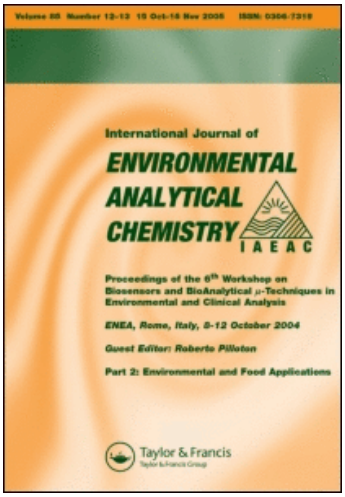

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LC-MS for Toxicological and Environmental Analysis: Recent Developments

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LC-MS FOR TOXICOLOGICAL AND ENVIRONMENTAL ANALYSIS: RECENT DEVELOPMENTS

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The coupling of liquid chromatography and electrophoretic separation techniques with mass spectrometry has attracted great interest in almost all areas of analytical chemistry, because it holds many promises. Some interface types are used in routine analysis already, although GC-MS is often more sensitive and more reliable. The foremost benefit of using LC-MS is that the identification and determination of substances is possible, which were intractable with mass spectrometry, such as sulfonates, glucuronides, salts and metal organic species. New insights in metabolism of hazardous materials and new strategies for risk assessment are possible. In this report, an overview over the state of the art in the interface technique and some recent developments is given and, with a few selected examples (e.g detection of highly polar herbicides, metabolic analysis and speciation), the strength of LC-MS in environmental analysis shall be highlighted.

KEY WORDS: Liquid chromatography-mass spectrometry, environmental analysis, speciation.

INTRODUCTION

It has been recognized that mass spectrometers may be used as universal and sensitive detectors in high performance liquid chromatography (HPLC) and, rather recently, in high performance capillary electrophoresis, but it is only very recently that LC-MS instruments are used in the routine laboratories.

As yet, the combination of mass spectrometry with gas chromatography is still most important (probably about 80% of all mass spectrometers are GC-MS instruments!), but the reason for the numerous activities in interfacing HPLC to mass spectrometry can be seen in the prospect of compatibility between the powerful, strongly developing liquid chromatographic and electrophoretic separation techniques and mass spectrometry without being forced to go destructive and time consuming detours such as the derivatization steps for gas chromatography.

Unfortunately, there is not "the" LC-MS interface for all the different techniques available. The reasons are on the one hand that the different HPLC techniques need

specialized interfaces. On the other hand, the interfacing techniques are greatly incompatible with each other; so there is no way to combine all of them.

In the following discussion, the LC-MS interfaces have been divided into three different groups: the first group comprises methods with sputter techniques such as FAB or laser desorption, the second group contains techniques with separate aerosol and ion generation and the third group is made up essentially from thermospray and electrospray, both techniques generating aerosol and ions in the same step. This structure is not only helpful for didactical reasons, but allows an organized discussion of the applications in environmental analysis as well.

Before discussing the techniques and to illustrate the challenge of interfacing that many different separation techniques with mass spectrometry, some keywords and typical figures may be given to summarize the situation.

Chromatography and electrophoresis

High Performance Liquid Chromatography: In HPLC, the flow rate can vary from a few µl/min up to 2 ml/min and the eluents may be organic solvents, water or buffer solutions.

reversed phase	eluents: H_2O, ROH's, AcCN, buffers, salts	1-2 ml/min
normal phase	organic solvents	1-2 ml/min
ion chromatogr.	strong buffer, salts	1-2 ml/min
microHPLC	same as above	1-100 µl/min

Supercritical Fluid Chromatography (SFC): Although supercritical fluid chromatography has a rather constricted domain of applications, it should be mentioned here in this context. The flow rates for capillary SFC is not problematic, but for packed column SFC, a separator is mandatory.

capillary SFC	CO_2, ROH's modifier	1 µl/min (= 1 ml gas)
packed columns	same as above	10 ml/min

High Performance Electrophoresis: In high performance electrophoresis, the flow—if there is any—is very low (from less than 1 µl to a few µl/min), since only the electroosmotic flow (EOF) can be used as driving force. Therefore, capillary zone electrophoresis (CZE) and isotachophoresis (ITP) with EOF can be interfaced to an MS. The high concentrations of buffers—in particular in ITP—can create severe problems, since most of the MS techniques employed are sensitive to high salt concentration.

Mass Spectrometry

Further difficulties are due to the complexity of mass spectrometry. There are so many different ionization mechanisms, types of experiments and analyzers that a combination of

capillary zone el.	buffers	0-2 nl/min
isotachophoresis	strong buffers	0-100 nl/min

even just a few is not trivial; indeed, some interfacing techniques itself may exclude the application of one technique or the other. The following list may give an indication:

Ion generation Some of the items of the following list are well known ionization techniques, some are directly results of the interfacing method (e.g. thermospray):

- electron impact (EI)
- chemical ionization (CI)
- plasma (CI)
- FAB-SIMS
- thermospray
- electrospray
- ion evaporation
- laser ionization
- laser desorption

Data acquisition methods In the following list some of the common methods in MS are listed; this may appear trivial, but a closer inspection reveals more implications with respect to resolution, accurate mass measurements, sensitivity, high mass capability a.s.o.; in particular the detector technology, ion optics and computer integration are of eminent importance in this respect.

- acquisition of full spectra (for identification, library searches)
- selected ion recording (for quantitation)
- MS-MS- ... experiments (for structure elucidation, sequencing, mapping)
  * daughter ion spectra
  * parent ions
  * neutral loss
- determination of molecular weights

Analyzers It is obvious that some of the different analyzers used today offer special advantages while unable to perform other experiments. The list of widely used analyzers became longer again recently, since the ion traps are on their way to become grown up mass spectrometers and the time of flight instruments are reborn.

- quadrupoles
- sector field instruments
- time of flight spectrometer
- ion traps
- ion cyclotron resonance (fourier transform) MS

Taking all this aspects together it is evident that the LC-MS problem has many solutions, dictated by the chromatography, the mass spectrometry / the mass spectrometer and, of course, the problems one has to solve.

THE INTERFACE TECHNIQUES:

Methods comprising desorption techniques

The first chapter in the discussion of techniques deals with interfaces based on sputter techniques. Although not an LC-MS technique as such, thin layer chromatography (TLC) with SIMS[1], FAB[2] and laser desorption[3] should be mentioned, which has recently given very useful results and is promising for the future in particular for environmental analysis, since method development with TLC is very efficient; TLC using ultra thin active layers or blotting techniques have to be optimized. The first interface to be mentioned is

The moving belt

The moving belt system, invented by W. McFadden on the basis of Scotts experiments using a moving wire[4] as one of the first LC-MS interfaces, was in the beginning not used in conjunction with sputter techniques, but rather with thermal desorption of the analyte from the surface of the belt either by direct or indirect heating.[5]

The stream of eluents from the LC is directed onto the surface (sometimes with the help of thermally assisted spraying[6], thermospray[7] and frit systems[8] with contact to the belt) of a belt made from pure nickel or polyimide, which runs through a series of vacuum stages into the ion source of the mass spectrometer. In order to minimize the memory effects and to clean the belt, infrared heaters and washing steps have been included[9]. Soon the capability of the belt using SIMS[10], FAB[8,11] or laser desorption[12,7] was noticed.

But the technical requirements and the rather high costs, only to mention additional vacuum systems and the problems in maintenance of the belt system limited the number of users to only a few; in addition, severe background problems and, at least when used with thermal desorption, the limitations due to vaporization have not been overcome, although this interface has the advantage of an complete separation of chromatography and mass spectrometry, therefore allowing a wide range of chromatographic and mass spectrometric methods. HPLC using reversed phases, straight phases, in normal and micro versions and supercritical chromatography have been used in conjunction with EI, CI, and with SIMS, FAB and laser desorption.

Continuous flow FAB (CFFAB)

The continuous flow FAB interface, sometimes named online FAB or, in slightly different version, frit FAB, was developed by R. Caprioli et al.[13] and the frit FAB by Y.Ito et al.[14] The technique has the advantage of technical simplicity and compatibility with virtually every mass spectrometric system, and can be used as a routine technique on a day to day basis. Special attention has been paid to the design of the targets and several versions have been developed to improve the reliability and stability of the total ion current, which can be a problem; the introduction of a wick of filter paper improved the situation considerably

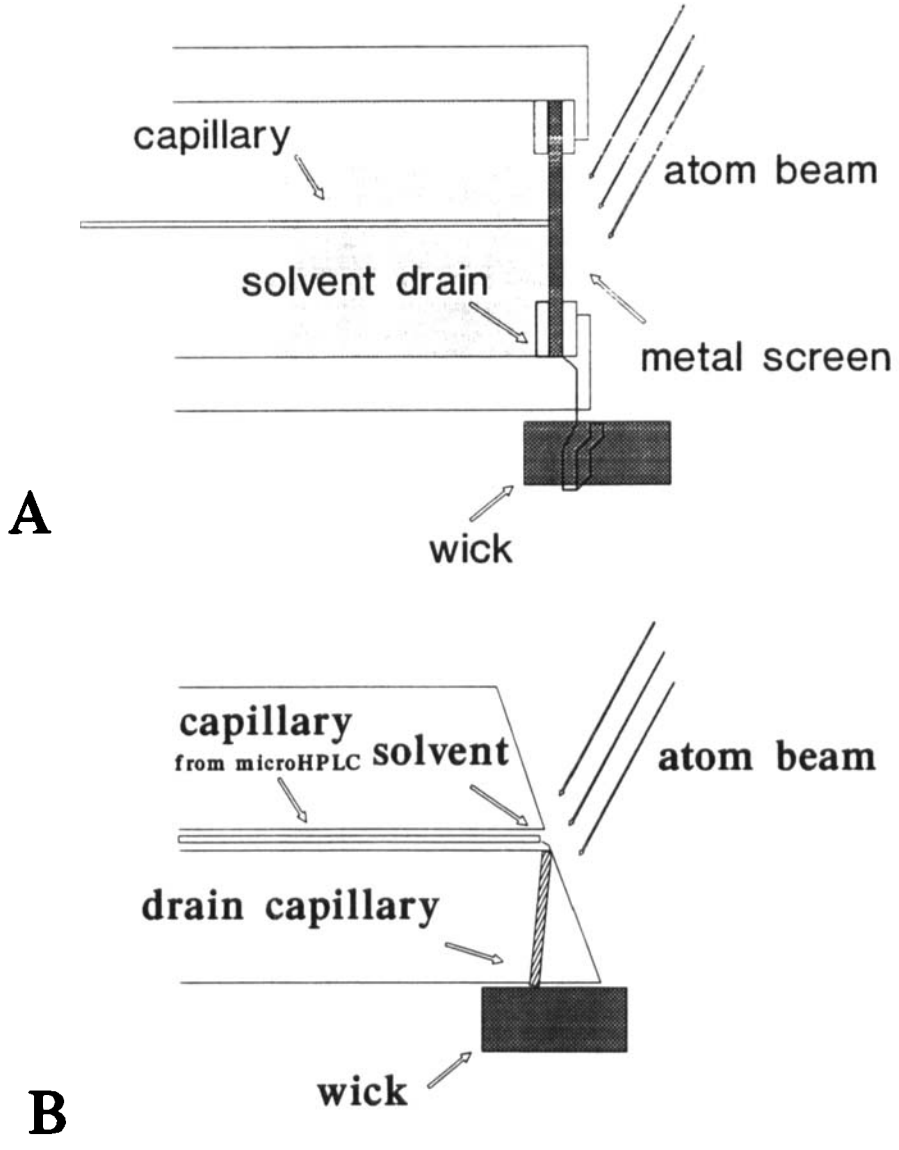

Figure 1 Continuous Flow FAB Target modifications to improve the stability of the signals; the top target is a frit-FAB type version, the bottom target has a drain capillary to force the fluid from the tip of the interface capillary into the wick. The small area exposed to the atom beam is sufficient for sputtering.

(Figure 1). The overall sensitivity is enhanced by adding high pumping capability to the source housing using an additional cryopump. Glycerol is necessary to enhance the desorption (as in FAB); this can be done by addition to the eluent (1–5%), using a post column setup or with concentric capillaries[15] to the target. The main limitation is that micro HPLC

has to be used with flow rates of 15 µl/min at maximum, although splitting of eluents is feasible. Recently, capillary zone electrophoresis has been interfaced with success[16,17], although serious problems due to very small amounts of sample and narrow peaks from the electrophoretic separation have to be handled. It seems that spectrometers with simultaneous detectors compare very favorably[18] to scanning instruments.

Methods using aerosols and additional ion generation

The second group of interfaces needs two main phases: in a first step an aerosol is generated, the droplets are further dried to decrease the size until the dissolved analyte remains and then, ions can be generated by any appropriate means. Several methods have been employed to produce aerosols with small droplets either in vacuum or under atmospheric pressure. In vacuum the problem of aggregation arises and careful control of heat becomes important; under atmospheric pressure, declustering can be achieved with collisions.

Direct Liquid Introduction (DLI) The direct liquid introduction was one of the first LC-MS interfaces to be used in modern organic mass spectrometry[19]. A flow of typically 10–20 µl/min is allowed to enter the ion source without any separation of eluent and analyte. Again, micro HPLC[20], a narrow capillary or a diaphragm as splitting devices[21] have to be used; the latter was build in commercial version[19].

Although this interface has merits in LC-MS and several attempts have been made to improve the sensitivity by adding make up gases[22,23], its disadvantages remain. The construction is relatively simple and common electron impact ion sources even without changing the pumping systems[24] have been used; the main handicaps are the inflexibility with respect to the ionizing method (CI only using the eluent as reactant gas) and the compounds, which could be analyzed, were not really different from those amenable to GC-MS. In addition, the technique makes the use of buffers difficult; only very volatile buffers may be used.

The Particle Beam Interface The particle beam interface (in the beginning called MAGIC by its developers, *M*onodisperse *A*erosol *G*enerator *I*nterface for *C*hromatography[25]) is different in so far, as the aerosol is produced under atmospheric pressure and dried to particles in an heated expansion chamber. A momentum separator serves to isolate the particles from the gas prior to reaching the ionizing chamber. The particles are destroyed by impact and the released sample are ionized using EI, CI[26,27] or even FAB[28]; EI spectra appear almost identical to common EI spectra obtained by direct probe or GC-MS, even allowing library searches.

A uniform distribution of droplets results in particles of a narrow size distribution, which can be handled more efficient by the separator and different technical versions of that interface have been designed. The problems of the technique are the unsatisfactory basic sensitivity, the strong variations in sensitivity for rather similar compounds and the difficulties in obtaining linear responses over a wider range of concentrations, resulting in complications in quantitative determinations. In addition, components eluting at the same time interfere rather strongly with unpredictable effects[29]. A rather interesting attempt has been

undertaken to introduce an online derivatization step into an particle beam to have the best of both worlds: the simple separation on reversed phase columns and the better spectra of derivatized highly polar materials[30].

The Supercritical Fluid Chromatography Interface From a technical point of view the SFC-MS interface is a direct introduction system with careful temperature control to the very end of the capillary[31]. The end of the capillary holds a frit or a diaphragm keeping the phase supercritical until it leaves the capillary into the ion source, otherwise the dissolved analyte would clog the end of the capillary. Since the gas load is rather high, only chemical ionization is possible with capillary SFC; when packed columns are used, momentum separators can reduce the pressure in the ion source and electron impact becomes possible[32]. Limitations of the method with respect to classes of compounds are mainly due to SFC itself and in most cases CI is an appropriate ionizing technique.

Chemical Ionization at Atmospheric Pressure The Atmospheric Pressure Ionization technique is one of the oldest principles for interfacing and has been described by Horning and coworkers already in 1960[33]. He noticed the potential of this setup for LC-MS applications, but almost 20 years were necessary to transform the technique, usually associated with electrospray, into a useful method, which holds promises for several important applications[34,35]; indeed it may come close to "the LC-MS technique". An aerosol is generated by spraying the liquid—an effluent of an LC—with a heated sheathflow of gas and a stable spray at atmospheric pressure is formed[36]. In the spray, ions are made by a corona discharge, forming a chemical ionization plasma. The ions are extracted into the mass spectrometer by means of a sampler—skimmer system with a curtain of drying gas to reduce the background cluster ions. It has been shown that in general basic compounds with high proton affinity can be detected with highest sensitivity[37] and in some cases a strong temperature dependence was observed[38].

Methods using aerosols incorporating ion generation

Two techniques, thermospray and electrospray, will be described. Both have in common that the formation of ions is an integrated part of the method, leaving no choice. The difference is that thermospray works under reduced pressure without external high voltage, whereas electrospray forms an aerosol at atmospheric pressure with the help of an external high tension. The success of both techniques depends largely on their unique features allowing for mass spectrometric information on compounds, which were hither to definitely intractable by MS.

The Thermospray Interface Thermospray, developed in 1980[39,40] is as yet the best adapted technique and has found the way into routine applications, although electrospray in conjunction with API/CI is moving in very fast. The effluent of an LC is rapidly heated in a steel capillary either by direct resistance heating[41,42] or by indirect heating using a cartridge system[43] to generate a fine aerosol with charged droplets; the details of the ion formation is still subject to discussions (Thomson and Iribarne[44,45], Röllgen[46] Vestal[47,48]). The ions are sampled into the mass spectrometer by means of a cone reaching into the center of the inner

chamber of the ion source, but the major part of the solvent is rapidly pumped away; improvements concerning the ion optics hence increasing the sensitivity of the technique are still being made[49]. The source has to be very tight to stabilize the pressure inside and the vacuum outside. It is possible to include a Townsend discharge or a filament and a repeller electrode to add plasma chemical ionization and the sensitivity, the selectivity and the fragmentation behavior is changed. The advantage of the technique can also be seen in the simplicity to adapt an already developed procedure in liquid chromatography, since the normal flow rates and some of the most common buffers can be used.

The Electrospray Interface/Ion Source Electrospray is most promising in biosciences due to its capability to measure molecular weights of proteins, nucleic acids and similar compounds with molecular weights exceeding 100,000 Daltons. Therefore, it attracts much attention. In addition, it becomes more and more evident that the technique is very well suited for small, highly polar substances as well. The most obvious difference to thermospray is—as already mentioned—that the spray is formed by charging droplets to an extent that the droplets explode by coulomb repulsion into smaller and smaller droplets. The setup is in brief as follows: A capillary is hold under high voltage at atmospheric pressure to generate the spray. The droplets are decreased in size by collisions with gas and finally, the highly charged ions from the core region of the droplets are extracted into the mass spectrometer by skimmer devices as explained for API/CI[50]. The main advantage is that due to the multiple charging even molecules with very high molecular weights can be detected at low m/z values allowing the use of rather inexpensive quadrupole instruments; up to 100 charges have been observed. In addition, the combination with capillary electrophoresis appears to be very powerful[51,52], although this interface is not fully developed yet.

APPLICATIONS

In general, LC-MS may be the method of choice always, when an LC separation is an essential step in an analytical procedure anyway, when the detector has to be sensitive and specific or when unknowns have to be identified. The advantage is that the development of

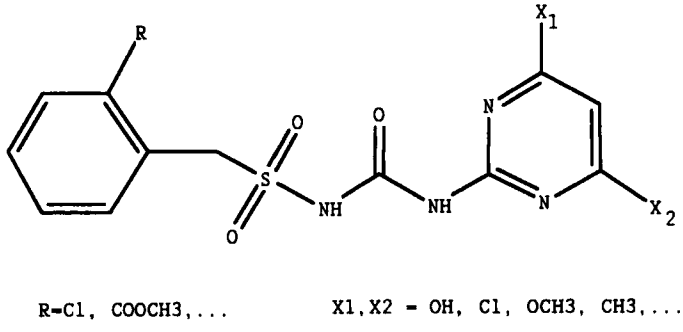

Figure 2 The general structure of the phenyl urea type herbicides Accent, Harmony, Ally, Glean, Oust, Londax, Express, and Classic.

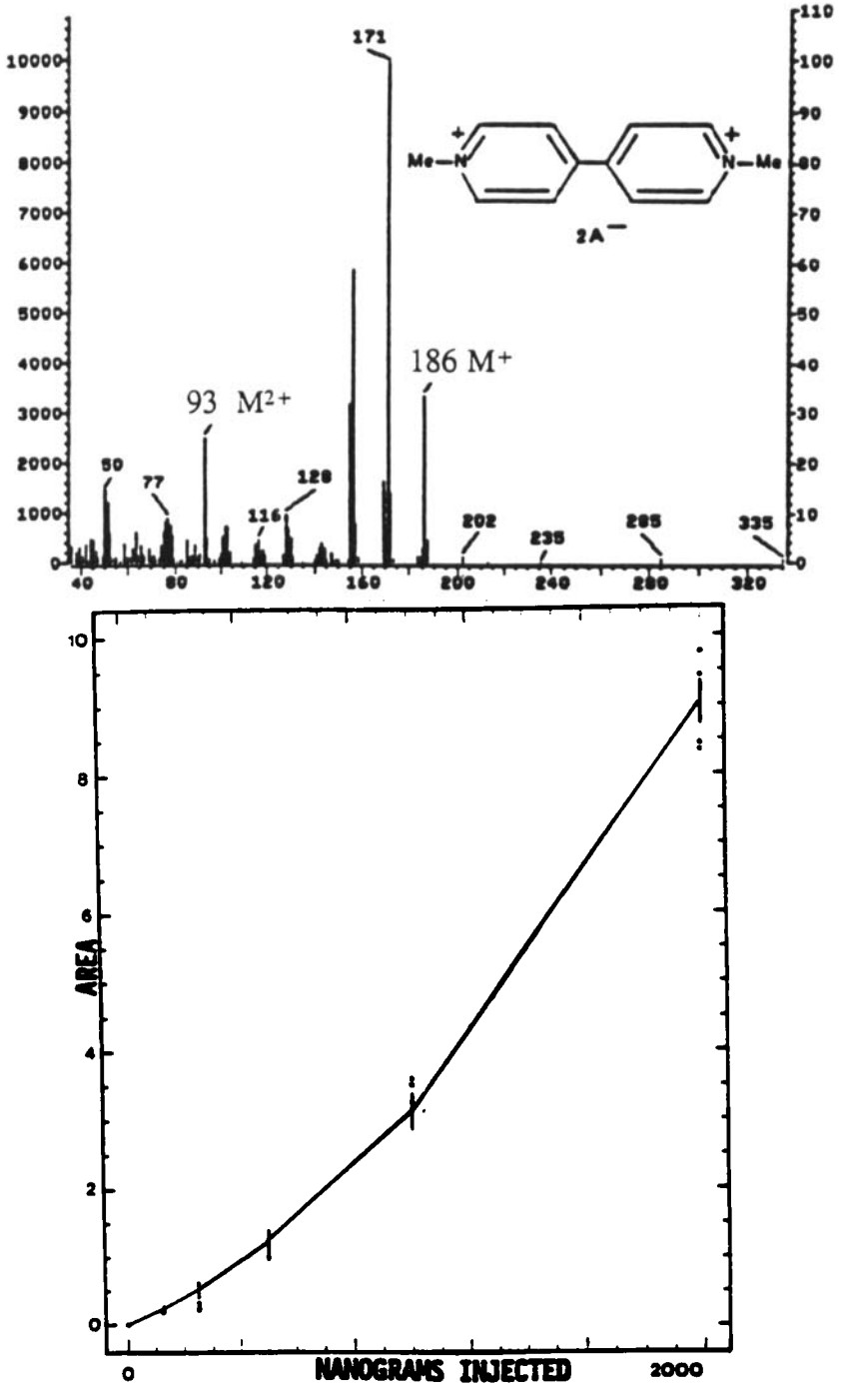

Figure 3 Particle Beam mass spectrum of the herbicide paraquat, a dication, showing the singly and the doubly charged ion as well as loss of a methyl group. The calibration curve in non linear over the full range[54].

a method needs no severe compromises for the adaption to mass spectrometry, the disadvantage is an added degree of complexity in instrumentation and, at least for precise quantitative work, the need for rather elaborated internal standards.

With emphasis on environmental applications, some of the principal domains will be discussed, where LC-MS is employed; instead of being comprehensive, I would rather like to address a few examples of convincing use.

Herbicides and metabolites To demonstrate this point, as the first example a study of the detection of sulfonylurea herbicides using continuous flow FAB[53] shall be given. The most convincing aspect here is that not only the herbicides can be identified with sufficient sensitivity (Figure. 2), but metabolic conversion and catabolic degradation can be studied with the same technique, which has been very difficult otherwise. Chromatograms and spectra of good quality have been obtained from hydroxylated and glucosylated metabolites of chlorsulfon and from some hydrolysis products.

Pollutants in waste water In the second application particle beam LC-MS is used to determine pollutants in waste samples[54]; it was possible to not only to detect, but also to quantify a rather long list of target compounds with good accuracy; in a laboratory evaluation study of the EPA concerning the detection of chlorophenoxy herbicides the LC-MS method was in the top 27% of all reporting laboratories; as illustration of the scope of particle beam LC-MS, the spectrum of paraquat and the quantitative results are given in Figure 3. In the same paper some indications were provided that the identification of unknown pollutants at very low levels is a new task, which became possible only through LC-MS.

Pollutants in drinking water The same task—the search for really unknown, even unexpected pollutants—is the objective of the third example; the author attempted to identify contaminants in drinking water[55] using thermospray LC-MS. Although only a few substances in the mixtures have been identified—several plasticizers on phthalate ester basis

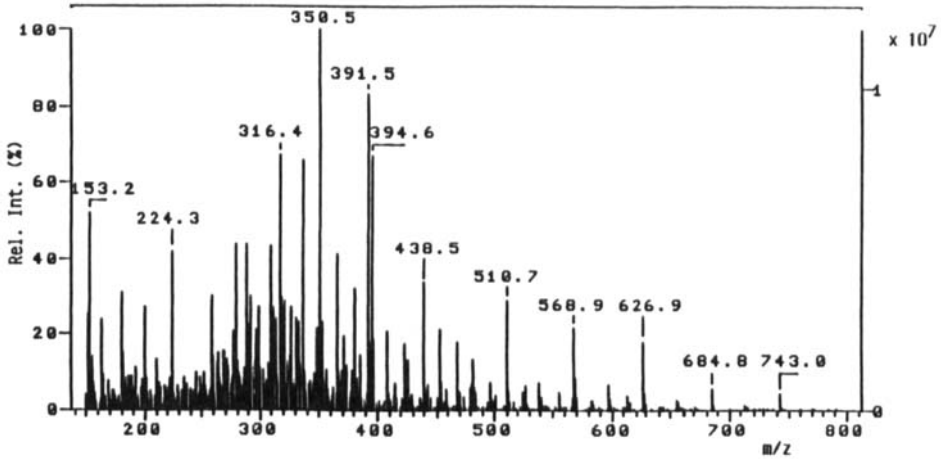

Figure 4 Thermospray mass spectrum of a drinking water extract showing a rather high content of plasticizers and surfactants as well as many unidentified compounds[55].

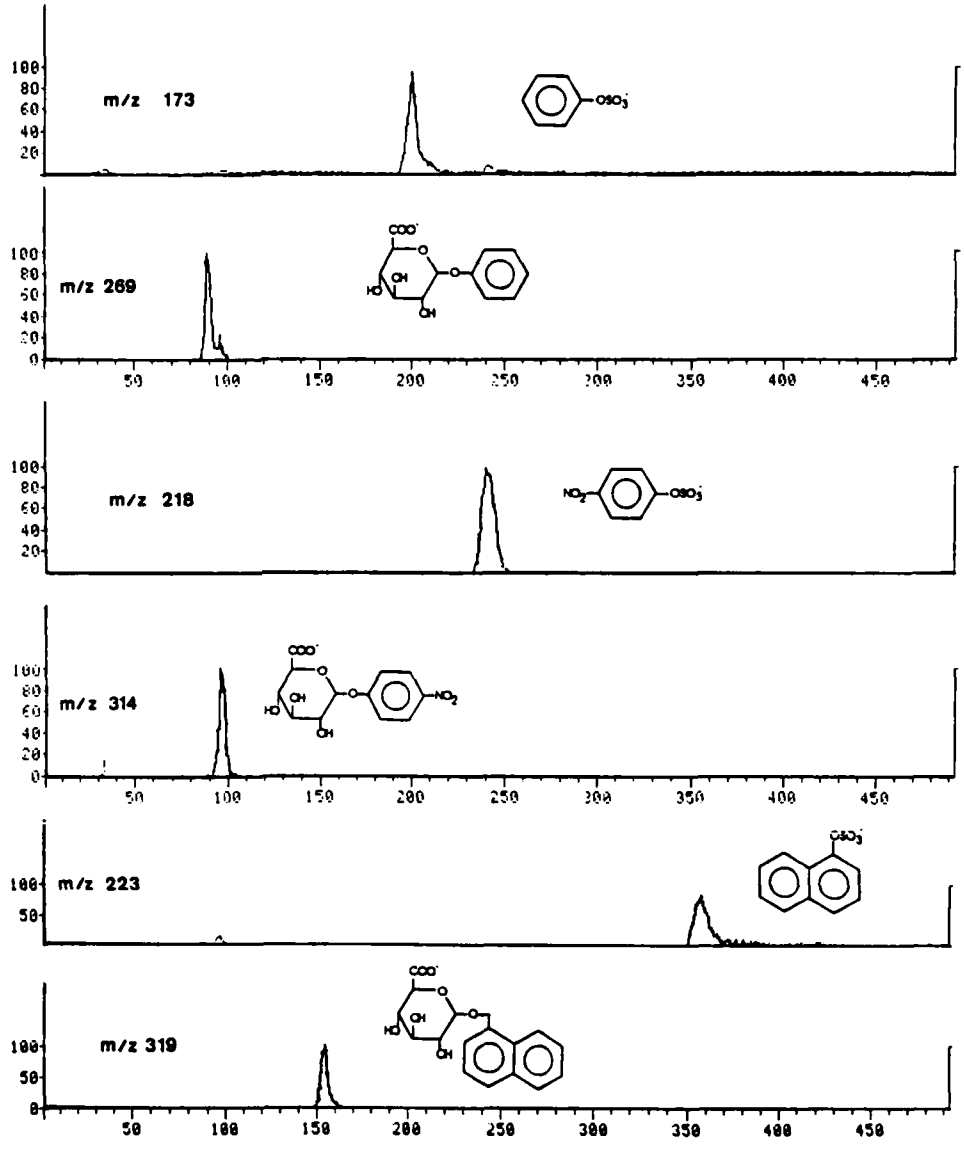

Figure 5 Separation of urinary metabolites of phenolic compounds on a strong anion exchange column using thermospray LC-MS with selected ion detection[56].

and materials with the propylene oxide moiety from surfactants—, a look on spectrum makes the problems evident. There are so many signals covering virtually every mass number that a comprehensive analysis is impossible (Figure 4). It evident also that the informations obtained by GC-MS and LC-MS complement each other.

Metabolites in urine The next example is different in so far, as it is aimed to identify metabolites of xenobiotic materials in urine, indicating risks for contaminated persons[56].

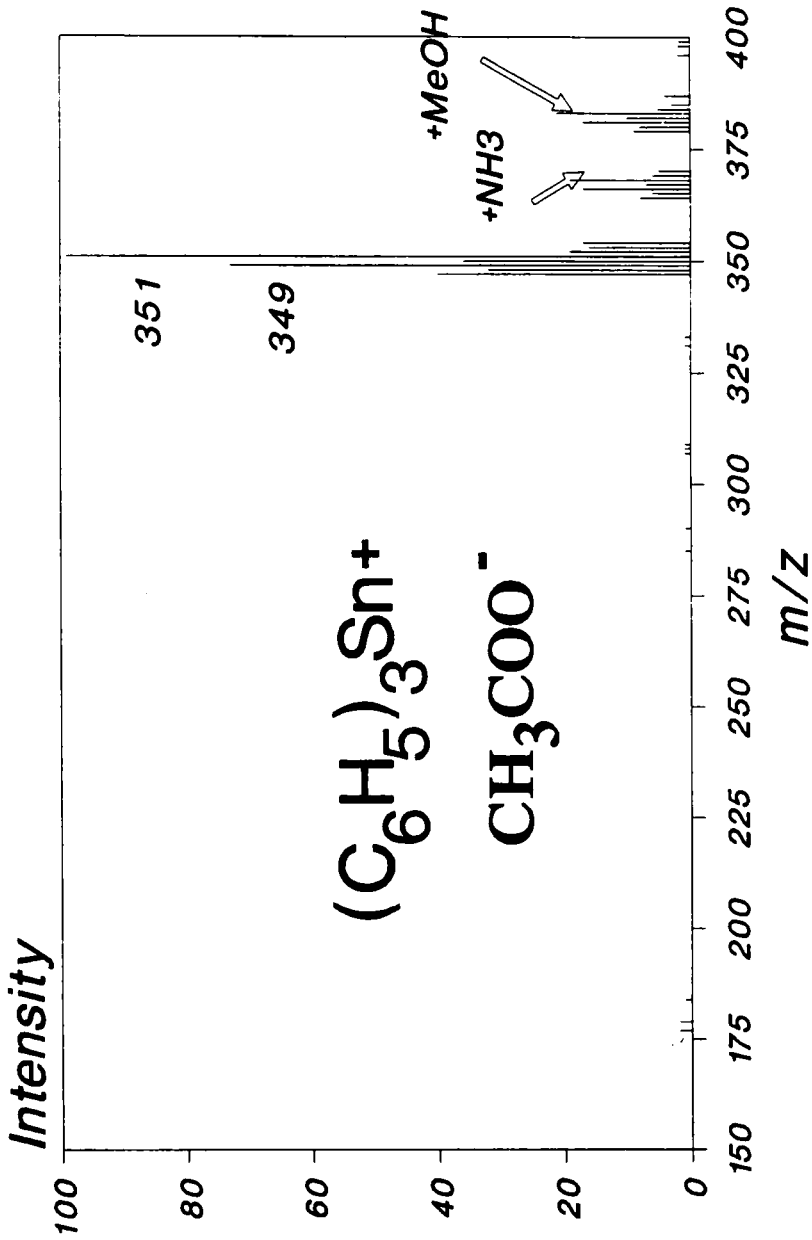

Figure 6 Thermospray mass spectrum of Fentin acetate (triphenyltin acetate), a fungicide; the cation and the adducts of ammonia and water are detected.

The metabolites of phenols—sulfates and glucuronates—are separated on a strong ion exchange column and detected using thermospray LC-MS (Figure 5) and LC-M -MS with reaction monitoring. This technique enhances the sensitivity further, but creates problems for quantitative measurements.

Heavy metal species Finally, the determination of species containing heavy metals, here: lead, tin and arsenic, using thermospray and atmospheric pressure ionization should be addressed, because speciation is most attractive. Trimethyllead has been found in urine of exposed workers using thermospray LC-MS and even quantitative information has been obtained, although no internal standard has been used[57]. The same technique was employed to obtain spectra of organotin compounds[58,59] like di- and tributyl tin cations and of the antifouling agent triphenyl tin acetate, which was recorded as cation (Figure. 6). Even better sensitivity has been obtained with atmospheric pressure ionization, although in this first study only flow injection without separation was used[60,61]; nevertheless, the techniques mentioned here appear very suitable to give insights in the fate of organo metal compounds in the environment and in human beings.

In conclusion, I would state: in my opinion there is no doubt that—at least today—, for most routine analytical work GC-MS is more sensitive, more reliable and, last not least, more affordable, in short: the better choice. This doesn't mean that LC/MS should not be developed; the contrary is true and hope, this point was made throughout this paper. But LC-MS should not be used to replace GC/MS, rather one should discover new answers to old questions and, equally important, it may serve to discover new questions (=problems?) in environmental chemistry.

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