample	Compound	Quant. ion	Amount calculated [mg/kg]		LC–MS LOD[c]	GC–MS LOQ[d]
			LC–MS	GC–MS		
1	Disulfoton	275	4.41	0.75[a]	0.24	1.3
	Methyl parathion	281	ND[b]	1.10	7.1	2.0
	Phorate	261	4.80	ND[b]	0.47	1.3
2	Dimethoate	230	1740	144	0.82	9.4
	Phorate	261	66.9	54.3	0.82	3.4
	Disulfoton	89	26.8	4.85	0.41	3.4
	Methyl parathion	281	28 500	28 700	12	5.4
3	Disulfoton	275	98.8	110	0.79	9.3
	Phorate	261	44.7	19.0	1.6	9.3
4	Disulfoton	89	45.0	130	0.51	2.5
	Methyl parathion	281	115	150	15	4.5

[a] Value indicates detected but below limit of quantification (LOQ).
[b] Not detected.
[c] Limit of detection.
[d] Limit of quantitation.

MS technique should be used in identification problems.

The same group (cf. above) investigated the possibility of gaining additional structural information under LC–TSP-MS and SFC–TSP-MS conditions [22]. Using the phenylurea herbicide diuron as an example, it was shown that the repeller voltage may sometimes be used to obtain structure-specific fragmentation, unfortunately at the cost of sensitivity (Fig. 10). From the reported experiments it follows that the repeller voltage is a critical parameter in TSP-MS and that the optimum voltage is not the same for each analyte.

LC–FAB-MS and LC–TSP-MS techniques were used to identify metabolites from the in vitro metabolism of an experimental Monsanto chloroacetanilide herbicide [103]. Analysis by these techniques has several advantages: very little sample clean-up is needed and the individual analytes do not have to be isolated. Moreover, compounds such as acids can be

Table 3
Comparison of techniques used for analysis of benzothiazole-derived compounds[a] [27]

Technique	Compounds[b]			
	1 (polar, stable)	22 (polar, labile)	12 (non-polar, stable)	10 (non-polar, labile)
LC–PB-MS	+	−	+	+ −
LC–TSP-MS	+	+	−[c]	+
GC–MS	+		+	+

[a] + = Good signal; + − = reasonable; − = poor or no signal.
[b] 1 = 2(3H)-Benzothiazolethione; 22 = 4-(2-benzothiazolylsulphonyl)morpholine; 12 = sulphur; 10 = 2,2′-dithiobisbenzothiazole.
[c] Sulphur is not sensitive to TSP ionization owing to insufficient proton affinity.

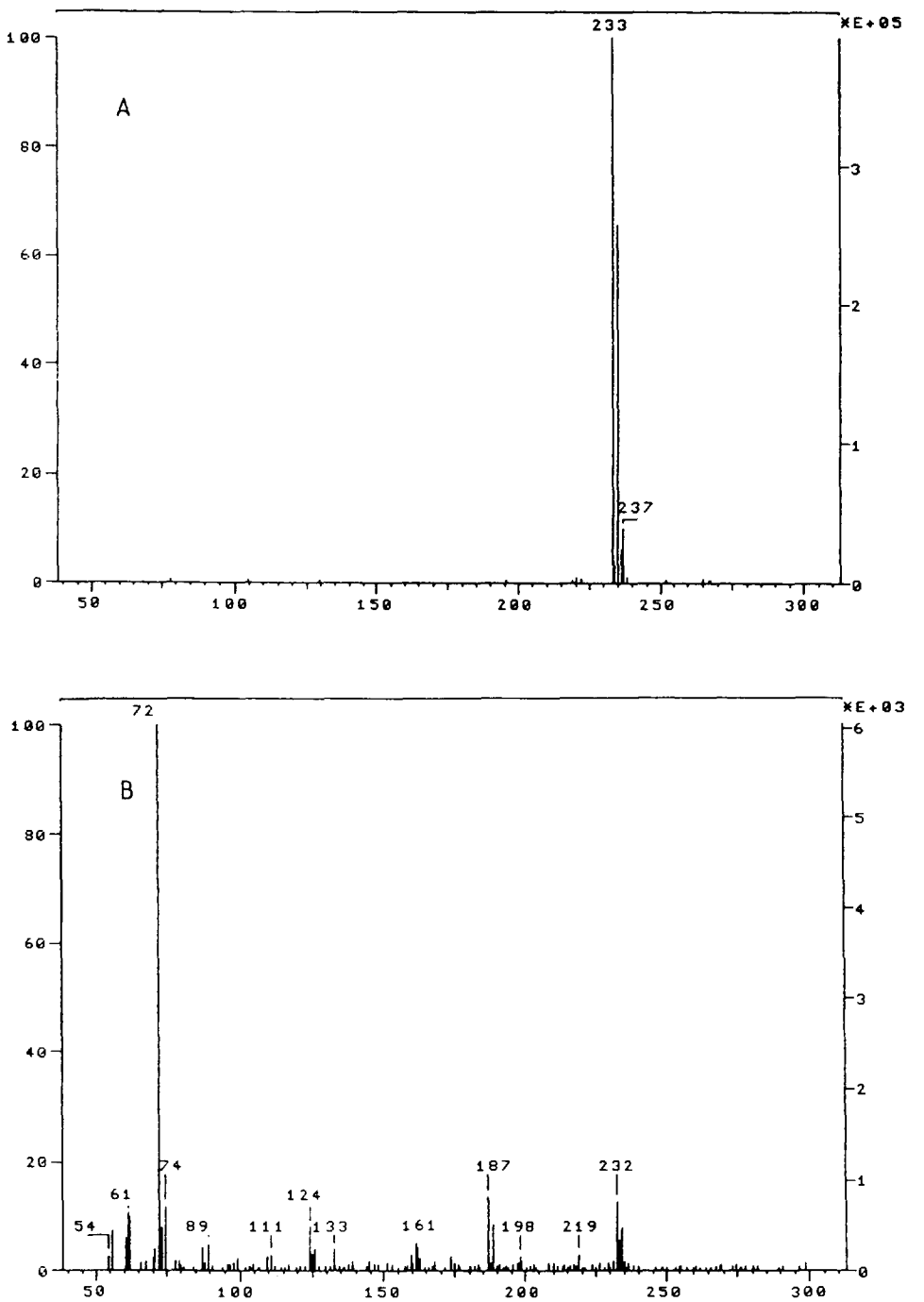


Fig. 10. TSP mass spectra of diuron at (A) low (20 V) and (B) high (180 V) repeller voltages. (Adapted from Ref. [22].)

analyzed directly, i.e., without derivatization. LC–FAB-MS yielded better results for the polar, and LC–TSP-MS for the less polar metabolites.

3.2. On-line and off-line trace enrichment

After initial studies, such as those discussed above, had shown the potential and limitations of LC–TSP-MS, it became clear that sample preconcentration and clean-up are necessary to reach the low detection limits required in environmental analysis. Interest expanded from studying MS processes to the total analytical approach.

Bellar and Budde explored the potential of off-line extraction and concentration techniques for the development of a broad-spectrum method for the determination of non-volatile target compounds in aqueous environmental samples [104]. They used liquid–liquid and liquid–solid extraction and subsequent gradient LC separation for samples spiked with carbamate, triazine, sulfonylurea, phenylurea and organophosphorus compounds. With the liquid–liquid preconcentration procedure, applied to pesticide levels of 2–50 μg/l, detection limits for 34 analytes varied from 0.2 μg/l for cyanazine to 18 μg/l for linuron in the filament-off, PI mode. Detection limits obtained using liquid–solid extraction, applied to pesticide levels of 20–500 μg/l, were approximately 10 times higher. The higher pesticide levels in the primary sample were necessary because of the small size and limited capacity of the extraction cartridges used in this study. Combination of retention time data, molecular mass information from the $[M + H]^+$ and $[M + NH_4]^+$ ions, evidence from isotope patterns, and occasional fragment ions, provided satisfactory information for the identification of target analytes without a large risk of false positives. Using a similar method for the determination of 20 carbamate and phenylurea pesticides in crops, SIM detection limits in the PI mode ranged from 250 μg/kg to 1 mg/kg [105,106].

Off-line solid-phase extraction was used for the concentration of 1 l river water samples to 1 ml methanol extracts [34]. Injection of 20 μl aliquots enabled the detection of several triazine and phenylurea pesticides at the 5 μg/l level with a double-focusing magnetic sector instrument, under full-scan conditions. A dichloromethane extract of a river water sample was used to provide confirmation of the identity of an alledged pollutant, isoproturon.

Volmer et al. [107] used off-line SPE and LC–TSP-MS, for the determination of pesticides in water samples. From a selection of 128 environmental pollutants, 95 compounds could be detected at the 0.1 μg/l level by using 1 l samples, gradient elution, post-column addition of the TSP buffer and PI time-scheduled SIM detection. The reproducibility of the LC–TSP-MS procedure was within 12% over a day. However, the long-term reproducibility generally was above 20%; besides the long-term variation in TSP sensitivity remains a problem. In addition, an elegant method for the confirmation of analytes was presented, in which post-column addition is applied to change the TSP reagent conditions; reactive ions with widely differing proton affinity were generated to induce or suppress molecular adduct ion formation.

Off-line trace enrichment on C_{18}-bonded silica or ion-exchange sorbents was used prior to LC–TSP-MS, for the analysis of atrazine and its metabolites in water [108]. LC–TSP-MS was applicable to both chlorotriazine and hydroxytriazine metabolites; the limits of detection were as good as those of conventional LC–UV diode array detection (ca. 1 ng). The authors also studied supercritical fluid chromatography (SFC) with ESP detection; a large advantage of SFC–ESP-MS is the short time of analysis (< 3 min) [108]. SFC–ESP-MS provided more than 10-fold better sensitivity (25 pg injected) than TSP, but only for the less polar chlorotriazine compounds.

A simple liquid–liquid extraction procedure has been applied prior to LC–TSP-MS to determine two sulfonylurea herbicides and a major metabolite of each of these in soil [109]. The method requires minimal sample preparation and enables the simultaneous analysis of four compounds down to the 20 μg/l level.

On-line trace enrichment prior to LC–TSP-MS was found to yield extremely low detection limits for phenylurea herbicides in surface and drinking

water as shown by Bagheri et al. [110]. After trapping the analytes from a 50-ml sample on a precolumn, packed with a styrene–divinylbenzene copolymer or on membrane extraction disks, desorption was effected in the backflush mode with methanol–0.1 *M* aqueous ammonium acetate (40:60, v/v) and the analytes were transferred on-line to a C_{18} analytical column for LC gradient separation. Using discharge ionisation PI detection, all phenylureas tested generated $[M+H]^+$ as the base peak, with $[M+NH_4]^+$ observed in some cases. In order to enhance selectivity and sensitivity, the chromatograms were recorded under time-scheduled SIM conditions. In river Rhine water samples spiked with a mixture of 15 phenylureas at levels ranging from 0.05 to 10 μg/l, detection limits for all compounds except linuron (60 ng/l) and chlorobromuron (120 ng/l) were found to be 5–15 ng/l. With this system, the presence of monuron and isoproturon at low ng/l levels in river Rhine water was confirmed.

The same system was used for the detection of 39 carbamate, triazine, phenylurea and organophosphorus pesticides [111]. Trace enrichment was carried out on precolumns packed with C_{18}-bonded silica. With 50 ml water samples detection limits for the solutes typically were in the 2–90 ng/l range using time-scheduled SIM (Fig. 11). Low levels (0.005–2 μg/l) of simazine, atrazine, isoproturon and diuron were detected in three European rivers, Amsterdam drinking water and even in HPLC-grade water (Fig. 12, Table 4). A similar method was used by Chiron et al. [112] for the determination of 30 pesticides and various degradation products. Nine carbamates, triazines and anilides were found in surface and ground water samples at the 0.01–

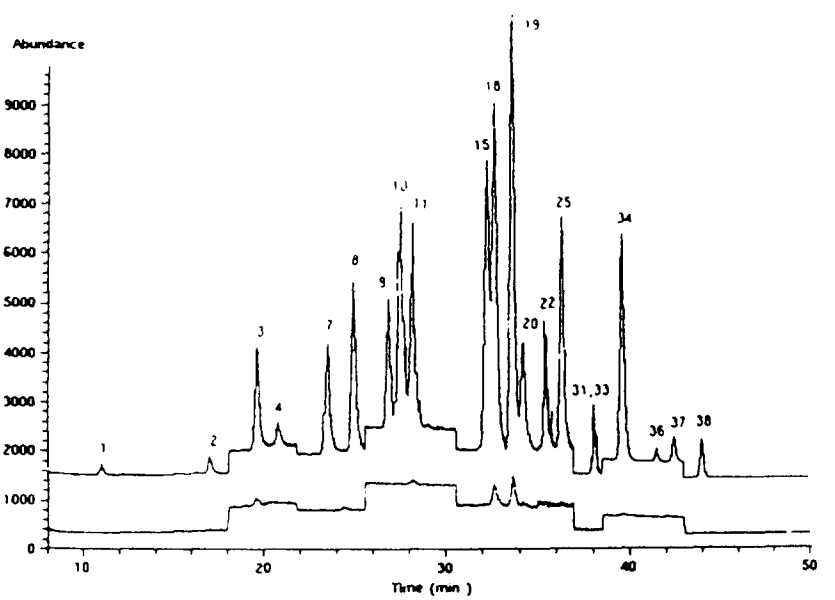


Fig. 11. LC–TSP-MS chromatogram recorded after on-line trace-enrichment of 50 ml river Rhine water (bottom) and river Rhine water spiked with a mixture of 21 polar pesticides at 1 μg/l (top). Column: 250 mm × 4.6 mm I.D. stainless-steel containing 5 μm C_{18}-bonded silica. Eluent: linear gradient of methanol–0.1 *M* ammonium acetate [10:90 to 90:10 (v/v) in 45 min]. MS: discharge PI mode, time-scheduled SIM. Compounds: 1 = aldicarb sulfone; 2 = 1-(3-chloro-4-hydroxy-phenyl)-3,3-dimethylurea; 3 = dimethoate; 4 = desmethylmetoxuron; 7 = monomethylmetoxuron; 8 = metoxuron; 9 = cyanazine; 10 = monuron; 11 = simazine; 15 = atraton; 18 = atrazine; 19 = isoproturon; 20 = diuron; 22 = azinphos-methyl; 25 = propazine; 31 = malathion; 33 = trietazine; 34 = prometryn; 36 = parathion-ethyl; 37 = diazinon; 38 = disulfoton [111].

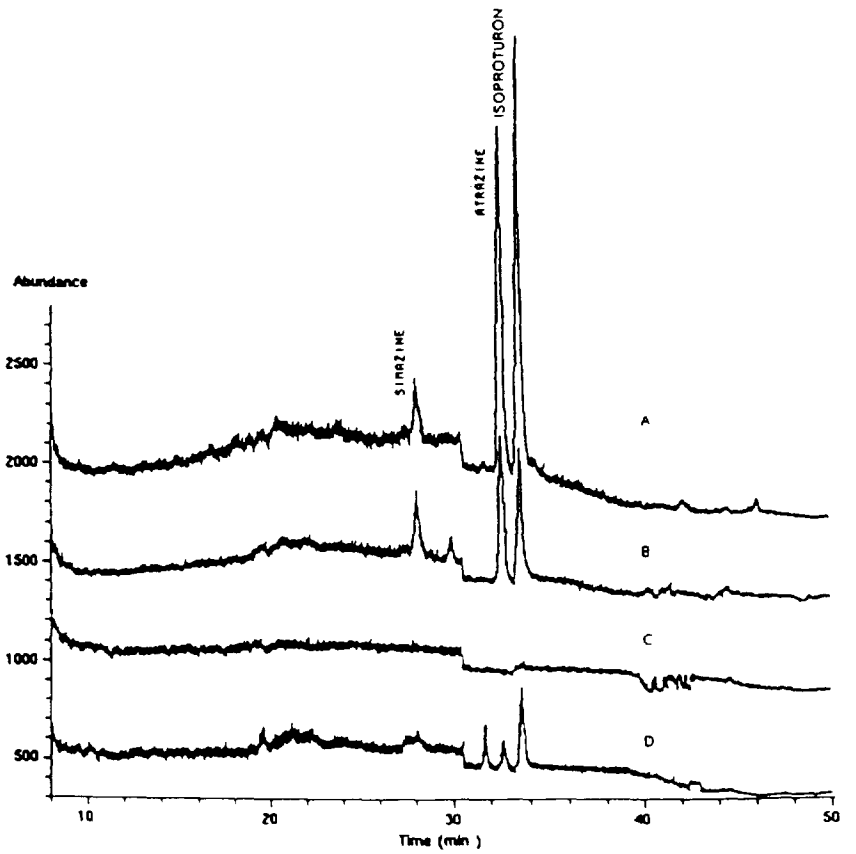


Fig. 12. On-line trace-enrichment LC–TSP-MS trace for 200 ml of (A) Rhine water, (B) Amsterdam drinking water, (C) blank without preconcentration and (D) HPLC-grade water. Column: 250 mm × 4.6 mm I.D. stainless-steel containing 5 μm C_{18}-bonded silica; eluent, linear methanol–0.1 *M* ammonium acetate gradient [10:90 to 90:10 (v/v) in 45 min]; MS, discharge PI mode, time-scheduled SIM [111].

Table 4
Pesticides detected in drinking and surface waters by on-line trace-enrichment LC–TSP-MS [111]

Water source[a]	Concentration (μg/l)			
	Simazine	Atrazine	Isoproturon	Diuron
Amsterdam drinking water	0.015	0.025	0.015	–
River Rhine	0.030	0.070	0.065	0.030
River Mersey	3.2	0.9	–	2.1
River Meuse	1.2	1.0	0.070	2.0
HPLC-grade water	–	<0.006	<0.007	–

[a] Sample volume, 200 ml.

0.5 μg/l level. The automation of such systems has meanwhile been accomplished, although with a PB interface [113].

Similarly low detection limits, 0.02 mg/l, were obtained in the determination of the total content of the fungicides carbendazim, benomyl and thiophanate-methyl in water, using a column-switching LC–TSP-MS [114]. The latter two analytes were quantitatively converted into carbendazim and an aliquot of 10 ml of the reaction mixture was injected into the analytical system. Because the conversion makes the compounds indistinguishable, the detection limit is expressed as the carbendazim equivalent. The analyte detectability was poorer when the compounds were analyzed by LC–PB-MS.

Both on-line and off-line SPE coupled with LC–TSP-MS were used for environmental monitoring of a series of nitrogen- and phosphorus-containing pesticides [115]. SIM detection limits for 51 selected compounds varied between 40–600 pg injected on-column, which is equivalent to less than 100 ng/l in drinking water. In addition, structure–spectrum relations were investigated by means of APCI, ESP, fast atom bombardment (FAB), ^{252}Cf plasma desorption and CID for several pesticides. As an example, the spectra of butachlor, obtained with each of these techniques, are presented in Fig. 13. Source and vaporiser temperature inducing thermal degradation, and post-column on-line derivatisation carried out by adding various alkylated amines to the LC eluent, were used to enhance the structure and molecular mass information from the TSP spectra.

One should note that the LC part of the system can be replaced by a simple FIA set-up, when neither analyte concentration nor separation is required. A fully-automated FIA–TSP-MS set-up [116] was used for structural confirmation of thousands of new agricultural chemicals. Switching the mass analyzer's polarity between subsequent mass scans, an interesting feature of the particular MS system used, was utilised to obtain PI and NI TSP spectra for each injected compound within one chromatographic peak. Control of sample delivery, data acquisition and data output by a central computer was essential for consistency with Good Laboratory Practice; the system may well become a new trend in the routine use of TSP-MS.

3.3. Tandem MS and related techniques

Another aspect that has rapidly gained interest, is the coupling of a TSP interface with tandem MS, with the goal of obtaining relevant structural information [23,24,30–32].

Abián et al. [23] applied PI- and NI-mode detection in LC–TSP-MS and LC–TSP-MS–MS for the identification of atrazine, simazine, cyanazine, desethylatrazine, hydroxyatrazine, and chlorodiamino-*s*-triazine. Detection limits in the SIM mode were below 400 pg; CID of $[M+H]^+$ ions, combined with daughter ion scans or neutral loss scans of m/z 42 (C_3H_6) often provided higher detection limits (Table 5). It is noted here that MS–MS methods generally cause detection limits to become less favourable due to the ion intensity loss in the collision process. However, the intensity loss is often compensated for by the gain in selectivity and, thus, a better signal-to-noise ratio. It should be added that proper use of the technique requires optimisation of the collision energy, collision gas pressure, and quadrupole off-set correction parameter for each of the analytes studied.

More recently, the same authors investigated some ions of hitherto unknown origin, commonly observed in the TSP background spectrum [117]. Among other methods, TSP-MS–MS led to the identification of contaminants, e.g. acetamide, in the widely used ammonium acetate and formate eluent additives. These contaminants, which result from specific production processes, can be removed by washing the additive salt with chloroform.

LC–TSP-tandem MS was used by Kienhuis for the screening of 20 pesticides [32]. Because of the difficulties encountered when using the MS–MS in the usual daughter, parent or neutral loss scan mode, a radio frequency-only daughter scan mode (RFD) was used in order to obtain more spectral information for the analytes studied. In the RFD scan mode the first quadrupole is operating as a high-pass mass filter, i.e., only

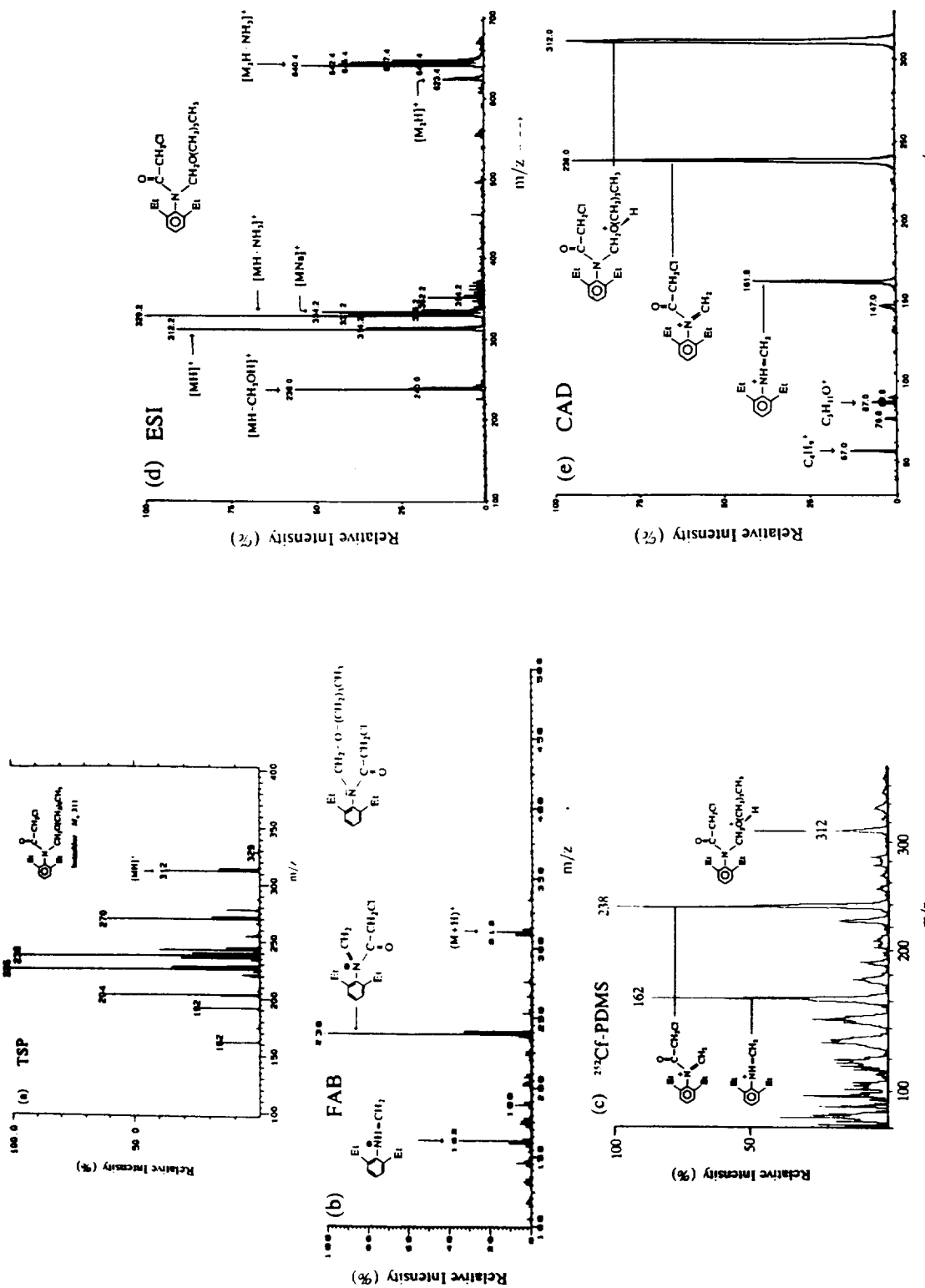


Fig. 13. Mass spectra of butachlor obtained by various ionisation techniques: (a) discharge-assisted thermospray, (b) FAB; (c) ^{252}Cf plasma desorption; (d) electrospray; (e) collision-induced dissociation. (Adapted from Ref. [115].)

Table 5
Detection limits (ng) for triazine standards in the various TSP-MS–MS acquisition modes (adapted from Ref. [23])

Acquisition mode	Compounds studied[a]						
	CAAT	DIAT	HYAT	DEAT	CYAN	SIMAZ	ATRAZ
SIM[b]	0.4	0.4	2	0.4	0.4	0.4	0.4
DAU[c] (SRM)[d]	0.4	4	4	0.4	4	4	0.4
	(146–43)	(174–132)	(198–156)	(188–146)	(241–214)	(202–132)	(216–174)
NL[c] 42[e]	4	4	4	4	ND	ND	4
NL[c] 28[e]	ND	40	ND	ND	ND	40	ND
NL[c] 42 (SRM)[f]	4	4	0.4	0.4	ND	ND	0.4

[a] CAAT = chlorodiamino-*s*-triazine; DIAT = deisopropylatrazine; HYAT = hydroxyatrazine; DEAT = desethylatrazine; CYAN = cyanazine; SIMAZ = simazine; ATRAZ = atrazine. Detection limits (ng) calculated from the corresponding ion chromatograms.
[b] Selected ion monitoring, alternate and continuous monitoring of the seven $[M + H]^+$ ions.
[c] DAU, daughter ion scan mode; NL, neutral loss scan mode.
[d] Transition for selected reaction monitoring, alternate and continuous monitoring of the seven indicated transitions.
[e] Acquisition in the scan range (Q1) 100–250 amu, 1 scan/s.
[f] Q1 focuses alternatively and continuously on the seven $[M + H]^+$ ions.

ions with masses equal to or above the arbitrarily selected cut-off mass will enter the collision cell. When using the cut-off mass, low mass signals due to CID of analytes become visible in a region of the mass spectrum which would otherwise be dominated by the solvent. The third quadrupole acts as a mass analyzer in the full-scan mode. By using two or three different alternating collision off-set voltages during one analysis, both molecular and daughter ions were acquired. By combining the diagnostic ions with different m/z values at both collision offset voltages, at least four ions, with an intensity of more than 10% of the base peak at each voltage, are available for 16 of the 20 compounds; no adduct ions were observed. Analyte detectability was at least as good as that obtained in the single-stage triple quadrupole MS scan mode. An off-line trace enrichment procedure with a carbon phase, followed by an LC separation, was used for the determination of ten pesticides. Using 500 ml spiked river Rhine water samples, 1 μg/l of each analyte could be detected.

Selectivity for characteristic ions of analytes is the main advantage of tandem MS. In some cases direct-introduction MS–MS, without any separation, may be used for pesticide analysis. In the work of Chiu et al. [30] structure-specific fragmentation in the triple-stage quadrupole CID spectra of eight carbamates was used for the rapid screening of a carbamate mixture without the need for chromatographic separation (Fig. 14). Relevant data for all carbamates are tabulated in Table 6.

A method for the rapid screening of water samples for eight phenoxyacetic acids and bentazone with FIA–TSP-MS–MS has been reported [31]. The analytes were introduced continuously into the system under NI conditions and two parent ion–daughter ion pairs were monitored for each analyte (one parent ion and three daughter ions for bentazone). An eluent of 0.1 *M* ammonium acetate–acetonitrile (90:10, v/v) was found to be the optimum carrier stream. Without sample concentration all compounds could be detected at the 1 μg/l level, using time-scheduled selected reaction monitoring. Using a 5-ml loop injection, the total time of analysis was only 10 min.

The dependence of the ion abundances in the TSP mass spectra on the vaporiser and gas-phase temperatures under CID conditions has been studied for anilides, carbamates, N-heterocycles, organophosphorus and phenylurea compounds [24]. In this study, 0.6 ml/min of a 150-m*M* buffer solution was added post-column to the LC

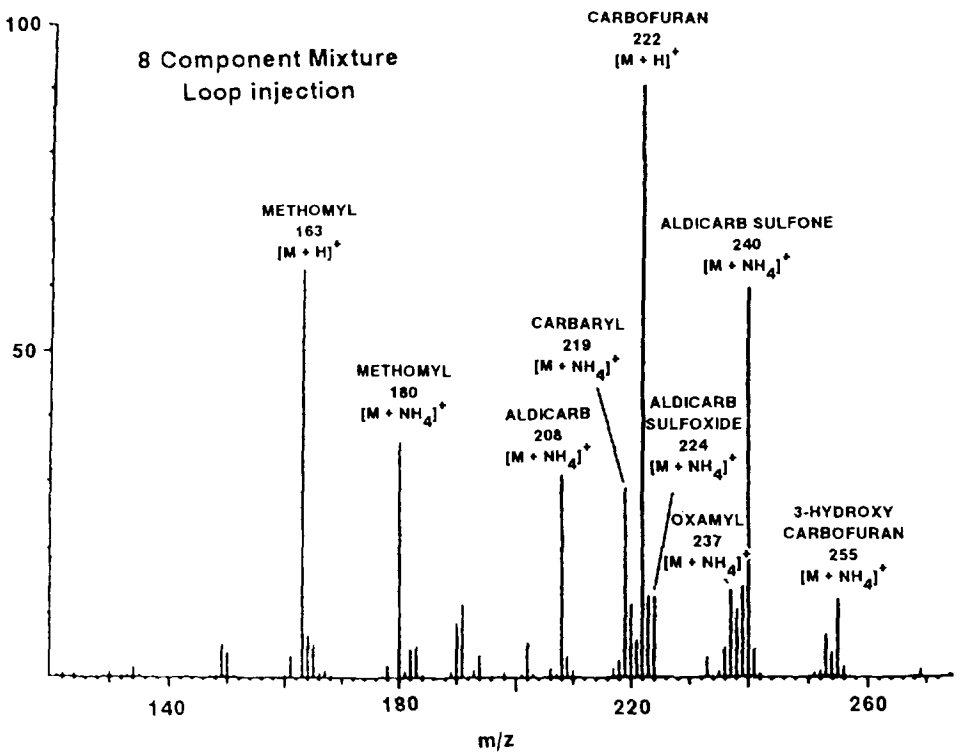


Fig. 14. Mass spectrum of the eight-component mixture obtained by FIA–TSP-MS–MS. Ions chosen for CID and related major daughter ions are reported in Table 6 [30].

eluent, which resulted in a final flow of 1.2 ml/min entering the TSP interface. A constant amount of added salt makes the limits of detection virtually independent of the gradient composition. A high water content was found to significantly improve the TSP sensitivity. For most of the analytes a linear relationship was found between the logarithm of the abundance ratio of the $[M + H]^+$ and $[M + NH_4]^+$ ions and the reciprocal of the absolute temperature of the gas phase (range: 150–320°C). This may be of some value for SIM experiments because the total ion current (i.e., the sum of the $[M + H]^+$ and $[M + NH_4]^+$ ions) is less dependent on the gas-phase temperature than the ion currents of the individual quasi-molecular ions. Fragmentation is enhanced at higher salt concentration, but this disadvantage is outweighed by the strong increase in sensitivity, as was demonstrated for paraquat. For asulam, additional structural information was obtained by applying CID (Fig. 15). No detection limits were reported.

Draper et al. [25] studied phenols and the corresponding glucuronide and sulphate conjugates by LC–TSP-MS–MS, using NI detection. Nine model compounds were baseline-separated on a strong anion-exchange LC column using an aqueous ammonium formate–acetonitrile eluent. The use of a strong anion exchanger for the separation of the metabolite conjugates, proved compatible with TSP-MS. Under CID conditions the aryl sulphates fragmented efficiently to phenols which were then detected as phenolate ions.

Coupling of a TSP interface to a magnetic sector MS [33] provides an interesting alternative to enhance the identification potential. With current data systems, an exact mass can be determined from a dynamic experiment where the analyte is introduced together with a refer-

Table 6
Daughter ion spectra obtained from eight-component carbamate mixture by FIA–TSP-MS–MS screening analysis [30]

Compound	Peak	Ion chosen for induced dissociation (m/z)	Daughter ion spectrum	
			m/z	Abundance (%)
Methomyl	$[M + H]^+$	163	106	100
			88	70
Carbaryl	$[M + H]^+$	202	145	100
			127	40
Aldicarb	$[M + NH_4]^+$	208	89	100
			116	30
Carbofuran	$[M + H]^+$	222	123	100
			165	30
Aldicarb sulfoxide	$[M + NH_4]^+$	224	89	100
			149	20
Oxamyl	$[M + NH_4]^+$	237	72	100
			90	20
Aldicarb sulfone	$[M + NH_4]^+$	240	166	100
			86	55
3-Hydroxycarbofuran	$[M + NH_4]^+$	255	163	100
			135	30

ence compound; the exact mass of the analyte is obtained from interpolation with respect to the known reference masses. In preliminary experiments, ten carbamate pesticides were analyzed in various fruits and vegetables; these compounds generally yielded a simple spectrum with $[M + H]^+$ or $[M + NH_4]^+$ as the base peak. Exact masses could also be obtained from a quadrupole MS, under special tuning conditions and using the data system capacities [37]. Although dynamic exact mass measurement under TSP conditions is not a routine procedure, neither with a magnetic sector nor with a quadrupole instrument, exact masses of molecular and fragment ions provide specific information for confirmation of analytes.

Recent progress in the field of environmental LC–TSP-MS is summarised in reviews by Lamoree et al. [10], Barceló [118] and Arpino [119].

3.4. Particle beam interface

Methods using the PB interface have successfully been applied to the analysis of a wide range of organic environmental pollutants since the appearance of the first systematic study on pesticides in 1990 [48]. In this pioneering work classical EI spectra were obtained for carbamates and phenylurea herbicides with instrument detection limits ranging from 10 to 440 ng in the full-scan mode. The potential of LC–PB-MS compared with LC–TSP-MS to obtain useful structural information is clearly demonstrated by the distinction of the isomeric triazine pesticides terbutylazine and propazine [120]. Unfortunately, the comparison of TSP and PB in terms of sensitivity was not addressed in that paper.

Miles studied the carbamate pesticide aldicarb and its degradation products, aldicarb sulfoxide and aldicarb sulfone, by a variety of methods, including GC–MS, LC–TSP-MS and LC–PB-MS [121]. LC–PB-MS yielded EI mass spectra with the characteristic fragment ion signals also observed in GC–MS. LC–PB-MS with CI detection did not provide more information than UV detection. The carbamate mesocarb was successfully screened with LC–PB-MS during the 1992 Olympic Games [122]. Its metabolite, a sulphate of *p*-hydroxymesocarb, could be detected in

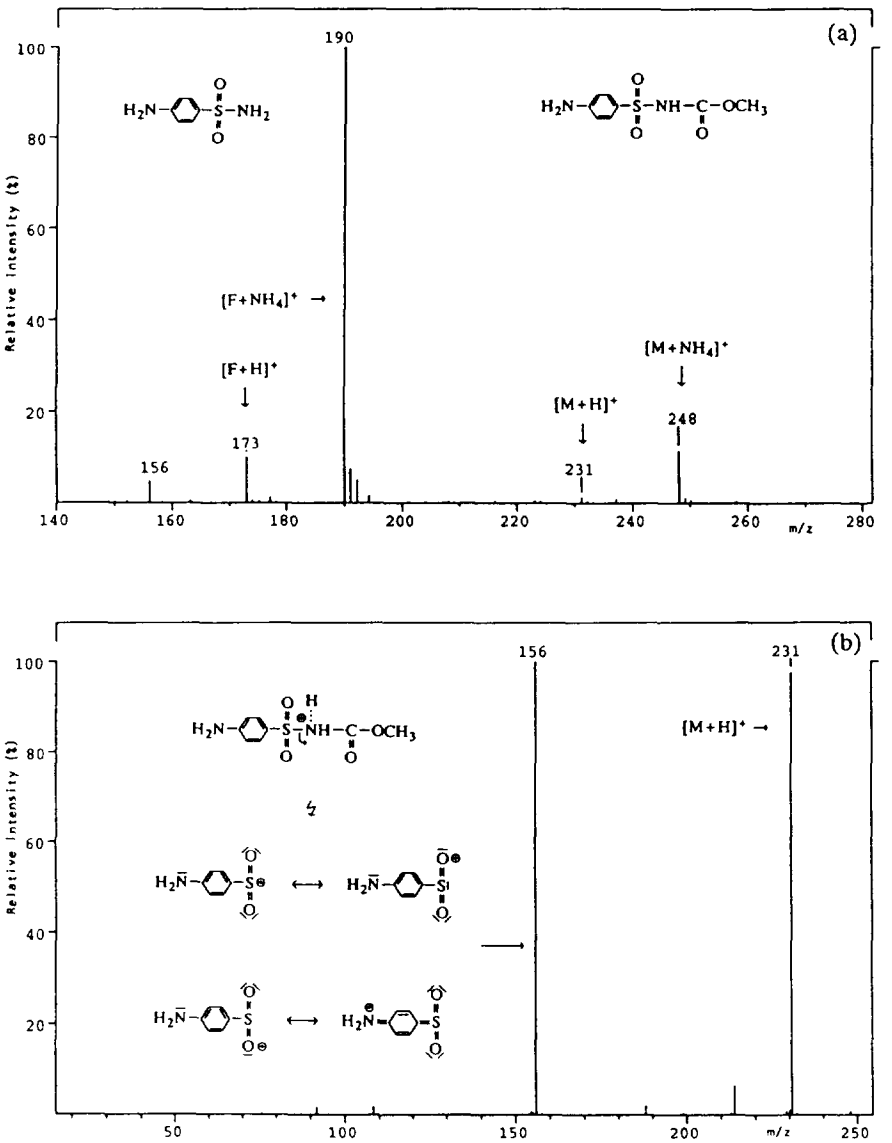


Fig. 15. CID TSP mass spectra of asulam. (a) TSP PI spectrum and (b) daughter ion spectrum (parent ion at m/z 248). Amount injected, 100 ng [24].

urine up to 48–72 h after the administration of a single 10 mg dose. This shows that some carbamates are amenable to LC–PB-MS, but that analyte detectability is not better than for other more conventional LC detection methods.

Sulphate and glucuronide conjugates of substituted phenols were also studied by LC–PB-MS, using anion-exchange chromatography and EI or PCI detection [123]. Although the sulphates and glucuronides could not be identified as such, the phenol-type decomposition products were identified by their EI mass spectra. Instrument detection limits were between 0.25 and 51 ng, for SIM detection under EI conditions.

Chlorinated phenoxyacetic acid derivatives were identified by LC–PB-MS, but quantifica-

tion was not reliable, because instrument response factors varied widely over a limited period of time [124,125]. Successful identification could be carried out by comparison with common library spectra and only small differences in the relative intensities were observed [124]. Evidence for thermal decomposition of chlorinated phenoxyacetic acid herbicides in LC–PB-MS was obtained by Betowski et al. [126]. Broadening of the profiles of some ions and variation in mass spectral quality were found to be dependent on the ion source temperature and analyte concentration; by implication, the instrument performance was found to depend upon the degree of fouling of the ion source. The authors suggested that PB mass spectra of chlorinated phenoxyacetic acid herbicides are composite spectra of the parent herbicides and their thermal decomposition products.

The performance of TSP and PB interfaces was compared in an interlaboratory study [127]. NI-TSP-MS performed best in low-level (5 mg/l) detection, but PB with EI detection provided good means of identification at higher levels (500 mg/l). In view of the fact that low, 0.5–1 ng, levels of the same analytes could be detected by using a carrier (see below) in LC–PB-NCI-MS [128], it is likely that EI detection limits can also be improved.

More than one hundred compounds from the US EPA National Pesticide Survey (NPS) were used in a study on the feasibility of LC–PB-MS for the identification and quantification of residues of non-volatile pesticides in ground water [129]. Detection limits were estimated to range from 5 ng, for carboxim sulfoxide, to 50 ng, for disulfoton sulfoxide. The authors concluded that adequate analysis is only provided when results from LC–PB-MS are combined with results from other LC–MS methods, because LC–PB-MS is not sufficiently sensitive for the determination of all 104 NPS compounds studied. In a similar study on 40 NPS compounds [130], detection limits were found to be between 0.4 and 19.2 ng.

The compatibility of LC and PB-MS was extended by the application of on-line, post-column desalination of the eluent [131]. Reversed-phase ion-exchange chromatography was performed using solutions of disodium carbonate and sodium hydroxide and chloride as the eluents, and desalination was achieved by cation exchange inside a microbore membrane suppressor, using a counter-current flow of sulphuric acid. Six aromatic sulphonic acids were separated and detected at the 0.4 μg/l level, using LC–PB-MS under full-scan EI conditions.

The above applications show that LC–PB-MS can be used successfully in pesticide analysis. However, the advantage of identification by PB-MS in the EI mode has to be set against the distinct disadvantage of rather poor analyte detectability and non-linearity of the detector response. Two main approaches have been developed to counteract these disadvantages: enhancement of sensitivity and linearity by the use of so-called carrier additives, and enhancement of sensitivity by off-line or on-line sample preconcentration. These aspects will be discussed below.

Various workers have used LC eluent additives to obtain improved detection limits. The effect of additives is generally two-fold: the dependence of the detector response on analyte concentration becomes linear over a larger range and the sensitivity of detection increases. Some studies on pesticide analysis have confirmed this 'carrier effect'. In contrast, possible interference due to a carrier effect was ruled out in the above-mentioned study of analytes from the US EPA NPS [129]. In this work the linear or exponential response curves were considered to reflect a compound-specific mass transport efficiency with a distinct physical basis, precluding the addition of 'carrier compounds' to the eluent. A carrier effect was initially supposed to be most efficient if structurally similar additives were used. An approximately two-fold intensity enhancement was observed for co-eluting isotopically labelled non-pesticide compounds [43]. A similar enhancement was not observed in the case of ethylenethiourea, a degradation product of the ethylenebis(dithiocarbamate) fungicides and a ^{13}C isotopomer [132]. Full-scan detection limits of 5 μg/l were obtained for ethylenethiourea, when using the isotopomer as an internal standard. Chlorinated phenoxyacetic

acid derivatives [128] and phenylurea herbicides [133] could be detected at low μg/l levels upon the addition of a few μg/l of a structurally similar 'carrier compound' to the eluent. Moreover, the linearity of the concentration-to-response ratio improved. Methane NCI, combined with SIM, led to limits of detection of 1.1 μg/l for 2,4-D, 2,4,5-T and silvex [128], 0.16 μg/l for diuron and 0.5 μg/l for linuron [133]. The 'carrier effect' has also been observed for additives which do not have any structural resemblance. In the initiating study mentioned above [48], ammonium acetate was added to the reversed-phase eluent in order to improve the transfer efficiency of the interface. With the analysis of the polar plant growth regulator daminozide, using anion-exchange LC–PB-MS under isobutane PCI conditions, the presence of 0.4 m*M* maleic acid in the eluent gave a 30-fold signal enhancement, and resulted in a linear response curve [47,134]. With 4 m*M* maleic acid in the eluent, a detection limit of 25 μg/l could be obtained.

A discussion on problems of mass transport and calibration in LC–PB-MS is presented by Ho et al. [46]. These authors used 13 pesticides for the comparison of two PB interfaces in a study on the dependence of the transport efficiency on the design of the interface, the nature of the mobile phase, the vapour pressure and concentration of the analyte and the presence of co-eluting carrier substances. In addition, twelve laboratories participated in an interlaboratory comparison of the analysis of four benzidines, in the 5–100 mg/l concentration range. R.S.D. values of single laboratory precision ($< 10\%$) and overall precision ($< 20\%$) were in the same order of magnitude as might be expected for GC–MS. External standards and a second-order regression curve gave satisfactory quantification results. However, on the basis of the observed enhancement of the signal by co-eluting substances, a calibration method of co-eluting isotopically labelled internal standards is suggested to be most reliable for real-world environmental samples. More details of isotope dilution in LC–PB-MS or GC–MS can be found in Ref. [45].

The use of LC–PB-MS for the analysis of effluent from waste water treatment plants was shown to complement GC–MS analysis [135]. Off-line sample preconcentration of 10 l waste water samples to 1 ml was followed by gradient LC, with the addition of 0.01% ammonium acetate as a carrier. The detection limit for triclocarban was found to be in the low μg/l range. Obviously, identification of small amounts of non-target compounds by LC–PB-MS is feasible, but large samples must be available and preconcentration should be carried out.

In a study following the successful coupling of microflow LC and PB-MS [50], the performance of the set-up was tested with 45 selected pesticides (among others: carbamates, triazines, anilides, polychlorophenoxyacetic acids, organophosphorus and phenylurea compounds) [51]. Using off-line solid-phase extraction with graphitized carbon black material, pesticides were transferred from 2 l water samples to 100 μl aliquots. Detection limits, in the SIM mode, ranged from 1 to 40 ng of analyte injected with an injection volume of 60 nl; this corresponds to a concentration range of 0.2–30 μg/l in the original samples (at the assumption of 100% recovery). Reversed-phase LC was performed with laboratory-made capillary columns (C_{18}; 250 mm × 250 μm I.D.) and using 0.1 *M* ammonium acetate or trifluoroacetic acid as additives to the acetonitrile–water eluent for the separation of basic and neutral or acidic analytes, respectively. The authors reported a better response for LC eluents with a high water content during gradient runs (as compared to conventional-size PB) and linear calibration curves. A significant reduction in solvent consumption results in less contamination of the ion source and the pumping system [51].

Off-line trace enrichment methods are widely used, but on-line methods have gained in popularity. On-line preconcentration using a precolumn with a PLRP-S sorbent, was applied for the analysis of water samples with LC–PB-MS [53]. Fig. 16 shows that four selected phenylurea compounds could be detected at the 30–50 ng/l level under full-scan EI conditions, using 100–250 ml samples. Calibration curves were linear in the 0.1–10 μg/l range and the day-to-day re-

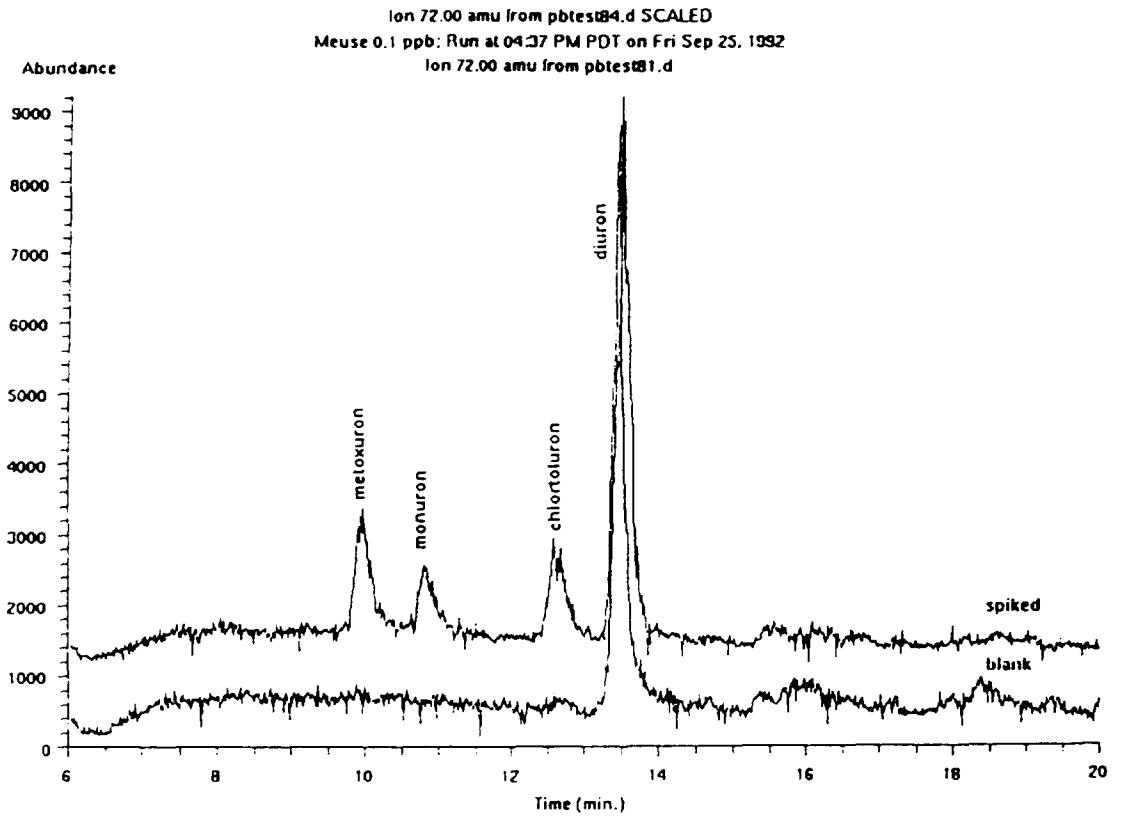


Fig. 16. On-line trace-enrichment LC–PB-MS chromatogram of 250 ml of (bottom) river Meuse water (blank) and (top) river Meuse water spiked with 0.1 μg/l of a mixture of four phenylureas. Column: 250 mm × 4.6 mm I.D. stainless-steel containing 5 μm C_{18}-bonded silica; eluent: linear acetonitrile–0.1 M ammonium acetate gradient [50:50 to 95:5 (v/v) in 30 min]; MS, full-scan EI mode. In the blank sample diuron was detected [53].

peatability of LC peak areas was 3.6–9%. The same set-up was used for the identification of unknown pollutants in surface and drinking water; the results are summarised in Table 7. Low levels (50–250 ng/l) of the phenylurea compounds chlortoluron and diuron could be detected in surface water. A breakdown product of diuron, 3,4-dichloroaniline, could be positively identified by LC–PB-PCI-MS, using methane as the reagent gas.

Automation of the overall LC–MS set-up, including sample handling, seems to be an important step for the establishment as a routine method for environmental analysis. A group of 48 carbamate pesticides and their degradation products were studied by means of automated on-line solid-phase extraction–LC–PB-MS [113]; ionisation was performed by EI and ammonia and methane PCI or NCI. Volumes of 100 ml surface water samples were enriched on a (10 mm × 3.0 mm I.D.) cartridge containing the sorbent of choice and, after switching of the eluent flow, the adsorbed pesticides were eluted by gradient LC onto a C_{18} analytical column. Due to efficient enrichment, it was possible to obtain detection limits of 0.1–8 μg/l in the EI full-scan mode for a group of 17 carbamates; R.S.D. values (peak areas) were between 5–20%. Ammonia PCI provided the best results of all CI modes used, while EI provided better sensitivity than PCI in most cases. Fig. 17 shows some typical changes in PCI spectra of ethiofencarb with various reaction gases used. An increase by 2–3 orders of magnitude in total ion

Table 7
Survey of environmental contaminants detected in various water samples using on-line trace enrichment LC–PB-MS (adapted from Ref. [53])

Compound	Concentration (μg/l)	Water source	Ionisation mode
Triphenylphosphine oxide[a]	1.00	River Rhine	EI
	0.05	Amsterdam drinking water	EI
Chlortoluron[a]	0.25	River Rhine	EI
Diuron[a]	0.25	River Rhine	EI
	0.05	River Ebro	EI
	0.50	River Meuse	EI
	7	Effluent water	EI
Bis(2-hydroxyphenyl)methane[a]	0.10	River Ebro	EI
Bis(4-hydroxyphenyl)methane[a]	0.10	River Ebro	EI
N-Butylbenzenesulphonamide	–	River Ob	EI
3,4-Dichloroaniline[a]	–	River Meuse	EI, PCI
N-(3,4-dichlorophenyl)-N′-methyl urea	–	River Meuse	EI, PCI, NCI
Tris(2-chloroethyl)phosphate	–	River Meuse	EI
Bentazone[a]	70	Effluent water	EI, NCI
2,4-Dichlorobenzoic acid[a]	–	Effluent water	EI, NCI
2(1H)-Quinolinone	–	Sewage sludge	EI
1H-Indole,2,3-dihydro-4-methyl	-	Sewage sludge	EI

[a] Checked by injection of standard.

current (TIC) abundance was observed for polar degradation products as compared with their parent compounds; therefore, analyte detectability of the more polar degradation products is better. Surprisingly, 28 from the 48 carbamates could be satisfactorily detected by GC–MS; both GC–MS and LC–PB-MS spectra could be identified by library search (Fig. 18). Obviously, the two techniques are complementary for the compounds analyzed.

In a new approach for the rapid analysis of organic micropollutants in aqueous samples a single column was used for both trace enrichment and separation; detection was performed by UV DAD and PB-MS [136]. Detection limits of four (from six) phenylurea herbicides were 1 μg/l and 0.1 μg/l in surface water, when the PB-MS was operated in the full-scan and SIM mode, respectively. With this set-up, the total time of analysis could be reduced to 32 min. The simplicity of the method should stimulate further research.

LC with a PB interface was recently coupled to an ion trap mass spectrometer [52]. The performance of PB-ITMS was tested with, among others, caffeine and carbaryl. Apart from the usual problems, such as relatively low sensitivity, non-linearity and analyte condensation on the first skimmer, ion–molecule reactions were found to occur at high analyte concentrations. Preliminary results show that instrument detection limits with PB-ITMS are in the low ng range (high μg/l range with the applied injection volumes).

The above examples show that the instrument detection limits in PB-MS generally are rather high. This is a serious disadvantage in environmental analysis. There is no doubt that the possibility to obtain reproducible EI and solvent-independent CI spectra is the main driving force for further development of PB; in this respect it is superior to the other LC–MS interfaces now applied. Improving the analyte detectability by adding specific additives does not seem to apply universally and attention is nowadays rather focused on efficient trace enrichment of analytes

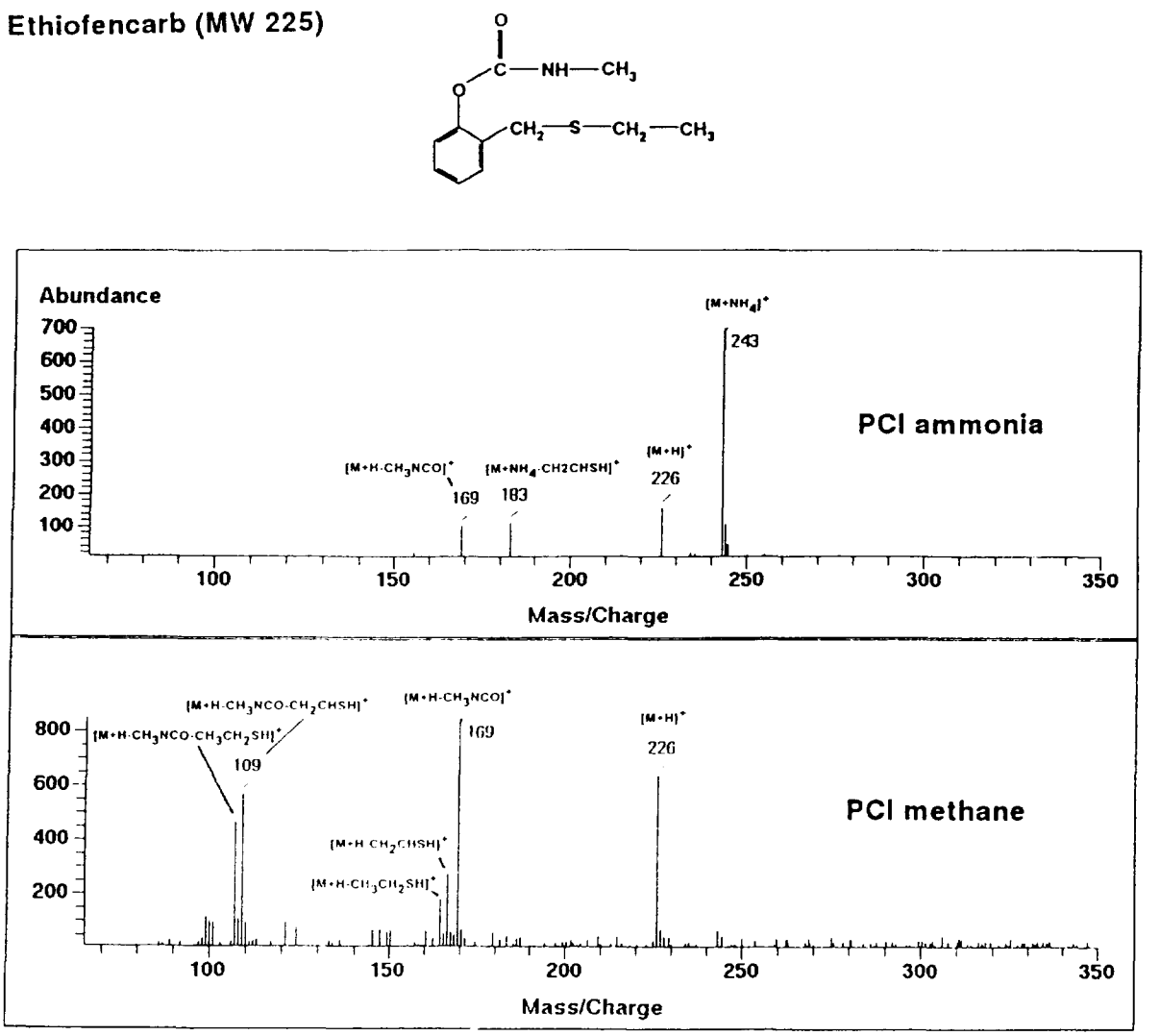


Fig. 17. FIA–PB-MS spectra of ethiofencarb (500 ng) in PCI mode using ammonia and methane as reagent gases [113].

of interest prior to LC separation. The efforts recently led to the incorporation of LC–PB-MS into a standard US EPA procedure for the determination of benzidines and nitrogen-containing pesticides in drinking water [137].

3.5. *Atmospheric pressure ionisation*

Very few studies on LC–API-MS for the determination of pesticides have been published so far, despite the potential of API-MS techniques in terms of sensitivity and the availability of structural information which is often claimed. Nevertheless, the published data strongly suggest that the method may indeed play an important role in environmental analysis in the near future.

A mixture of selected carbamates and phenylureas was analyzed by means of simultaneous ISP-MS and APCI-MS (with heated pneumatic nebulisation), using gradient LC with ammonium formate as an additive [65]. The double detection was achieved by splitting the effluent of the

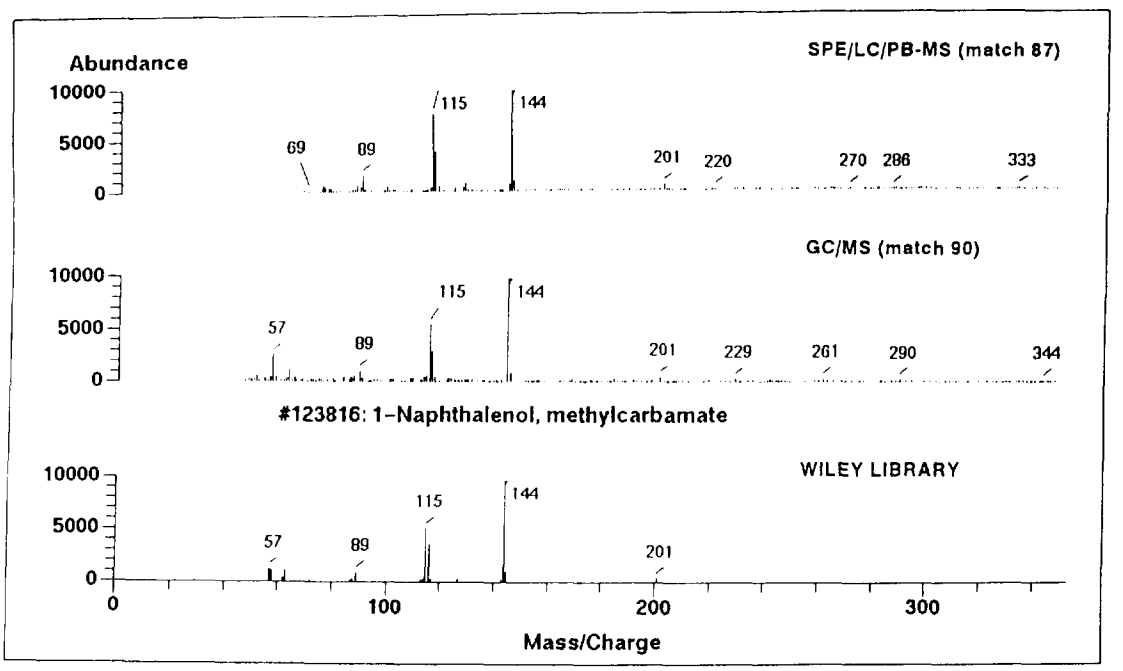


Fig. 18. EI spectra of carbaryl (M_r 201) obtained after on-line trace-enrichment LC–PB-MS of 1 μg/l of analyte in 100 ml surface water, GC–MS of 2 ng analyte injected on-column, and Wiley/NBS spectral library search. Values in brackets indicate the quality of spectral match in comparison with standard reference spectrum in Wiley/NBS library (maximum 100) [113].

analytical column (0.4 ml/min) to deliver ca. 20 μl/min to the APCI interface. A potential of 20–40 V over the ion sampling capillary and the first skimmer was used to effect solvent cluster breaking and pre-analyzer CID; this resulted in an improved signal-to-noise ratio. The observed difference in the TIC responses from ISP and APCI was attributed to thermolability of the analytes and to differences in the ionisation mechanism. The CID-ISP and CID-APCI mass spectra displayed several characteristic fragment ions. Unfortunately, no detection limits or repeatability data were reported.

The performance of two API-based (ISP and APCI) LC–MS procedures and of the more established TSP and PB methods was compared in a detailed study on N-methylcarbamates [138]. Mass spectra of methomyl in the PI mode (Fig. 19), exemplify that ISP, APCI and PB have the advantage of identification over TSP. As regards the sensitivity of detection (Table 8), APCI showed approximately 10-fold better detection limits than ISP and TSP. Results obtained with PB-MS were the least satisfactory: in some instances this method was almost four orders of magnitude less sensitive than APCI-MS. Carbaryl could easily be detected in green pepper extracts at the 0.1 mg/kg level by ISP-MS and ISP-MS–MS (Fig. 20). At this level, confirmatory full-scan spectra of methomyl, aldicarb and carbaryl could be obtained with LC–APCI-MS.

LC–ISP-MS was utilised for determination of nine organophosphorus pesticides [57]. Off-line trace enrichment of a 500-ml water sample on various Empore disks or C_{18} cartridges was used for concentration of the analytes. Limits of detection from direct on-column injections were in the range from 10–200 pg. With 1 ng of each compound injected, the repeatability varied from 12–17% and the long-term reproducibility was 22–30%. With the complete method, it was possible to detect 0.1 μg/l of each analyte in SIM mode of the $[M + Na]^+$ adduct ions. Unfortunately, no full-scan detection limits are

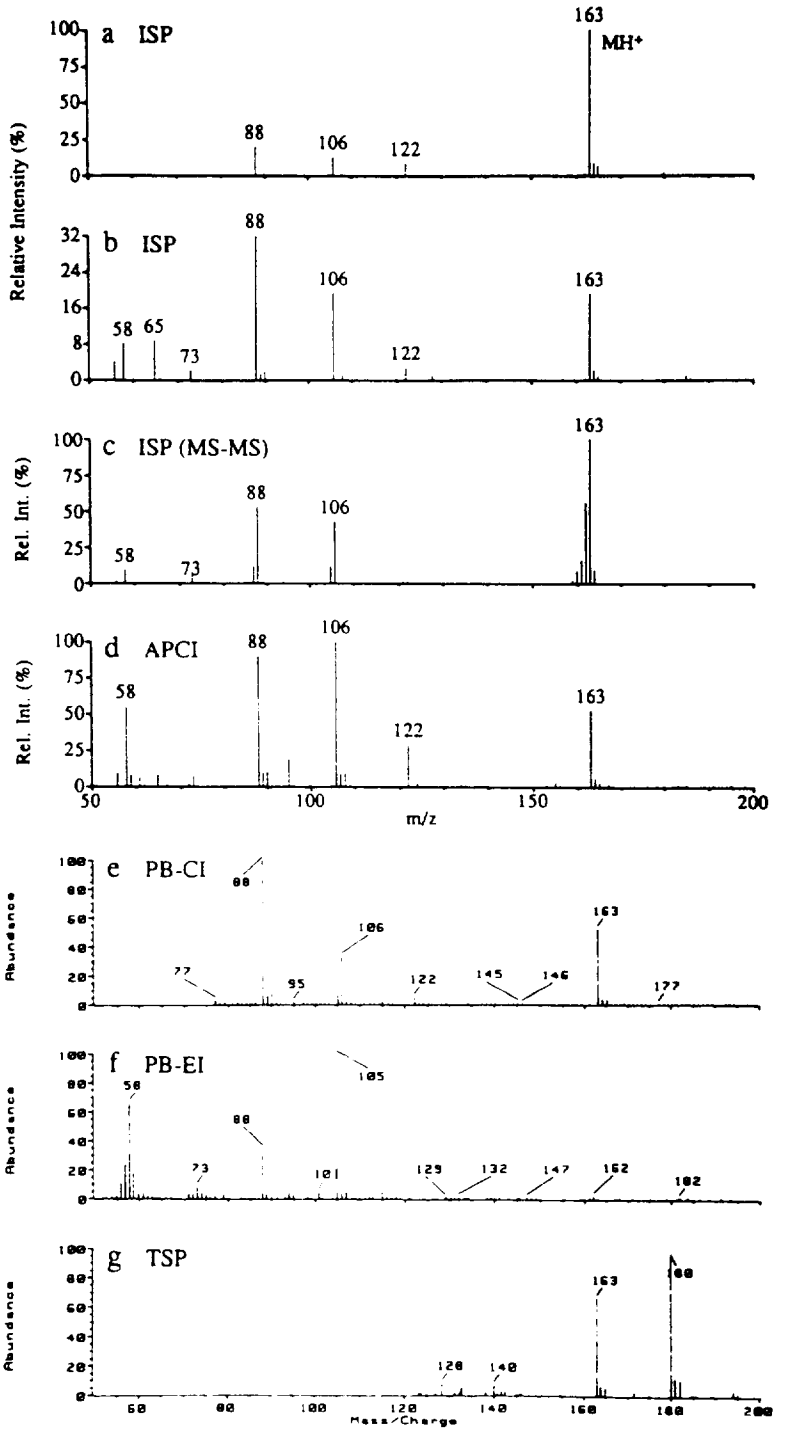


Fig. 19. Background-subtracted FIA spectra of methomyl obtained by ISP-MS (250 ng) at orifice voltages of (a) 50 V and (b) 70 V, (c) ISP-MS–MS (250 ng), (d) APCI-MS (50 ng), (e) PB-CI (2 μg), (f) PB-EI (2 μg), and (g) TSP-MS (250 ng). Conditions: eluent; aqueous methanol for d, e and f, modified with 0.1% formic acid for a,b and c, and with 0.08 *M* ammonium acetate for g. Flow-rates 50 μml/min for a, b and c; 600 μl/min for d; 400 μl/min for e and f; and 1.2 ml/min for g [138].

Table 8
Comparison of limits of detection obtained for eight carbamates using various LC–MS techniques (adapted from Ref. [138])

Compound	LC–MS technique			
	TSP	PB-EI	APCI	ISP
Methomyl	2.8	254	0.06	0.40
Aldicarb	0.9	>500	0.07	1.5
Aldicarb sulfoxide	2.5	152	0.18	1.0
Aldicarb sulfone	1.1	79	0.1	1.8
Carbaryl	0.8	10	0.05	1.0
Methiocarb	0.8	19	0.07	0.6
Carbofuran	0.8	55	0.05	0.3
3-Hydroxy-carbofuran	1.1	7	0.07	1.0

given. The authors observed that ISP spectra display diagnostic ions of organophosphorus pesticides which could be used for identification of unknowns. Comparison of LC–ISP-MS with TSP-MS analysis of the same compounds, showed that ISP is to be preferred: it has ca. 100-fold better sensitivity and thermal degradation of trichlorfon, observed for TSP, was not found with ISP.

Seventeen pesticides from the US EPA NPS of ground water contaminants, among others triazines, carbamates, phenylureas and organophosphorus compounds, were analyzed by LC–APCI-MS [67,139]. Detection limits ranged from 0.8 to 10 ng under full-scan conditions, and from 0.01–1 ng under SIM conditions. Table 9 shows that full-scan APCI-MS detection is less sensitive to differences in analyte structure (range, 10-fold) than TSP-MS (50-fold) or PB-MS (150-fold), at least for the present pesticides. Compared with the above-mentioned study, the detection limits of four (from eight) analytes in APCI-MS were about the same as in TSP-MS, while PB-MS showed reasonable performance. The pre-analyzer CID-APCI mass spectra of aldicarb sulfone and carbaryl provided useful structural information and were found to be virtually identical to the triple-quadrupole MS–MS CID mass spectra.

Conboy at al. [140] used a combination of ion chromatography coupled on-line with ion-pairing agent removal technology, and ISP-MS. The LC column effluent was led into a cation suppressor, between two ion-exchange membranes which were continuously regenerated by a counterflow of aqueous acid (see Fig. 21). The suppressor dead volume was less than 50 μl, to avoid peak broadening. After cation suppression, the 0.8–1.0 ml/min LC flow was split, such that 10–20 μl could be directed to an ISP-MS interface. This method was used to study quaternary ammonium compounds, using MS and MS–MS for detection. The limit of detection of 40 pg tetrapropylammonium, injected on-column, is an order of magnitude better than that obtained with a conductivity detector. For the identification of some alkyl sulphates and sulphonates using NI detection no limits of detection are given. The fact that the method is applicable to polar, ionic and zwitterionic compounds, justifies further research for environmental analysis.

The introduction of a high-flow LC–ISP-MS system [66] may well cause a breakthrough in this area. Conventional LC flow-rates of 1–2 ml/min were used in ISP with a heated ion sampling capillary and a liquid shield. This system was reported to provide mass spectra of low ng quantities of compounds with on-column injections. Non-volatile phosphate buffers in LC eluent could be used without major problems. Fig. 22 shows that 100 ng/l of mexacarbate could be detected in spiked pond water, after solid-phase extraction of a 150-ml sample over a C_{18} cartridge; the entire extract, which contained 3 ng of the analyte, was injected on-column. Mexacarbate, monuron, propoxur and siduron were determined in the SIM mode, using 10–25 ng on-column injections. Carbamates could be detected at low ng levels, using gradient LC for separation. The high-flow ISP system parameters have been studied more recently by the same group, using alkyl benzoate esters, monuron and carbofuran as model compounds [60].

Kawasaki et al. used LC–APCI-MS with a magnetic sector instrument for the analysis of 21 organophosphorus pesticides [71] and eight carbamate pesticides [141] in blood from patients suffering acute poisoning. LC separation was obtained on a C_{18} column, with a methanol–

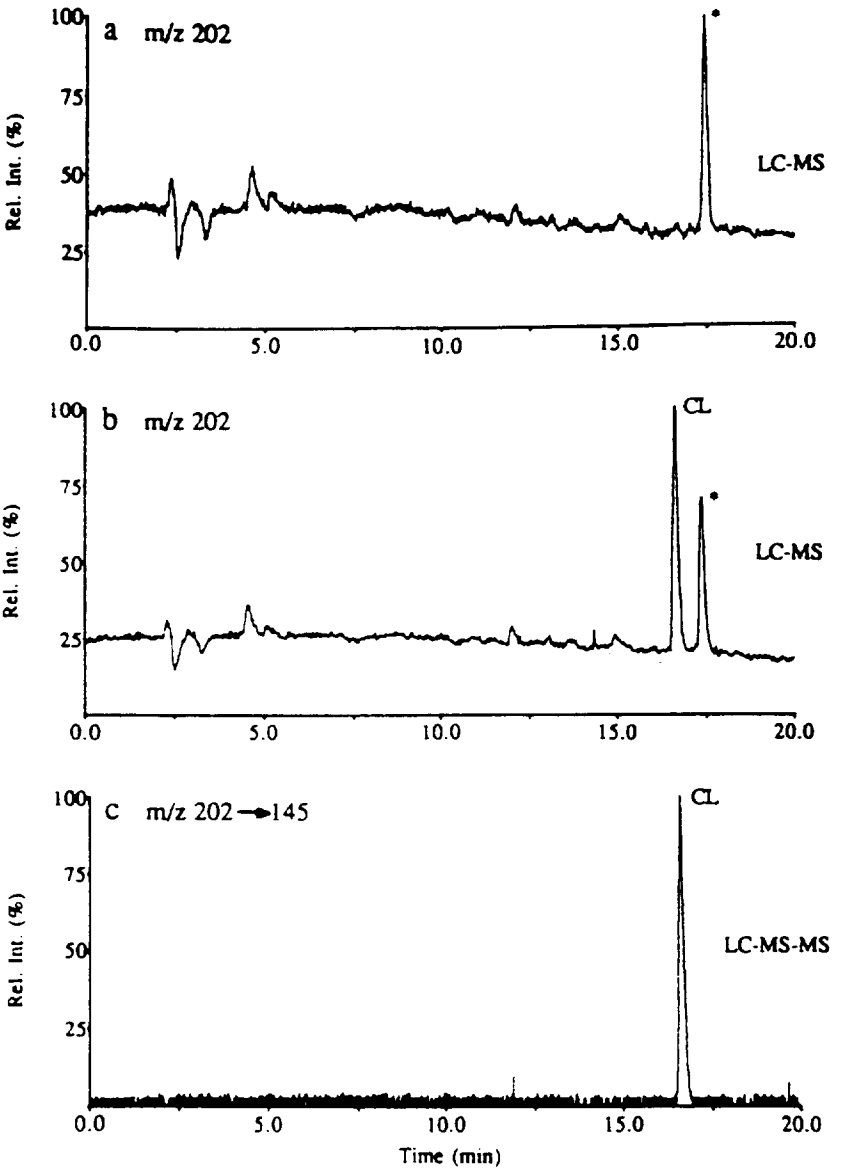


Fig. 20. Analysis of a green pepper extract by (a and b) LC–ISP-MS and (c) LC–ISP-MS–MS. SIM traces of the protonated molecule of carbaryl (CL, *m/z* 202) from (a) control and (b) spiked (0.1 ppm) pepper extracts; (c) SRM trace of dissociation of MH^+ ion of carbaryl (m/z 202) to its $[MH-57]^+$ ion (*m/z* 145) from spiked pepper extract. Asterisk denotes endogenous peak observed in control extract [138].

water gradient and ammonium acetate as an additive. The addition of higher levels (>10 m*M*) of ammonium acetate was shown to cause a 10-fold reduction of the sensitivity of detection for most compounds. Unequivocal identification of the pesticides could be achieved with both PI and NI detection. The instrument limits of detection, as determined from SIM experiments, are 2–20 ng (100 μl injections) for organophosphorus compounds best amenable to PI detection, and 2–1000 ng for organophosporus compounds best amenable to NI detection. The use of the PI

Table 9
Detection limits (ng) obtained for various NPS pesticides using LC–MS with an APCI, TSP, or PB interface [139]

Pesticide	Interface		
	APCI (ng)	TSP (ng)	PB (ng)
Atrazine	2.5	20[b]	19
Ametryn	1.0	20–60[b]	11
Cyanazine	1.0	–	2.0
Hexazinone	4.0	20–60[b]	0.4
Fluometuron	0.8	–	1.4
Diuron	4.0	50–80[a]	0.4
Neburon	2.5	–	3.4
Linuron	4.0	4–8[a]	4.4
Propanil	8.0	–	0.6
Aldicarb sulfone	7.0	–	3.0
Carbofuran	2.5	1–4[a]	9.0
Carbaryl	5.0	3 – 5[a]	6.0
Diazinon	1.0	–	–
Fenamiphos	8.0	–	4.2
Alachlor	8.0	10–20[a]	68
p-Nitrophenol	10.0	–	12

[a] Voyksner and Haney [84].
[b] Voyksner et al. [80].

mode, with SIM detection of the $[M + H]^+$ ions, led to instrument detection limits of 12–60 ng for the carbamates. Compounds with a molecular mass below 200 a.m.u. were found to suffer from baseline instability, which caused less sensitive detection. Preventing cluster ion formation, or cluster ion breaking, may give improved detection performance. The authors note that quantification by means of LC–APCI-SIM-MS is as good as that by GC–MS, but that the sensitivity of full-scan qualitative analysis is inferior to that of GC–MS.

The analysis of pesticides with ESP-ITMS was reported by Lin et al. [70]. When using pre-analyzer CID or MS–MS CID, full-scan ESP spectra could be obtained at 10–30 pg of compound, which corresponds with low μg/l detection limits in spiked water samples. The product ions from pre-analyzer CID and MS–MS CID of aldicarb sulfone were shown to be identical, although the signal-to-noise ratio of the MS–MS spectra was much better (Fig. 23). This stresses the point that the LC separation should be such that only single compounds are introduced into the ESP, in order to obtain useful pre-analyzer CID spectra.

ISP-MS in conjunction with immunoaffinity trapping was used by Rule et al. [142] for the highly selective determination of carbofuran. An immunoaffinity precolumn was employed for selective enrichment of the analyte; the trapping was followed by desorption and on-line chromatographic separation and MS detection. The whole procedure was automated by means of a gradient controller. Full-scan detection limits were 40 ng/l for spiked surface water samples and 2.5 ng/g for crude potato extract. The selectivity towards carbofuran was demonstrated in experiments dealing with the co-elution of fluometuron: this compound could not be observed when using the immunoaffinity precolumn.

In a recent study, continuous-flow FAB (CF-FAB) and ESP were combined with a magnetic sector instrument for the quantitative analysis of

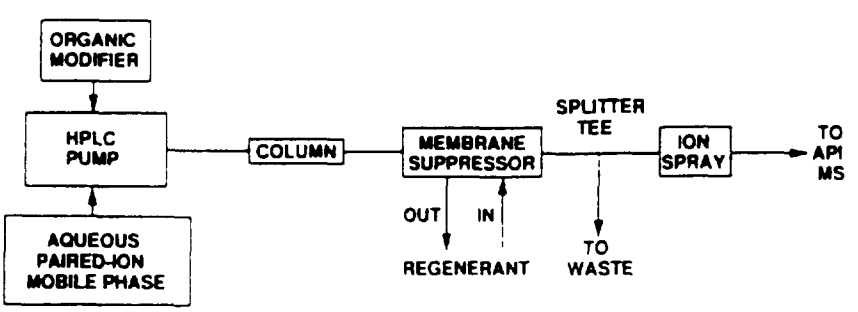


Fig. 21. Schematic diagram of combined ion chromatography–API-MS [140].

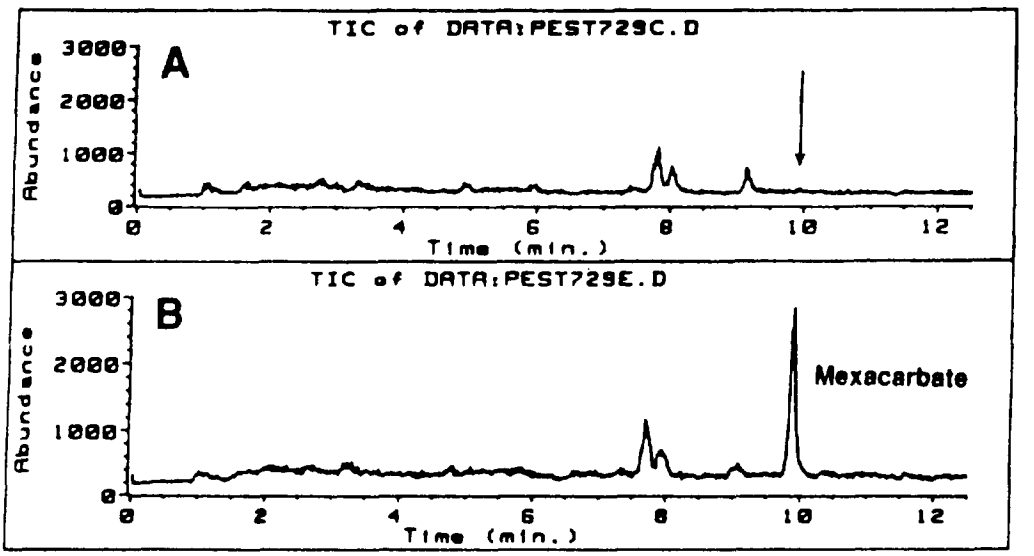


Fig. 22. High-flow ion spray SIM-mode LC–CID-MS: (A) extract of blank pond water; (B) extract of pond water spiked with 100 ng/l mexacarbate (3 ng injected). Conditions: 5 μm Zorbax RX-C_{18} column (150 mm × 4.6 mm I.D.), acetonitrile–5 m*M* ammonium formate gradient at 1 ml/min with liquid shield; SIM mode, $m/z = 223$, 166, and 151; dwell time, 300 ms; CID energy, 95 V [66].

four sulfonylurea herbicides [62]. NI-ESP led to the successful identification of a sulphate conjugate of hydroxylated bromacil in goat urine. In all analyses, LC band broadening was observed for CF-FAB, but not for ESP. CF-FAB and ESP yielded similar spectra for the compounds studied (Fig. 24): both ionisation methods generate prominent quasi-molecular anions or cations. However, ESP spectra were more sensitive to changes in the LC eluent composition and analyte concentration than FAB spectra. Especially the metal adduct ions, e.g. $[M + Na]^+$ and $[M + K]^+$, and cluster ions, e.g. $[2M + Na]^+$, which are observed with both methods, adversely affect quantification and the interpretation of spectra of unknowns. Amounts of 1–10 ng (1–100 mg/l with the 0.1–1 μl injection volumes used) of the sulfonylureas could easily be detected with both ionisation modes, provided that an MS-array detector was used instead of a common electron multiplier. Both techniques allowed accurate high-resolution mass measurements but CF-FAB was more straightforward with structure elucidation.

The identification of organotin pesticides has been studied by ESP-MS and ISP-MS. These pesticides have not been analyzed by any of the other LC–MS methods, because they are often amenable to GC–MS (or GC–AED). Tributyltin compounds were extracted from sediment and the extracts were directly subjected to FIA–ISP-MS–MS. Selected reaction monitoring (SRM), scanning the loss of two butene molecules from the tributyl–$^{122}Sn^+$ isotopomer ion, was found to provide sufficient selectivity for reliable quantification [143]. The detection limit for tributyltin compounds was established at 5 pg (0.2 mg Sn equivalent per kg of sediment). A wide variety of alkyl- and aryltin compounds was studied by Jones and Betowski, who used LC–ESP-MS [63]. Specific fragmentation and acetate adduct ion formation (acetate coming from the acetic acid eluent additive) generally allowed unequivocal identification of the analytes. The published data show that LC–ESP-MS has a good potential for the detection of organotin compounds; however no detection limits were determined.

A more fundamental study on the determination of CID pathways and cross-sections of 19

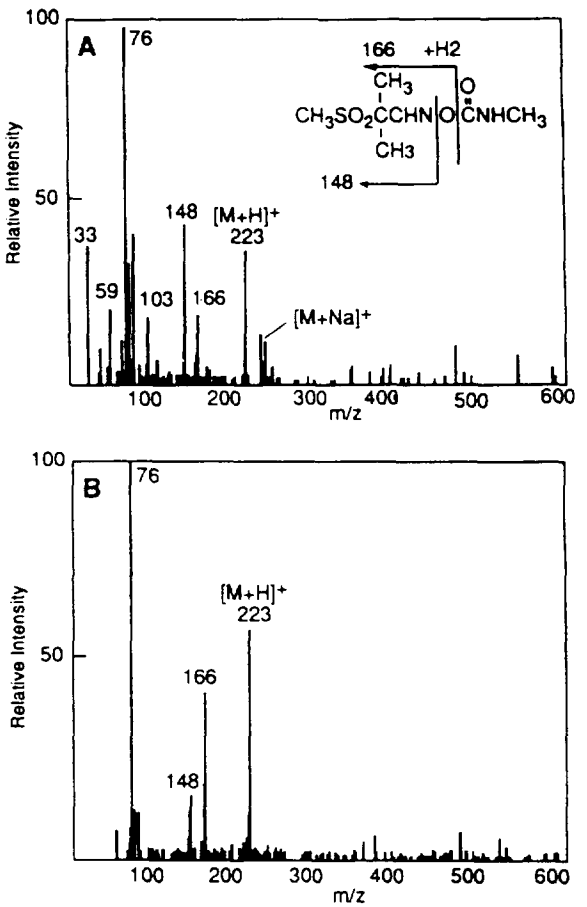


Fig. 23. ESP CID spectra of 1 ng of aldicarb sulfone (M_r 222): (A) CID spectrum obtained in the ESP pre-analyser region at a repeller setting of 15 V; (B) CID spectrum of the $[M + H]^+$ ion (m/z 223) obtained in the ion trap [25].

organophosphorus compounds by APCI-MS–MS was presented in ref. [144]. A generalised scheme for dissociation of the studied classes of analytes was derived from CID experiments and a simple model for the determination of CID cross-sections was developed. APCI-MS–MS was thus shown to be a useful diagnostic tool in the analysis of organophosphorus compounds.

In a recent review, Voyksner summarised the potential of LC–API-MS for environmental analysis [9], using the determination of carbamates and aromatic amines by means of LC–APCI-MS and LC–ESP-MS as examples. The possibility of efficient ionisation and gaining structural information by pre-analyzer CID is mentioned as a main advantage of the API-based techniques. The author concludes that acid and basic compounds are most effectively analyzed by LC–ESP-MS, while less polar compounds are better amenable to LC–APCI-MS.

A general overview on API-MS instrumentation, techniques and selected applications is given in Refs. [15,16].

4. Conclusions

The present review clearly shows that LC–MS using TSP, PB and API interfaces is a powerful tool in environmental analysis, with the possibility of obtaining the low-microgram per litre (kilogram) detection and/or identification limits often required in trace-level studies. One should add that, today, there certainly is no single 'best' interface. The proper choice of the LC–MS technique to be used in a specific situation depends on the analyte class that has to be studied, the goal (detection, confirmation, identification) one has in mind, and the sample type offered for analysis.

Generally speaking, LC–TSP-MS is the method most frequently used, and the results obtained often are quite satisfactory in terms of analyte detectability and confirmatory power. However, the structural information at best is limited, and this situation is not really improved if additives in the LC eluent are used. Recently, several studies have been published which indicate that coupling LC with TSP-tandem MS is a good means to provide the structural information required. Optimisation of such an analytical system is, however, rather complicated, which makes the set-up less robust.

When PB and API interfacing techniques are used, much more structural information can be obtained, and unambiguous identification of unknowns —i.e., analysis of non-target next to target analytes— becomes possible. LC–PB-MS provides EI mass spectra which can be confidently compared with those from available libraries, and valuable solvent independent CI spectra. Unfortunately, partly as a result of the rather

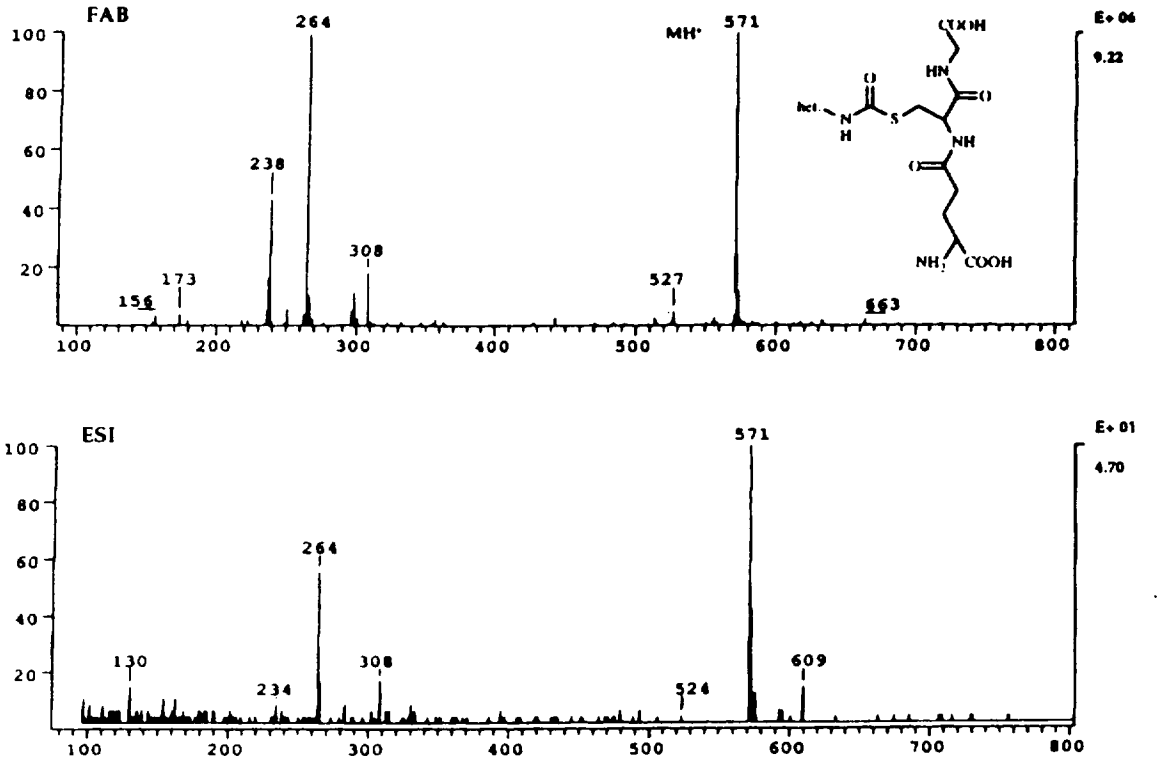


Fig. 24. CF-FAB and ESP mass spectra of an isolated plant metabolite of a sulfonylurea herbicide [62].

inefficient analyte transfer process in the interface, analyte detectability is rather poor in PB-MS. This is an aspect which clearly requires more attention in future studies. The several types of API-MS have been introduced only recently and it is obviously too early to make definite statements concerning their performance now. Still, good analyte detectability has been claimed in several instances, and relevant structural information is often recorded. ESP and ISP are probably best suited for the analysis of polar analytes containing an acidic or basic group, while less polar compounds can best be addressed by means of LC–APCI-MS. In the near future, much more attention should be devoted to the quantitative determination of analytes in real-life samples. Furthermore, the advantages of high-flow API techniques should be demonstrated more convincingly.

Finally, an aspect of much current interest is that the notorious problems of insufficient sensitivity of most LC–MS techniques, can largely be solved by combining them, preferably on-line, with an adequate trace-enrichment procedure such as solid-phase extraction. It has now convincingly been demonstrated that on-line solid-phase extraction-LC–MS of 10–100 ml aqueous samples or sample extracts easily improves analyte detectability (expressed in concentration units for the initial samples) by one or two orders of magnitude. Simultaneously, the total time of analysis can be reduced significantly, and the overall set-up can be easily automated. Today, detection and determination limits at or below the low μg/l or μg/kg level can be obtained for most of the frequently used classes of (polar) pesticides and also, of course, for many related compounds of environmental interest.

Acknowledgement

The authors acknowledge financial support from the EU Environmental project EV5V-CT92-0105.

References

[1] T. Cairns and E.G. Siegmund, *ACS Symp. Ser.*, 420 (1990) 1.
[2] D. Barceló, *Chromatographia*, 25 (1988) 928.
[3] T.R. Covey, D.D. Lee, A.P. Bruins and J.D. Henion, *Anal. Chem.*, 58 (1986) 1451A.
[4] P. Arpino, *Fresenius J. Anal. Chem.*, 337 (1990) 667.
[5] P. Arpino and G. Guiochon, *Anal. Chem.*, 51 (1979) 682A.
[6] W.M.A. Niessen and J. van der Greef, *Liquid Chromatography–Mass Spectrometry, Principles and Applications*, Marcel Dekker, New York, 1992.
[7] R.D. Voyksner and T. Cairns, *Anal. Methods Pestic. Plant Growth Regulators*, 17 (1989) 119.
[8] P.T. Holland, *Pure Appl. Chem.*, 62 (1990) 317.
[9] R.D. Voyksner, *Environ. Sci. Technol.*, 28 (1994) 118A.
[10] M.H. Lamoree, R.T. Ghijsen and U.A.Th. Brinkman, in D. Barceló (Editor), *Environmental Analysis: Techniques, Applications and Quality Assurance*, Elsevier, Amsterdam, 1993, pp. 521.
[11] R.E. Ardrey, *Liquid Chromatography–Mass Spectrometry*, VCH Publishers, Weinheim, 1994.
[12] M.R. Clench, S. Scullion, R. Brown and J. White, *Spectrosc. Europe*, 6 (1994) 16.
[13] C.S. Creaser and J.W. Stygall, *Analyst*, 118 (1993) 1467.
[14] A.P. Bruins, *Mass Spectrom. Rev.*, 10 (1991) 53.
[15] A.P. Bruins, *Trends. Anal. Chem.*, 13 (1994) 37.
[16] A.P. Bruins, *Trends. Anal. Chem.*, 13 (1994) 81.
[17] J.S.M. de Wit, K.B. Tomer and J.W. Jorgenson, *J. Chromatogr.*, 462 (1989) 365.
[18] K.J. Krost, *Appl. Spectrosc.*, 47 (1993) 821.
[19] P. Arpino, *Mass Spectrom. Rev.*, 8 (1989) 35.
[20] C.R. Blakley and M.L. Vestal, *Anal. Chem.*, 55 (1983) 750.
[21] P. Arpino, *Mass Spectrom. Rev.*, 9 (1990) 631.
[22] W.M.A. Niessen, R.A.M. van der Hoeven, M.A.G. de Kraa, C.E.M. Heermans, U.R. Tjaden and J. van der Greef, *J. Chromatogr.*, 478 (1989) 325.
[23] J. Abián, G. Durand and D. Barceló, *J. Agric. Food Chem.*, 41 (1993) 1264.
[24] D. Volmer, A. Preiss, K. Levsen and G. Wünsch, *J. Chromatogr.*, 647 (1993) 235.
[25] W.M. Draper, F.R. Brown, R. Bethem and M.J. Mille, *J. Am. Soc. Mass Spectrom.*, 1 (1990) 253.
[26] L.D. Betowski and T.L. Jones, *Environ. Sci. Technol.*, 22 (1988) 1430.
[27] W.M.A. Niessen, C.C. McCarney, P.E.G. Moult, U.R. Tjaden and J. van der Greef, *J. Chromatogr.*, 647 (1993) 107.
[28] R.D. Voyksner, W.H. McFadden and S.A. Lammert, in J.D. Rosen (Editor), *Applications of New Mass Spectrometry Techniques in Pesticide Chemistry*, Wiley, New York, 1987, Ch. 17, pp. 247–258.
[29] R.D. Voyksner, P. Pack, C. Smith, H. Swaisgood and D. Chen, *ACS Symp. Ser.*, 420 (1990) 14.
[30] K.S. Chiu, A. van Langenhove and C. Tanaka, *Biomed. Environ. Mass Spectrom.*, 18 (1989) 200.
[31] R.B. Geerdink, P.G.M. Kienhuis and U.A.Th. Brinkman, *J. Chromatogr.*, 647 (1993) 329.
[32] P.G.M. Kienhuis, *J. Chromatogr.*, 647 (1993) 39.
[33] (a) J.M. Curtis and B.N. Green, *Spectroscopy* 7 (1989) 123; (b) P. Dobberstein and E. Schröder, *MAT 90 Application Data Sheet No. 5*, Finnigan MAT, Bremen, 1988.
[34] I. Hammond, K. Moore, H. James and C. Watts, *J. Chromatogr.*, 474 (1987) 175.
[35] M.L. Vestal, *Anal. Chem.*, 56 (1984) 2590.
[36] W.C. Davidson, R.M. Dinallo and G.E. Hansen, *Biol. Mass Spectrom.*, 20 (1991) 389.
[37] J. Wellby and P. Watkins, *TSP Report 1*, Finnigan, San José, CA, 1987.
[38] R.C. Willoughby and R.F. Browner, *Anal. Chem.*, 56 (1984) 2625.
[39] G. McFadden, *Techniques of Combined Gas Chromatography/Mass Spectrometry: Applications in Organic Analysis*, Wiley, New York, 1975.
[40] R.C. Willoughby and F. Poeppel, *Proc. 35th ASMS Conf. Mass Spectrom. Allied Topics*, 1987, p. 289.
[41] J.G. Wilkes, C.H. Vestal and M.L. Vestal, *Proc. 38th ASMS Conf. Mass Spectrom. Allied Topics*, 1990, p. 31.
[42] J.A. Apffel and M.L. Perry, *J. Chromatogr.*, 554 (1991) 102.
[43] T.A. Bellar, T.D. Behymer and W.L. Budde, *J. Am. Soc. Mass Spectrom.*, 1 (1990) 92.
[44] F.R. Brown and W.M. Draper, *Biol. Mass Spectrom.*, 20 (1991) 515.
[45] (a) D.R. Doerge, M.W. Burger, S. Bajic, *Anal. Chem.*, 64 (1992) 1212; (b) D.R. Doerge, *Anal. Chem.*, 65 (1993) 1489; (c) D. Stockl, *Anal. Chem.*, 65 (1993) 1489.
[46] J.S. Ho, T.D. Behymer, W.L. Budde and T.A. Bellar, *J. Am. Soc. Mass Spectrom.*, 3 (1992) 662.
[47] I. Suk Kim, F.I. Sasinos, R.D. Stephens and M.A. Brown, *J. Agric. Food Chem.*, 38 (1990) 1223.
[48] T.D. Behymer, T.A. Bellar and W.L. Budde, *Anal. Chem.*, 62 (1990) 1686.
[49] T.A. Bellar, W.L. Budde and D.D. Kryak, *J. Am. Soc. Mass Spectrom.*, 5 (1994) 908.
[50] A. Cappiello and F. Bruner, *Anal. Chem.*, 65 (1993) 1281.

[51] A. Cappiello, G. Famiglini and F. Bruner, *Anal. Chem.*, 66 (1994) 1416.
[52] M.E. Bier, P.C. Winkler and J.R. Herron, *J. Am. Soc. Mass Spectrom.*, 4 (1993) 38.
[53] H. Bagheri, J. Slobodník, R.M. Marce Recasens, R.T. Ghijsen and U.A.Th. Brinkman, *Chromatographia*, 37 (1993) 159.
[54] E.C. Huang, T. Wachs, J.C. Conboy and J.D. Henion, *Anal. Chem.*, 62 (1990) 713A.
[55] T. Wachs, J.C. Conboy, F. Garcia, J.D. Henion, *J. Chromatogr. Sci.*, 29 (1991) 357.
[56] A.P. Bruins, T.R. Covey and J.D. Henion, *Anal. Chem.*, 59 (1987) 2642.
[57] C. Molina, M. Honing and D. Barceló, *Anal. Chem.*, 66 (1994) 4444.
[58] C.M. Whitehouse, R.N. Dreyer, M. Yamashita and J.B. Fenn, *Anal. Chem.*, 59 (1985) 675.
[59] P. Kebarle and L. Tang, *Anal. Chem.*, 65 (1993) 972A.
[60] G. Hopfgartner, K. Bean, J.D. Henion and R. Henry, *J. Chromatogr.*, 647 (1993) 51.
[61] R. Straub, R.D. Voyksner and J.T. Keever, *J. Chromatogr.*, 627 (1992) 173.
[62] R.W. Reiser and A.J. Fogiel, *Rapid Commun. Mass Spectrom.*, 8 (1994) 252.
[63] T.L. Jones and L.D. Betowski, *Rapid Commun. Mass Spectrom.*, 7 (1993) 1003.
[64] R.F. Straub and R.D. Voyksner, *J. Am. Soc. Mass Spectrom.*, 4 (1993) 578.
[65] K.L. Duffin, T. Wachs and J.D. Henion, *Anal. Chem.*, 64 (1992) 61.
[66] G. Hopfgartner, T. Wachs, K. Bean and J.D. Henion, *Anal. Chem.*, 65 (1993) 439.
[67] D.R. Doerge and S. Bajic, *Rapid Commun. Mass Spectrom.*, 6 (1992) 663.
[68] J.P. Toth and A.P. Snyder, *Biol. Mass Spectrom.*, 20 (1991) 70.
[69] A.P. Snyder, *Anal. Chem.*, 12 (1993) 296.
[70] Hung-Yu Lin and R.D. Voyksner, *Anal. Chem.*, 65 (1993) 451.
[71] S. Kawasaki, H. Ueda, H. Itoh and J. Tadano, *J. Chromatogr.*, 595 (1992) 193.
[72] R.B. Cody, J. Tamura and B.D. Musselman, *Anal. Chem.*, 64 (1992) 1561.
[73] J. Zhao and D.M. Lubman, *Anal. Chem.*, 65 (1993) 866.
[74] W.L. Shen and R.D. Satzger, *Anal. Chem.*, 63 (1991) 1960.
[75] D. Barceló, *Biomed. Environ. Mass Spectrom.*, 17 (1988) 363.
[76] D. Barceló and J. Albaigés, *Hyphenated Methods LC/TSP-MS, LC/DLI-MS, LC/TID) for Analyzing Organophosphorus Priority Pollutants*, Commission of the European Communities, Organic Micropollutants in the Aquatic Environment, 1988, p. 75.
[77] A. Farran, J. de Pablo and D. Barceló, *J. Chromatogr.*, 455 (1988) 163.
[78] D. Barceló and J. Albaigés, *J. Chromatogr.*, 474 (1989) 163.
[79] D. Barceló, *Chromatographia*, 25 (1988) 295.
[80] R.D. Voyksner, J.T. Bursey and E.D. Pellizzari, *Anal. Chem.*, 56 (1984) 1507.
[81] L.M. Shalaby, in J.D. Rosen (Editor), *Applications of New Mass Spectrometry Techniques in Pesticide Chemistry*, Wiley, New York, 1987, Ch. 12.
[82] L.M. Shalaby and S.W. George, *ACS Symp. Ser.*, 420 (1990) 75.
[83] R.D. Voyksner, in J.D. Rosen (Editors), *Applications of New Mass Spectrometry Techniques in Pesticide Chemistry*, Wiley, New York, 1987, Ch. 11.
[84] R.D. Voyksner and C.A. Haney, *Anal. Chem.*, 57 (1985) 991.
[85] D. Barceló, *Org. Mass Spectrom.*, 24 (1989) 219.
[86] G. Durand, N. de Bertrand and D. Barceló, *J. Chromatogr.*, 562 (1991) 507.
[87] D. Barceló, *ACS Symp. Ser.*, 420 (1990) 48.
[88] R.J. Vreeken, U.A.Th. Brinkman, G.J. de Jong and D. Barceló, *Biomed. Environ. Mass Spectrom.*, 19 (1990) 481.
[89] D. Barceló, G. Durand, R.J. Vreeken, G.J. de Jong, H. Lingeman and U.A.Th. Brinkman, *J. Chromatogr.*, 553 (1991) 311.
[90] M. Honing, D. Barceló, B.L.M. van Baar, R.T. Ghijsen and U.A.Th. Brinkman, *J. Am. Soc. Mass Spectrom.*, 5 (1994) 913.
[91] R.J. Vreeken, W.D. van Dongen, R.T. Ghijsen and U.A.Th. Brinkman, *Int. J. Environ. Anal. Chem.*, 54 (1994) 119.
[92] D. Barceló, G. Durand, R.J. Vreeken, G.J. de Jong and U.A.Th. Brinkman, *Anal. Chem.*, 62 (1990) 1696.
[93] D. Barceló, *Org. Mass Spectrom.*, 24 (1989) 898.
[94] A. Farran, J.L. Cortina, J. de Pablo and D. Barceló, *Anal. Chim. Acta*, 234 (1990) 119.
[95] D. Barceló, G. Durand and R.J. Vreeken, *J. Chromatogr.*, 647 (1993) 271.
[96] M. Yoshida, T. Watabiki, T. Tokiyasu and N. Ishida, *J. Chromatogr.*, 628 (1993) 235.
[97] D.L. Fisher, M.A. Moseley, J.O. Mullis and D.L. Norwood, *Rapid Commun. Mass Spectrom.*, 8 (1994) 65.
[98] G. Durand, N. de Bertrand, D. Barceló, *J. Chromatogr.*, 562 (1991) 507.
[99] D. Barceló, *Org. Mass Spectrom.*, 24 (1989) 898.
[100] D. Barceló, G. Durand, N. de Bertrand and J. Albaiges, *Sci. Total Environ.*, 132 (1993) 283.
[101] V. Lopez-Avila and T.L. Jones, *J. Assoc. Off. Anal. Chem. Int.*, 76 (1993) 1329.
[102] T.L. Jones, L.D. Betowski and V. Lopez Avila, *Trends Anal. Chem.*, 13 (1994) 333.
[103] H. Fujiwara, R.C. Chott and R.T. Solsten, *Biol. Mass Spectrom.*, 21 (1992) 431.
[104] T.A. Bellar and W.L. Budde, *Anal. Chem.*, 60 (1988) 2076.
[105] G.C. Mattern, C.-H. Liu, J.B. Louis and J.D. Rosen, *J. Agric. Food Chem.*, 39 (1991) 700.
[106] C.-H. Liu, G.C. Mattern, X. Yu, R.T. Rosen and J.D. Rosen, *J. Agric. Food Chem.*, 39 (1991) 718.

[107] D. Volmer, K. Levsen and G. Wünsch, *J.Chromatogr. A*, 660 (1994) 231.
[108] S. Nélieu, M. Stobiecki, F. Sadoun, H. Virelizier, L. Kerhoas and J. Einhorn, *Analusis*, 22 (1994) 70.
[109] L.M. Shalaby, F.Q. Bramble, Jr., and P.W. Lee, *J. Agric. Food Chem.*, 40 (1992) 513.
[110] H. Bagheri, E.R. Brouwer, R.T. Ghijsen and U.A.Th. Brinkman, *Analusis*, 20 (1992) 475.
[111] H. Bagheri, E.R. Brouwer, R.T. Ghijsen and U.A.Th. Brinkman, *J. Chromatogr.*, 647 (1993) 121.
[112] S. Chiron, A.F. Alba and D. Barceló, *Environ. Sci. Technol.*, in press.
[113] J. Slobodník, M.E. Jager, S.J.F. Hoekstra-Oussoren, B.L.M. van Baar and U.A.Th. Brinkman, submitted for publication.
[114] T. Gomyo, M. Ozawa and S. Kobayashi, *Anal. Sci.*, 8 (1992) 687.
[115] D. Volmer and K. Levsen, *J. Am. Soc. Mass Spectrom.*, 5 (1994) 655.
[116] M.J. Hayward, J.T. Snodgrass and M.L. Thomson, *Rapid Commun. Mass Spectrom.*, 7 (1993) 85.
[117] J. Abián, F. Sánchez-Baeza, E. Gelpí and D. Barceló, *J. Am. Soc. Mass Spectrom.*, 5 (1994) 186.
[118] D. Barceló, *Anal. Chim. Acta*, 263 (1992) 1.
[119] P. Arpino, *Mass Spectrom. Rev.*, 11 (1992) 3.
[120] R.D. Voyksner, T. Pack, C. Smith, H. Swaisgood and D. Chen, *ACS Symp. Ser.*, 420 (1990) 14.
[121] C.J. Miles, *Environ. Sci. Technol.*, 25 (1991) 1774.
[122] R. Ventura, T. Nadal, P. Alcalde and J. Segura, *J. Chromatogr.*, 647 (1993) 203.
[123] F.R. Brown and W.M. Draper, *ACS Symp. Ser.*, 420 (1990) 232.
[124] I. Suk Kim, F.I. Sasinos, R.D. Stephens, J. Wang and M.A. Brown, *Anal. Chem.*, 63 (1991) 819.
[125] M.A. Brown, R.D. Stephens and I. Suk Kim, *Trends Anal. Chem.*, 10 (1991) 330.
[126] L.D. Betowski, C.M. Pace and M.R. Roby, *J. Am. Soc. Mass Spectrom.*, 3 (1992) 823.
[127] T.L. Jones, L.D. Betowski, B. Lesnik, T.C. Chiang and J.E. Teberg, *Environ. Sci. Technol.*, 25 (1991) 1880.
[128] M.J.I. Mattina, *J. Chromatogr.*, 542 (1991) 385.
[129] C.J. Miles, D.R. Doerge and S. Bajic, *Arch. Environ. Contam. Toxicol.*, 22 (1992) 247.
[130] C.J. Miles, D.R. Doerge and S. Bajic, *Particle Beam LC/MS, Analysis of Pesticides in Ground Water*, Fisons Instruments/VG BioTech, Application Note, 1992.
[131] J. Hsu, *Anal. Chem.*, 64 (1992) 434.
[132] D.R. Doerge and C.J. Miles, *Anal. Chem.*, 63 (1991) 1999.
[133] M.J.I. Mattina, *J. Chromatogr.*, 549 (1991)237.
[134] M.A. Brown, I. Suk Kim, F.I. Sasinos and R.D. Stephens, *ACS Symp. Ser.*, 420 (1990) 198.
[135] L.B. Clark, R.T. Rosen, T.G. Hartman, J.B. Louis and J.D. Rosen, *Int. J. Environ. Anal. Chem.*, 45 (1991) 169.
[136] W.A. Minnaard, J. Slobodník, J.J. Vreuls, K.-P. Hupe and U.A.Th. Brinkman, *J. Chromatogr.*, in press.
[137] *EPA method 553, Methods for the Determination of Organic Compounds in Drinking Water, Supplement II; Revision 1.1*, US Environmental Protection Agency, Research Triangle Park, NC, 1993.
[138] S. Pleasance, J.F. Anacleto, M.R. Bailey and D.H. North, *J. Am. Soc. Mass Spectrom.*, 3 (1992) 378.
[139] S. Bajic, D.R. Doerge, S. Lowes and S. Preece, *Int. Lab.*, 13 (1993) 4.
[140] J.J. Conboy, J.D. Henion, M.W. Martin and J.A. Zweigenbaum, *Anal. Chem.*, 62 (1990) 800.
[141] S. Kawasaki, F. Nagumo, H. Ueda, Y. Tajima, M. Sano and J. Tadano, *J. Chromatogr.*, 620 (1993) 61.
[142] G.S. Rule, A.V. Mordehai and J. Henion, *Anal. Chem.*, 66 (1994) 230.
[143] K.W.M. Siu, G.J. Gardner and S.S. Berman, *Anal. Chem.*, 61 (1989) 2320.
[144] C.S. Harden, A.P. Snyder and G.A. Eiceman, *Org. Mass Spectrom.*, 28 (1993) 585.
[145] A. Apffel, presented at '*Short Course on LC/MS Techniques*', Hewlett-Packard, Amstelveen, October 1992.