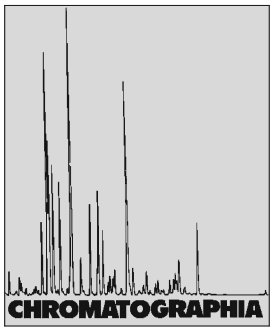
Modern Methods of Sample Preparation for GC Analysis



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Abstract

Today, a wide variety of techniques is available for the preparation of (semi-) solid, liquid and gaseous samples, prior to their instrumental analysis by means of capillary gas chromatography (GC) or, increasingly, comprehensive two-dimensional GC (GC × GC). In the past two decades, a large number of 'modern' sample-preparation techniques has been introduced, which have partly superseded their 'classical' counterparts. These novel techniques include off-line and on-line (sometimes semi- or fully automated) procedures, and exhaustive extraction as well as equilibrium techniques. In order to improve overall performance, aspects such as essentially organic solvent-less approaches, large-volume injection and miniaturization receive increasing attention. In most recent applications, mass spectrometric or element-selective detection have been used. The present review discusses the advantages and disadvantages, and relative performance, of most of the modern sample-preparation techniques and cites a number of illustrative applications for each of them.

Keywords

Gas chromatography
Sample preparation

Introduction

In the past 30 years, sample preparation/pre-treatment prior to chromatographic analysis has risen from near-obscurity to the prominent place it now holds in most studies on the trace-level determination of organic micro-contaminants in real-life samples. Traditionally, sample preparation is stated to be necessary for several reasons:

- improvement of the chromatographic behaviour of the analyte(s),
- improvement of detectability of the analyte(s), or
- isolation of the analyte(s) from the matrix.

Today, the first aim has become relatively unimportant because of both the quality of column packings in gas (GC) as well as column-liquid (LC) chromatography and the essential superfluousness of derivatizing or labelling polar analytes to allow their determination by means of GC. The other two aims, viz. improved detectability and efficient separation from interfering sample constituents, are, however; as important as they were several decades ago. Over the years, it has increasingly been realized that, in many cases, sample preparation is the most time-consuming, tedious and error-prone step of the total analytical procedure. In addition, sample preparation often cannot easily be coupled on-line (or at-line) with the subsequent instrumental separation-plus-detection step, thereby making automation of sample preparation (but without sample pre-treatment; see Fig. 1 below) plus GC analysis essentially impossible. Moreover, it frequently

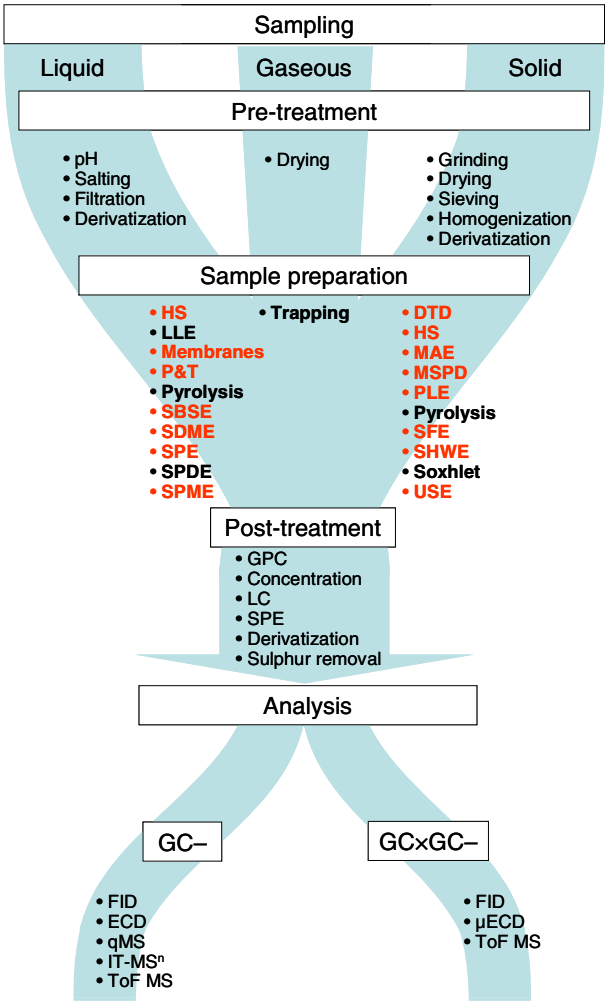

Fig. 1. Typical strategies for the GC determination of organic micro-contaminants in liquid, gaseous and solid samples. See Glossary for acronyms

adversely affects the overall performance of an analysis through effects such as loss and/or decomposition of target analytes, and introduction of extraneous contaminants. Such effects self-evidently have become more serious in recent years, with (inter)national directives and guidelines continually demanding improved performance—that is, reliable detection, identification and quantification at ever lower analyte concentrations.

Over the years, many groups of workers have attempted to improve the situation by designing new sample-preparation techniques (somewhat loosely called modern sample-preparation methods by most authors) to replace traditional methods such as Soxhlet, liquid–liquid (LLE) and ambient-pressure solid–liquid extraction—where one should immediately add that the former two methods are still widely used today, specifically in routine applications and, in the case of Soxhlet extraction, for reference purposes. The modern sample-preparation techniques range from highly selective methods to be used for one, or a few, target analyte(s) of special interest to wide-ranging, and usually rather non-selective procedures primarily meant for screening purposes, i.e., for target analytes as well as unknowns. Many methods can be made part of on-line (and, thus, automatable) systems, while others typically are off-line procedures. To enable their implementation, suitable sorbents, chemicals, membranes, low-dead-volume connections, cartridges, mini-columns, disks, etc., have been synthesized and/or designed and, whenever required, instrumentation and ancillary equipment was constructed and, frequently, commercialized. Over the years, a variety of applications for widely different analyte/matrix combinations have been published to demonstrate the practicality of the various approaches. Attention has been devoted, e.g., to designing integrated analytical systems, to miniaturization and to adequately matching the sample-preparation and instrumental-analysis time. The main aims were, and still are, to increase sample throughput, improve the overall quality of the sample-preparation procedures, and decrease the required sample sizes and/or the use of organic solvents and sorbents, and the amount of waste.

One more aspect of interest should be mentioned here, that of improving detection limits. In the past ten to fifteen years, there has been an increasing, and fully justified, emphasis on the proper identification and/or identity confirmation of all analytes of interest in each sample. As a consequence, quadrupole- or ion-trap-based mass-spectrometric (MS) detection is the state-of-the-art approach today for a large majority of all challenging analytical procedures. The overriding importance of MS detection will readily become apparent from the many tables included in the Applications section of this review. Even element-selective detection only plays a modest role today. Its most prominent application areas are the trace-level determination of organo-chlorine (and -bromine) micro-contaminants by GC with electron-capture detection, and the selective screening of organo-sulphur compounds by GC with S-based chemiluminescence detection.

Today, a wide variety of analytical methods is available for the GC determination of organic micro-contaminants in sample types such as air, water and other liquid samples, soils and sediments, fish and food, and biota. A typical schematic which displays most of the more important routes is shown in Fig. 1. In the present review, we focus on the sample-preparation step—with examples primarily relating to liquid and solid samples—and, more specifically, on

the characteristics of the modern techniques, i.e., those introduced in the past twenty or so years. These are marked in grey (electronic version in red) in the figure. All acronyms used in this figure and throughout the review are summarized in the glossary at the end of this review article. In the sub-sections, each of the separate techniques will be briefly described, and a number of selected applications, strategies and on-going developments will be given to illustrate the merits and demerits of each of these. For each technique, a number of recent reviews and/or other general reference sources will be given; in many cases, these have been used as the backbone of this chapter. Aspects such as spiking and recovery of analytes, and quantification (inclusive of validation and matrix effects) will not be discussed.

Sample Preparation Methods

Pressurized Liquid and Subcritical Hot-Water Extraction

Pressurized liquid extraction (PLE) involves extraction with solvents at elevated pressures (up to ca. 20 MPa) and temperatures (up to ca. 200 °C) without their critical point being reached, to achieve rapid and efficient extraction of trace-level analytes from a (semi-) solid matrix. Since its introduction in 1995 [1], PLE, also known as accelerated solvent extraction (ASE) and pressurized fluid extraction (PFE), several reviews have been published [2–5] and the technique has been shown to have significant advantages over competing techniques such as Soxhlet, Soxtec, and microwave-assisted extraction (MAE) extraction: enhanced solubility and mass-transfer effects and the disruption of the surface equilibrium are the main beneficial causes. As a consequence, compared with Soxhlet extraction, both time and solvent consumption are dramatically reduced. Originally, the use of PLE mainly focused on the isolation of organic micro-contaminants from environmental matrices such as soil, sediment and sewage sludge [1, 6]. Today, the technique is also used for the analysis of, e.g., food and biological samples. Instead of an organic solvent, pure water can also be used for extraction. In that case, the technique is usually called subcritical hot-water (SHWE) or pressurized hot-water (PHWE) extraction (see below).

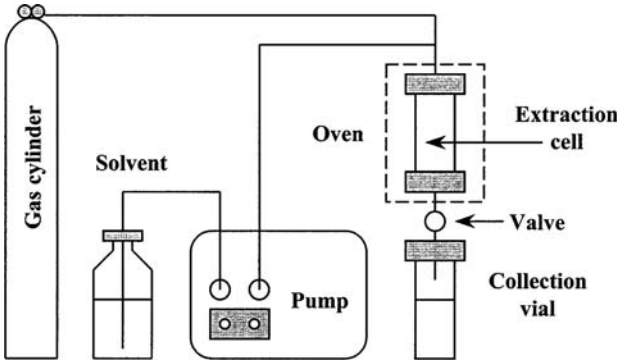

Fig. 2. Schematic representation of a PLE system [7]

The basic set-up of a PLE instrument is shown in Fig. 2. The system consists of a stainless-steel extraction cell in which the sample is placed; the programmed parameters (temperature and pressure) are kept at their specified values by electronically controlled heaters and pumps. The liquid extract is collected in a vial. The instrument used in most published studies is the ASE 200 (Dionex, Sunnyvale, CA, USA), in which up to 24 samples can be placed in a carrousel; extraction cells of 11–33 mL are available, and 40- and 60-mL vials for extract collection. Recently, Dionex introduced two new systems, ASE 150 and ASE 350. The former is a single-cell system; the latter enables automated extraction of up to 24 samples. Both systems accommodate seven, 1–100-mL, extraction cells. In several studies, SFE extractors have successfully been used for PLE of a variety of samples [8, 9]. In most cases, PLE is carried out in the static mode: once the sample has been placed in the extraction cell, organic solvent is added and the cell pressurized. After heating to the required temperature, static extraction is carried out for, typically, 5–20 min. Next, the valve is opened and the solvent allowed to flow to the collection vial. Fresh solvent (some 60% of the cell volume) is added to rinse the system, with a final brief nitrogen purge to guarantee complete removal of the solvent from the system. In the dynamic mode, the solvent (in most applications, water) is continuously pumped through the extraction cell at a constant flow-rate. Dynamic PLE is usually carried out in SFE extractors or in-house constructed devices.

If samples are semi-solid, a uniform distribution over an inert support such as sand prior to packing and completely filing the cell with the mixture are recommended. Recently, Dionex introduced a chemically inert material for samples pre-treated with acids or bases, Dionium. For heterogeneous samples, grinding—frequently to 63–150 μm d_p—is recommended. Grinding is anyway beneficial because it will shorten the diffusion pathways and increase the surface area. Drying the sample is important since moisture may diminish the extraction efficiency, specifically when non-polar solvents are used for extraction. If more polar solvents are used to extract wet samples, the drying step becomes less crucial. Finally, filters or glass wool plugs should be inserted at both ends of the extraction cell to prevent blocking of the connective tubing by small particles.

Next to what has been said above, several parameters influencing the PLE process should be briefly discussed. Often, the same solvent as used for conventional, e.g., Soxhlet, extractions is initially tested. It is also important to take into account the compatibility with subsequent steps of the procedure such as extract clean-up or target analyte

enrichment (actually, during enrichment, a change of solvent can often be effected). Generally speaking, the polarity of the solvent or solvent mixture should be close to that of the target compound(s). When analytes covering a wide range of polarities have to be extracted, mixtures of low- and high-polar solvents generally provide better results than single solvents. Alternatively, two extractions—one with a non-polar, and the second one with a more polar solvent—can be applied [10, 11].

In general, higher temperatures will cause an increase of the PLE efficiency due to enhanced sample wetting, better penetration of the extraction solvent, and higher diffusion and desorption rates of the analytes from the matrix to the solvent. They are therefore recommended provided there are no limitations associated with thermolabile analytes and/or matrices. To quote an example, a temperature of 100 °C is often selected as 'default value' and used for the PLE of POPs (persistent organic pollutants) from a variety of matrices with different solvents [12], while mixtures containing toluene often require temperatures close to 200 °C to provide maximum recoveries.

Pressure essentially plays no role other than to keep the extraction solvent liquid at the high temperatures used [1, 12, 13]. However, with wet samples [12] or highly adsorptive matrices [14], a high pressure can help to enhance the PLE efficiency by forcing the organic solvent into the matrix pores. This may explain why little effect of the pressure was observed during PLE of herbicides from dry soils, while in the case of moistened soils increasing the pressure from 4 to 10 MPa was beneficial.

Subcritical Hot-Water Extraction

SHWE is a PLE-type technique based on the use of water as extraction solvent at temperatures between 100 and 374 °C (critical point of water, 374 °C and 22 MPa) and at pressures sufficient to keep it in the liquid state. Under these conditions, the dielectric constant of water, ε, i.e., its polarity, can be easily and dramatically lowered by increasing the temperature. Pure water at ambient temperature and pressure has an ε of 79, while increasing the temperature to 250 °C at a pressure of 5 MPa effects a significant reduction to about 27 [14]. This value is similar to that of ethanol at 25 °C and 0.1 MPa and, consequently, low enough to dissolve many medium-polarity compounds. As with PLE, increasing the temperature at moderate pressure also reduces the surface tension and viscosity of water, which results in an enhanced solubility of the analytes. Since pressure has only a limited influence on the solvent characteristics of water as long as it remains in the liquid state, one can increase the pressure to avoid the formation of steam—which is highly corrosive and can degrade the analytes—at the high temperatures used in SHWE without comprising the achieved decrease of polarity.

One should note that, since water is not a GC-compatible solvent, after SHWE the analytes in the extract must be transferred to a GC-compatible medium, e.g., by liquid–liquid extraction (LLE) [15], or by solid-phase micro extraction (SPME) or stir-bar sorptive extraction (SBSE) [16].

Applications Selected PLE and SHWE applications for the isolation of a wide range of compounds from a variety of matrices are given in Table 1. As an example of a typical PLE-based analysis, Frenich et al. [17] reported the multiresidue analysis of organochloro (OCPs) and organophosphorus pesticides (OPPs) in muscle of chicken, pork and lamb. 5 g of freeze-died sample were mixed with Hydromatrix and extracted by PLE using ethyl acetate as extraction solvent. After GPC clean-up followed by concentration, 10 µL of the final extract were analysed by GC–QqQ-MS; LODs were in the range of 0.02–2 µg kg^{-1}. Compared with Soxhlet extraction, PLE was found to yield improved extraction efficiency and precision. Moreover, the extraction time was shorter and the consumption of solvents much lower.

One aspect that merits attention is that, for most applications, PLE/SHWE has to be combined with a clean-up step to remove co-extracted matrix constituents such as, e.g., lipids, pigments or resins. Clean-up procedures typically are the same as used in classical procedures. Recently, several authors used matrix solid-phase dispersion (MSPD) for in situ clean-up in the extraction of trace compounds from a variety of samples: sometimes MSPD conditions (see section on MSPD below) can be selected to retain particular compounds by choosing an appropriate dispersion material/eluent combination. A novel approach for PAHs in soils and sediments is to purify the PLE extract by direct large-volume injection (LVI) in a programmed temperature vaporiser (PTV) equipped with a liner packed with an appropriate sorbent [18]. The PLE efficiencies and performance data compared well with those obtained by 6-h Soxhlet extraction and other conventional procedures [19]. As an example, Fig. 3 shows a 50-µL LVI–GC–MS trace obtained after miniaturized PLE of only 50 mg of a naturally contaminated organic soil and 100 µL of toluene.

As regards SHWE, Richter et al. [15] reported the determination of pesticides in soil using continuous SHWE (270 °C, 8.2 MPa, 2 mL min^{-1}, 90 min). The pesticides in the aqueous extract were quantitatively transferred by LLE with dichloromethane and injected into a GC–MS system. For the 17 pesticides studied, LODs were 3–140 µg kg^{-1}. Comparison with Soxhlet extraction showed the analytical performance to be quite similar. The main advantage of SHWE over Soxhlet extraction was the time involved in the extraction process: SHWE was some 10 times faster. Furthermore, less than 10 mL of solvent was used compared with 300 mL for Soxhlet extraction.

Several applications involving on-line coupling of SHWE with GC have been reported (e.g., [20, 21]). On-line coupling of SHWE with GC is simpler than coupling of PLE, because the aqueous solubility of the analytes decreases dramatically when the water is cooled to ambient temperature. Trapping of the extract on, e.g., a solid-phase trap is thus relatively easy. Using a somewhat different approach, Lüthje et al. [20] analysed pesticides in grapes by SHWE–microporous membrane liquid–liquid extraction (MMLLE)–GC–MS. Grape

Table 1. Selected applications of PLE and SHWE combined with GC

Analytes	Sample (g or mL)	Pre-treatment	Conditions				Post-treatment	Detector	LOD (μg kg^{-1})	Recovery (%)	Ref.
			P (MPa)	T (°C)	Extraction time (min)	Solvent					
PLE											
PCBs, OCPs	Fish (10)	70 g Na_2SO_4	10	90–120	3 × 5	Hex–DCM (1:1), Hex–Acet (4:1)	GPC, conc., dissolve	ECD	–	–	[22]
PCBs, pesticides	Sediment (5)	Sieve, 2 g Na_2SO_4	6.9	100	5	DCM	Conc., dissolve, SPE, conc., dissolve	MS	0.2–0.6	80–105	[23]
PCBs, PCDD/Fs	Food	Grind, Na_2SO_4	13.8	100	2 × 5	Hep	Conc.	HRMS	–	81–97	[24]
PCBs	Meat (0.5)	Blend with Na_2SO_4 and SiO_2–H_2SO_4	12	100	2 × 10	Hex	Silica	ECD	0.009–0.3	–	[25]
PAHs	Mussel (5), salmon (1.3), fish feed (1.5)	Homogenise	10.3	100	2 × 5	DCM	Filter, GPC, conc.	MS	0.1–20 ng kg^{-1}	77–118	[26]
PAHs	Soil (0.050)	Dry, sieve	15	200	1 × 10	Tol	PTV	MS	0.8–30		[18]
OCPs	Soil (1)	Dry, 0.25 g diatom. earth	10.3	100	5	Hex–Acet (1:1)	Carbon, conc., dissolve		–	83–141	[27]
OCPs, OPPs	Chicken, pork, lamb (5)	Freeze-dry, 7 g Hydromatrix	10.8	120	2 × 5	EtOAc	Conc., dissolve, GPC, conc., dissolve	QqQ-MS	0.02–2	70–90	[17]
OCPs	Vegetables (0.3)	Grind, 0.075 g diatom. earth	10	110	5	Hex–Acet (1:1)	Conc., SPE	ECD	2–6	80–120	[28]
Pesticides	Sludge (1)	Freeze-dry, grind, sieve, 1 g Florisil, 1 g Hydromatrix	13.8	120	2 × 5	DCM–Acet (1:1)	Conc., SPE, deriv.	MS	1–30	36–98	[29]
Chloroacetanilides, triazines, phenylureas	Soil (15)	Dry, 0.25 g diatom. earth	10	50	3 × 3	Acet	Conc., dissolve	MS	0.2–2	>85	[30]
Alkyl parabens, triclosan	Indoor dust (0.5)	3 g Florisil	13.8	103	3 × 1	EtOAc	Conc., deriv.	MS/MS	0.4–1	76–98	[31]
Oil contamination	Soil (7)	3 g Celite 545	14	100	5	Hex–Acet (1:1)	Conc.	FID[a]	–	–	[32]
SHWE											
PAHs	Soil (–)		1	300	50	Water (0.5 mL min^{-1})	MMLLE	FID	0.2–0.6		[21]
Atrazine	Kidney (0.5)	2 g Hydromatrix, dispersion (2 g XAD-7 HP), 0.3 g diatom. earth	5	100	3 × 10	Water–EtOH (7:3 *v*/*v*)	SPME	MS	20	104	[33]
Pesticides	Grapes (0.5)	Dry	–	120	40	Water (1 mL min^{-1})	MMLLE	MS	0.1–0.6	9–28	[20]
Volatiles	*Ziziphora taurica* (1)	Dry, grind	6	150	30	Water (2 mL min^{-1})	SPE	ToF MS[a]	–	–	[34]
Ligustilides	*Ligusticum chuanxiong*, *Angelica sinensis* (0.20)	Dry, grind	4	150	10	Water (2 mL min^{-1})	HS-SPME	MS	–	–	[35]
Essential oils	*Achillea monocephala* (1), *Origanum onites* (1.5)	Dry, grind	6	150	30	Water (2 mL min^{-1})	SPE	ToF MS[a]	–	>97	[36, 37]
Essential oils	*Fructus amomi* (0.050)	Dry, grind	5	230	5	Water (1 mL min^{-1})	HS-SPME	MS	–	90	[38]
Essential oils	*Coriandrum sativum* L. (4)	Grind	2	125	120	Water (2 mL min^{-1})	LLE	FID, MS	–	–	[39]

[a] GC × GC instead of GC analysis

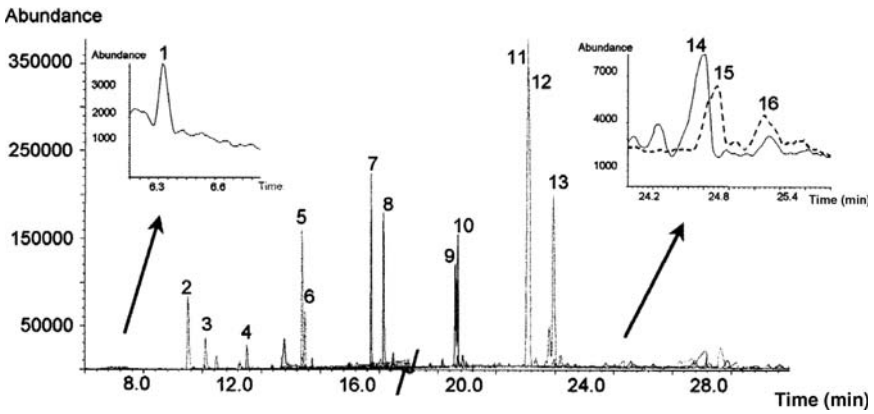

Fig. 3. 50-µL LVI–GC–MS (SIM) of endogenous PAHs extracted from 50 mg of an organic soil with a miniaturized PLE using 100 µL of toluene at 200 °C and 15 MPa. Peak identification: **1** = Naphthalene, *m/z* 128/102; **2** = Acenaphthylene, *m/z* 153/152; **3** = Acenaphthene, *m/z* 153/152; **4** = Fluorene, *m/z* 165/166; **5** = Phenanthrene, *m/z* 178/176; **6** = Anthracene, *m/z* 178/176; **7** = Fluoranthene, *m/z* 202/101; **8** = Pyrene, *m/z* 202/101; **9** = Benzo[*a*]anthracene, *m/z* 228/226; **10** = Chrysene, *m/z* 228/226; **11** = Benzo[*b*]fluoranthene, *m/z* 252/250; **12** = Benzo[*k*]fluoranthene, *m/z* 252/250; **13** = Benzo[*a*]pyrene, *m/z* 252/250; **14** = Indene[1,2,3-*cd*]pyrene, *m/z* 278/276; **15** = Benzo[*ghi*]perylene, *m/z* 278/276; **16** = Dibenzo[*a,h*]anthracene, *m/z* 278/267. Slash in the *x*-axis indicates change in the ions monitored [18]

samples mixed with sea sand were dynamically extracted by SHWE. The extract was led to the donor side of the MMLLE unit (see section on membranes for use of MMLLE) and MMLLE extraction took place during SHWE. Next, the (static) acceptor solvent was transferred on-line to the GC–MS system. However, the recoveries were only 9–26% due to the low efficiency of the MMLLE step; LODs were 0.1–0.6 µg kg^{-1}.

Microwave-Assisted Extraction

Today, MAE is widely recognized as a versatile extraction technique, especially for solid samples. MAE utilizes electromagnetic radiation to desorb analytes from their matrices. The microwave region is considered to exist at frequencies of 300 MHz to 100 GHz. Although the whole of this region is potentially available for use, all (domestic and scientific) ovens operate at 2.45 GHz only.

The main advantages of MAE are the usually high extraction rates due to the very rapid heating and the elevated temperatures, and the ease of instrument operation. A drawback is that the heating is limited to the dielectric constant of the sample/solvent. The primary mechanisms for energy absorption in MAE are ionic conductance and rotation of dipoles. Ionic-conductance heating is due to the electrophoretic migration of ions when a microwave field is applied. The resistance of the matter to this flow will generate heat as a consequence of friction. Dipolar molecules couple electrostatically to the microwave-induced electric field and tend to align themselves with it. Since the microwave field is alternating in time, the dipoles will attempt to realign as the field reverses and so are in a constant state of oscillation at the microwave frequency. Frictional forces cause heat to be developed due to the motion of the dipoles [40].

In MAE, sample and organic solvent are subjected to radiation from a magnetron. There is a high cost differential between microwave ovens for domestic use and for MAE, which sometimes precludes the purchase of a dedicated MAE system. However, for safety reasons (explosions in the presence of an organic solvent), it is strongly recommended to use only dedicated systems. Although the application of several brands and models is reported in the literature, there is a tendency for the models of CEM (Matthews, NC, USA) and Milestone (Shelton, CT, USA). There are two types of heating system [41]—either the sample is heated in an open glass vessel fitted with an air or water condenser [focused microwave-assisted extraction (FMAE)], or a closed sample vessel constructed in microwave-transparent material is used [pressurized microwave-assisted extraction (PMAE)]. In an open-style system, the individual sample vessels are heated sequentially. The system operates at 0–100% power increments which can be operated in stages and for different time intervals. Sample and appropriate solvent are introduced into a glass vessel which is connected to the condenser to prevent loss of volatile analytes and/or solvent. In a common closed system, up to twelve extraction vessels can be irradiated simultaneously. Safety and relevant experimental features (temperature and pressure control, in one extraction vessel) are incorporated in such systems, and extraction conditions can be varied according to either the percentage power input or by in situ measuring of the temperature and pressure in the monitoring vessel [41–43]. Figure 4 shows the schematic of a closed-vessel MAE system and of a standard as extraction vessel. The use of PMAE is preferred in the case of volatile compounds. However, after extraction one has to wait for the temperature to decrease before opening the vessel, which increases the overall extraction time. PMAE is quite similar to PLE, as the solvent is heated and pressurized in both systems, the only difference being the means of heating. Consequently, as for PLE, the number of parameters is limited, which makes application of the technique quite simple [42, 43]. However, one should be aware that, in MAE, re-adsorption of the extracted analytes is still possible during the final cooling step, while re-adsorption is negligible in PLE where the extraction solvent is removed from the cell while still warm. With regard to the extraction efficiencies, FMAE and PMAE systems were shown to have similar performances [44, 45].

The nature of the solvent is of prime importance in MAE. Next to the fact that the solvent should efficiently solubilize the analytes and be able to desorb them from the matrix, its microwave-

absorbing properties have to be considered. Most of the time, the solvent is chosen to absorb the microwaves without causing strong heating to avoid analyte degradation. For thermolabile compounds, the microwaves may be absorbed only by the matrix, which will result in heating the sample and release of solutes into the cold solvent [47]. This last mechanism can also be used when an absorbing material (e.g., Weflon) is added to the sample [48, 49].

Applications PAHs, PCBs, phthalate esters and pesticides are prominent classes of target analytes and sample types include soils [50, 51], sediments [52] and various types of biological matrices [53, 54]. Relevant information on a selected number of recent MAE-based applications is presented in Table 3. Post-treatment is (almost) always needed. The operating conditions have to be optimized for each analyte–matrix combination, but it is possible to give some general recommendations: temperature, 60–150 °C; pressure, <1.4 MPa; extraction time, 5–30 min; solvent, 5–50 mL per 0.1–25 g sample, with hexane–acetone being often used. MAE-relevant characteristics of this mixture and of other solvents also frequently used are presented in Table 2.

As is to be expected from the above discussion, almost all MAE applications involve off-line procedures. However, in recent years, several studies were published which use an on-line approach, which is usually combined with dynamic MAE (DMAE) [40, 52, 56]. Interfacing was based on solid-phase trapping on a copolymer sorbent with subsequent drying with nitrogen and large volume injection (LVI) to enable introduction of the whole sample extract into the GC system. Methanol was used for MAE, with a 1:4 dilution with water prior to the solid-phase trap to ensure efficient analyte retention. Figure 5 shows a schematic of the on-line DMAE–SPE–GC system. In one study [40], organophosphate esters were determined in air samples. The total sampling-plus-analysis time was less than 1.5 h, analyte recoveries were over 97% and NPD-based LODs were 60–190 pg m^{-3}.

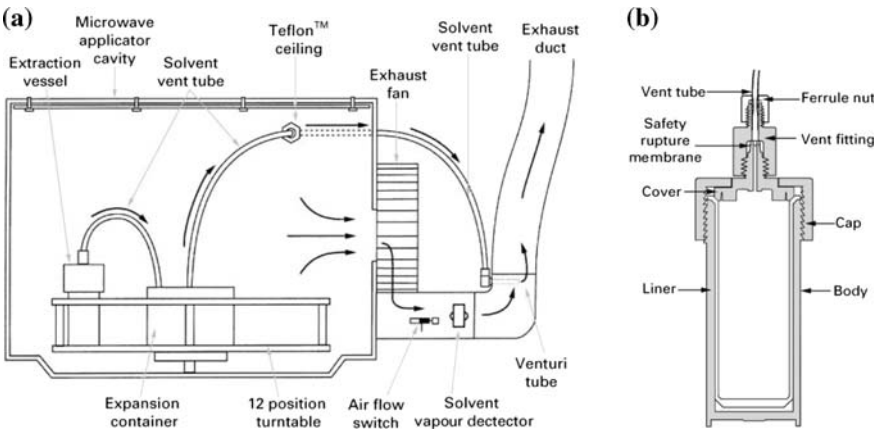

Fig. 4. Schematic of (**a**) a closed-vessel MAE system, and (**b**) a standard lined extraction vessel [46]

Table 2. MAE solvent characteristics [55]

Solvent	Dielectric constant	Boiling point (°C)	Closed-vessel temperature (°C)[a]
Hexane	1.89	68.7	–
Hexane–acetone	–	52.0[b]	156
Dichloromethane	8.93	39.8	140
Acetone	20.7	56.2	164
Methanol	32.6	64.7	151
Acetonitril	37.5	81.6	194

[a] At 1.2 MPa
[b] Experimentally determined

As regards miniaturization, Ericsson and Colmsjö [52] inserted a preheating column in front of the extraction cell in the microwave cavity. Using this configuration the authors demonstrated the feasibility of DMAE coupled on-line with SPE for the accurate determination of PAHs in a reference sediment (recoveries, 88–104%; RSDs, 1–10%) although only 60 mg of sample were used. Sample preparation was complete in ca. 45 min and the final extracts, collected by back-extraction of the analytes concentrated on a 10 mm × 2 mm PLRP-S SPE cartridge with 400 µL of MTBE, were directly analysed by 1-µL injection in a GC–PID system.

MAE was compared with Soxhlet, USE (ultrasound-assisted extraction) and SFE for the extraction of 94 compounds listed in EPA Method 8250 [57]. Freshly spiked soil samples and two reference materials were extracted using MAE (conditions: sample, 10 g; solvent, 300 mL hexane–acetone, 1:1; temperature, 115 °C; extraction time, 10 min), Soxhlet extraction (conditions: sample, 10 g; solvent, 300 mL hexane–acetone, 1:1; extraction time, 18 h), and SFE (sample, 5 g; solvent, 10% MeOH-modified supercritical CO_2; pressure, 45 MPa; temperature, 100 °C; extraction time, 60 min). The recoveries for MAE and Soxhlet were found to be similar—those for USE were slightly higher, and for SFE clearly lower. Precision was best with MAE and worst with Soxhlet extraction.

Ultrasound-Assisted Extraction

In ultrasound-assisted extraction (USE), acoustic vibrations with frequencies above 20 kHz are applied to extract analytes from permeable (semi-)solid matrices. The top end of the frequency range is limited only by the ability to generate the signals; frequencies in the GHz range have been used in some applications. Sound waves are intrinsically different from electromagnetic waves: while the latter can pass through

Table 3. Selected applications of MAE combined with GC

Analytes	Matrix (g or mL)	Pre-treatment	Solvent (mL)	Temperature (°C)	Extraction time (min)	Pressure (MPa)	Post-treatment	Detector	LOD (μg kg^{-1})	Recovery (%)	Ref.
FMAE											
PCBs	Ash (1.5)		DMSO (30)	120	10		Dilution with water, SPME	ECD, MS	–	83–111	[58]
PCBs, chlorinated alkanes	Sediments (5)		Hex–Acet (1:1) (30)	115	15		Florisil, conc.	ECD, MS	0.008–0.02; 1.5	90	[59]
PBDEs	Marine biological tissues	Grind with Na_2SO_4	Pen–DCM (1:1) (25)	115	15		GPC, conc.	MS	<0.1	89–97	[60]
PBDEs	Domestic dust (0.8)		Hex (8) + 10% NaOH (4)	80	15		Na_2SO_4, Florisil, conc.	MS/MS	0.3–0.6	92–114	[61]
PBDEs	Sediment (5)	Freeze-dry, pulverize, sieve	Hex–Acet (1:1) (48)	152	24		Filter, GPC, conc.	MS/MS	0.004–0.02	75–95	[62]
Organo-P flame retardants	Indoor dust (0.5)		Acet (10)	130	30		Centrifuge, SPE, silica, conc.	NPD	–	85–104	[63]
PAHs	Airborne particles		Acet–Tol (5:95) (20)	(150 W)	20		Silica, conc.	MS	–	77–116	[64]
Pesticides	Soil (1)	Sieve	Water–MeCN–Hex (1:1:1) (1) + Hex (5)	130 (250 W + 900 W)	2 + 10		Conc.	ECD	–	72–101	[65]
OCPs	Vegetables (0.3)	Grind	Hex–Acet (1:1) (15)	(800 W)	4		Filter, conc., SPE	ECD	0.2–2	80–120	[66]
OCPs	Sesame (5)	Grind	Water–MeCN (5:95) (40)	100	10		Centrifuge, Na_2SO_4, Florisil	MS	1	84–102	[67]
Pyrethroids	Soil (2)		Tol (10) + water (1)	(700 W)	9		Florisil, conc., copper wires	ECD, MS	0.3–200	97–106	[68]
Pyrethroids	Strawberries (25)		MeCN–water (1:1) (30)	65	5		SPME	MS	1–14	–	[69]
POPs	Marine sediments (1)		Water (8)	80	20		LPME hollow fibre membrane	MS	0.1–0.7	73–117	[70]
Volatile organic acids	Tobacco (0.4)	Dry, grind	10 mM HCl (20)	120 (950 W)	20		pH 2–3, filter	FID	–	–	[71]
SVOCs	Sebum	Deposit on sebutape	Hex–Acet (2:1) (10)	60	10		SPME	MS	20–300	94–100	[72]
Nonylphenol, octylphenol	Paper (2)		Water (15)	65	5		SPME	MS	0.1 (OP) 5 (NP)	–	[73]
Chlorophenols	Sludge (0.5), sediment (1)	Freeze-dry, sieve	Acet–MeOH (1:1) (30)	130	20		Centrifuge, SPE, deriv.	MS/MS	–	78–106	[74]
PMAE											
PAHs, PCBs, phthalates, nonylphenols	Sediments (1)	Mix with 1 g activated copper	Acet (15)	(80% of full power)	15	0.15	Florisil, conc.	MS	0.5–11 (PAH) 0.4–1.0 (PCB) 0.5–20 (Ph) 100 (NP)	–	[75]
OCPs	River sediments (5)		Hex–Acet (1:1) (25)	120	20	2	Centrifuge, conc., silica, conc.	MS	–	–	[76]
Endocrine disrupters	River sediments (5)	Drying (100 °C, 4 h)	MeOH (25)	110	15	1.4	Conc., silica (EtOAc–Hex (4:6)), conc., deriv.	MS	0.2–1	61–133	[77]
Irgarol 1051	Marine sediments (3)		Water (30)	115	10	1.4	SPE, conc.	MS	1–2	85–114	[78]
DMAE											
PAHs	Sediment and soil (0.060)		MeOH (24) (800 μL min^{-1})	110	20	3	On-line SPE	MS (SIM)	–	88–108	[52]
Organo-P esters	Air (62 500)	Gas-solid extraction	MeOH (5) (500 μL min^{-1})	110	10	3	On-line SPE	NPD	60–190 pg m^{-3}	97–103	[40]

vacuum, sound waves must travel in matter, as they involve expansion and compression cycles travelling through a medium. In a liquid, the expansion cycle produces negative pressure and bubbles or cavities are formed. When a bubble can no longer efficiently absorb the energy from the ultrasound, it implodes. The whole process, known as 'cavitation', takes place within about 400 μs. Rapid adiabatic compression of gases in the cavities produces extremely high temperatures and pressures, estimated to be about 5,000 °C and roughly 100 MPa, respectively. The high temperatures and pressures cause the formation of free radicals and other compounds; for example, the sonication of pure water causes thermal dissociation into hydrogen atoms and OH radicals, the latter forming hydrogen peroxide by recombination [79].

When cavitation occurs in a liquid close to a solid surface, cavity collapse is asymmetric and produces high-speed jets of liquid. Liquid jets driving into the surface have been observed at speeds close to 400 km h^{-1}. Such a strong impact can result in serious damage to impact zones and can produce newly exposed, highly reactive surfaces. The very high effective temperatures (which increase solubility and diffusivity) and pressures (which favour penetration and transport) at the solvent/solid matrix interface, combined with the oxidative energy of radicals created during sonolysis, result in high extractive power. Sonication times for real-life applications vary widely, i.e., from 1–10 to 30–120 min (Table 4). For excellent reviews on USE and its applications, the reader should consult references [80, 81].

There are two common devices for ultrasound application, bath and probe systems. The baths are more widely used, but have two disadvantages, which adversely affect experimental precision, viz. a lack of uniformity of the distribution of ultrasound energy (only a small fraction of the total liquid volume in the immediate vicinity of the source will experience cavitation) and a decline of power over time. The probes have the advantage over baths that they focus their energy on a localized sample zone

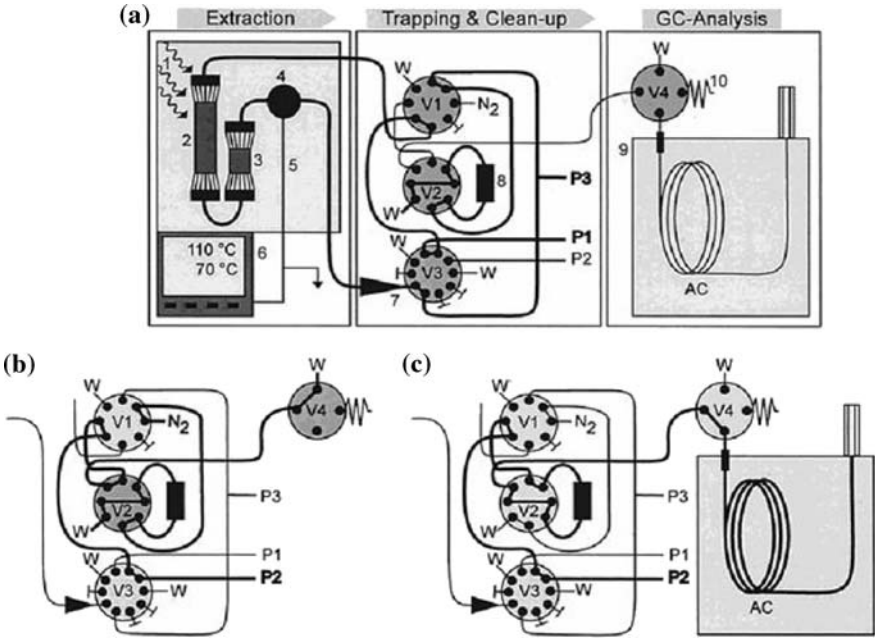

Fig. 5. Schematic of DMAE–SPE–LVI–GC system: **1**, Microwave oven; **2**, Pre-heater; **3**, Extraction vessel; **4**, Mixing tee; **5**, Thermocouple; **6**, Temperature regulator; **7**, Restrictor; **8**, SPE cartridge; **9**, PTV–GC–NPD; **10**, Fused-silica leak; **V1**–**V4**, Valves; **P1**–**P3**, Pumps. Working modes: (**a**) extraction and trapping; (**b**) system clean-up and drying with nitrogen; (**c**) transfer and GC analysis [40]

and, thus, provide more efficient cavitation in the liquid.

In bath systems, the transducer is usually placed below a stainless-steel tank, the base of which is the source of the ultrasound. Some tanks are provided with a thermostatically controlled heater. The ultrasound power levels delivered by most commercial ultrasonic baths are sufficient for cleaning, solvent degassing and extraction of adsorbed metals and organic pollutants from environmental samples, but are less effective for extraction of analytes bound to the matrix. The power should be great enough to cause cavitation within the extraction vessel placed inside the bath. For a bath with a single transducer on the base, the extraction vessel must be located just above the transducer, since power delivery will be at maximum at this position (cf. above). In order to obtain reproducible results, the bath must be either thermostated or preheated at the maximum temperature measured in the liquid under continuous running conditions since most cleaning baths warm up slowly during operation. An important drawback of most cleaning baths is the lack of power adjustment control. In the literature not a real tendency can be found in models and brands of sonication baths applied.

Probe-type systems can deliver up to 100-fold greater power to the extraction medium than a bath. One main feature for the successful application of ultrasonic probes is that the ultrasonic energy is not transferred through the liquid medium to the extraction vessel but introduced directly into the system. The probe consists of the following components: (1) a generator which is the source of alternating electrical frequency, and which allows tuning to be carried out for optimum performance; (2) the possibility of pulsed-mode operation of the ultrasonic processor to allow the medium to cool between sound pulses; (3) the upper horn element, a piece of titanium to which the removable horn is attached, forming both the emitter or booster, and the detachable horn itself, usually made of a titanium alloy, which allows the vibration of the fixed horn to be transmitted to a chemical system. Tip erosion can occur as a result of cavitation. Since ultrasound irradiation by means of

Table 4. Selected applications of (D)USE combined with GC

Analytes	Sample (g or mL)	Pre-treatment	Solvent (mL)	Sonication time (min)	Post-treatment	Detector	LOD ($\mu g\ kg^{-1}$)	Recovery (%)	Ref.
USE bath									
PCBs	Sediment (3)	Dry	Hex–DCM (4:1) (50)	120	Na_2SO_4, Florisil/alumina, conc.	MS	–	–	[92]
PAHs	Sediment (15)	Dry	Hex–acet (1:1) (50), 28 °C	2 × 30	Filter, conc.	MS	–	75–119	[93]
Pesticides	Soil (5)	–	EtOAc (5)	3 × 15	Na_2SO_4, conc., dissolve	MS	0.05–7	69–118	[87]
Fungicides	Soil (5)	Sieve	EtOAc (4)	2 × 15	Filter, conc., Na_2SO_4	ECD, NPD, MS (SIM)	2–10	87–111	[94]
Pyrethroids	Air (100 L)	Tenax TA	EtOAc (1)	10	–	μECD	<1	97–106	[95]
Flumethrin degradation products	Honey (5)		Hex–DCM (1:1) (20), 25 °C	2 × 20	Conc., SPE, conc.	ECD	0.9–1.0	90–106	[89]
Volatiles	Citrus flower (5)	–	Pen–diethyl ether (1:2) (30), 25 °C	10	$MgSO_4$, conc.	MS	–	–	[96]
Volatiles	Honey (40)	Mix with 22 mL water and 1.5 g $MgSO_4$	Pen–diethyl ether (1:2) (15)	10	Add NaCl, centrifuge, conc.	MS	–	–	[96]
Volatiles	Wine (25)	–	DCM (10)	15	–	FID	23–26	9–50	[97]
Nicotine	Chewing gum	Grind	Hep (15)	60	Dilute	FID	–	–	[98]
USE probe									
Phthalates	Plastics (1)	Grind	Hex (10)	2 × 10	Conc., C_{18}-SPE, conc., dissolve	MS (SIM)	10	82–106	[99]
Total fat	Sunflower, soybean, rape seed (–)	Mill, sieve	Hex (100), 75 °C	90 Soxhlet cycles × 10 sec	Conc.	FID		99–100	[90]
Triterpenes	Olive leave (1)	Dry, mill	EtOH (30)	20	Centrifuge, conc., deriv. (USE; 5 min)	MS		83–103	[91]
DUSE bath									
Organophosphates	Air (180 L)	Cutting	Hex–MTBE (7:3), 70 °C	2 × 20	Conc.	NPD	–	100	[82]
Organophosphates	Air (180 L)	Cutting	Hex–MTBE (7:3), 200 $\mu L\ min^{-1}$, 70 °C	3		On-line-PTV–NPD	25–180 $pg\ m^{-3}$	86	[83]
DUSE probe									
Nitro-PAHs	Soil (4)	Sieve, dry	DCM (8), 2 $mL\ min^{-1}$ forward-backward, 20 °C	10	Conc., dissolve	MS/MS	Low pg	–	[100]
Environmental pollutants	Sediment (1)	Mix with 3 g sand	Hex (6), 1 $mL\ min^{-1}$	15	Conc., dissolve	ToF MS[a]	–	–	[84]

[a] GC × GC instead of GC analysis

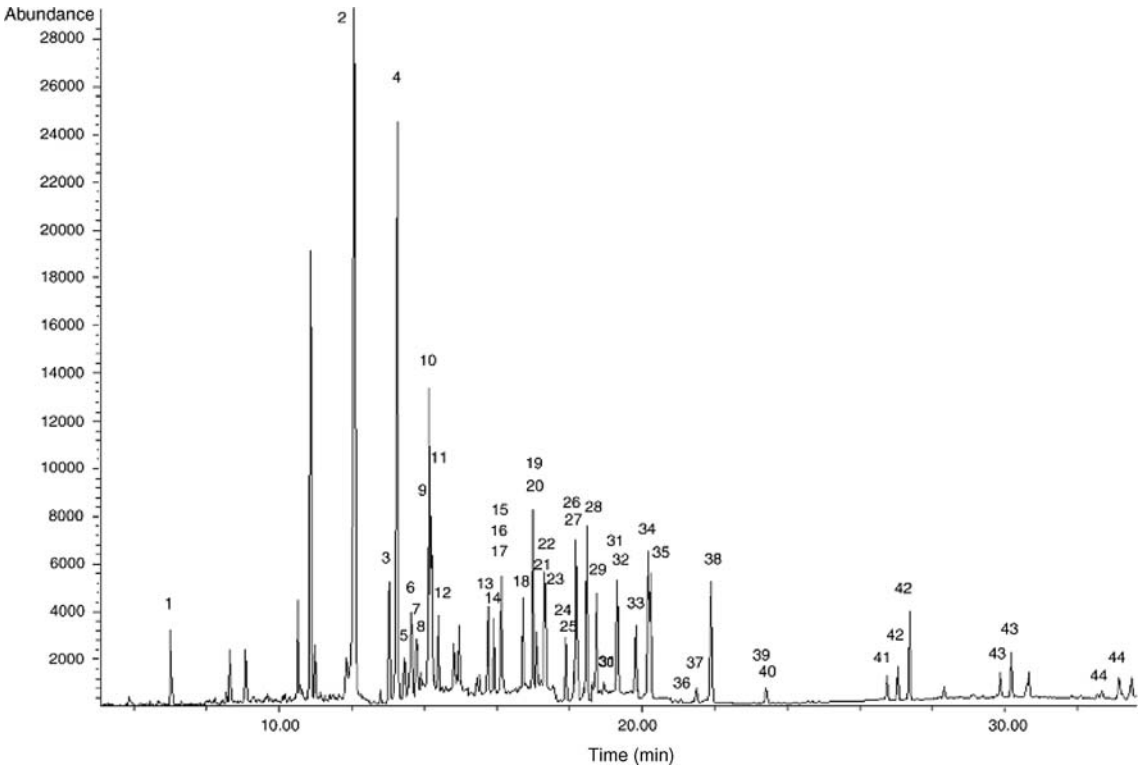

Fig. 6. GC–MS (SIM) chromatogram of a USE extract of a soil spiked at 50-μg kg^{-1} concentration level [87]. **1** = Dichlorvos; **2** = Desethylatrazine; **3** = Hexachlorobenzene; **4** = Dimethoate; **5** = Simazine; **6** = Atrazine; **7** = Propazine; **8** = Lindane; **9** = Terbutylazine; **10** = Propyzamide; **11** = Fonofos; **12** = Diazinon; **13** = Metribuzin; **14** = Parathion-methyl; **15** = Simetryn; **16** = Alachlor; **17** = Heptachlor; **18** = Fenitrothion; **19** = Malathion; **20** = Metolachlor; **21** = Aldrin; **22** = Chlorpyrifos; **23** = Parathion-ethyl; **24** = Isodrin; **25** = Chlorfenvinphos; **26** = Pendimethalin; **27** = Heptachlor epoxide; **28** = Chlorfenvinphos; **29** = Procymidone; **30** = γ-Chlordane; **31** = Tetrachlorvinphos; **32** = Endosulfan, I; **33** = Fenamiphos; **34** = 4,4'-DDE; **35** = Dieldrin; **36** = Endrin; **37** = Endosulfan, II; **38** = 4,4'-DDD; **39** = Endosulfan, sulfate; **40** = 4,4'-DDT; **41** = Azinphos-methyl; **42** = λ-Cyhalothrin; **43** = α-Cypermethrin; **44** = Deltamethrin

probes generates a large amount of heat, some cooling of the sonication vessel is required. One should also be aware that volatile sample constituents can be lost due to the 'degassing' effect of the ultrasound power. The probe system mostly used for the applications reported in the literature is the Sonifier 450 (Branson, Danbury, CT, USA).

Most USE applications have been developed using a bath or a probe. Dynamic systems (DUSE) have been used in a few cases only, even though this approach will speed up the USE process considerably. There are two DUSE approaches, open and closed systems.

In open systems, fresh extractant flows continuously through the sample, so the mass transfer equilibrium is displaced to the solubilization of the analyte(s) into the liquid phase. This mode has the disadvantage of serious extract dilution which implies that subsequent time-consuming concentration by solvent evaporation [82] or coupling to SPE is required. Somewhat surprisingly, despite its ease of implementation, the latter approach has not been reported yet. Sanchez et al. [83] coupled DUSE to LVI–GC utilizing a PTV injector to analyse organophosphate esters in air. Air filters were desorbed by DUSE with a 200 μL min^{-1} flow of hexane–MTBE. With the PTV in the solvent-vent mode, the entire extract volume was introduced into the GC–NPD system without any clean-up. The LODs of the organophosphate esters were in the range of 25–180 pg m^{-3} (average recovery, 86%, RSD, 5–14% ($n = 5$) at 1 ng/filter).

In closed systems, a pre-set volume of extractant is continuously circulated through the solid sample. Consequently, dilution is less serious than with an open system. The direction of the extractant can be changed at pre-set intervals to avoid undesirable compaction of the sample and any increase in pressure in the dynamic system. After extraction, a valve either directs the extract for collection in a vial or drives it to a continuous manifold for on-line performance of other steps in the analytical process, such as pre-concentration [84].

Applications A selected list of (D)USE applications for the isolation of a range of compounds from a variety of matrices is shown in Table 4. USE is mainly used for environmental (soil, sediment, air) and food and beverage (soybean, honey, wine) samples. In most applications, USE is combined off-line with GC, but there are also several examples of on-line set-ups [83–86].

As an example of a typical USE-based analysis, we quote the protocol for pesticide residue analysis in soil, designed to expand the range of applicability of EPA Method 3550C [87, 88]. 5 g of soil were placed in a small Erlenmeyer flask and 5 mL ethyl acetate added.

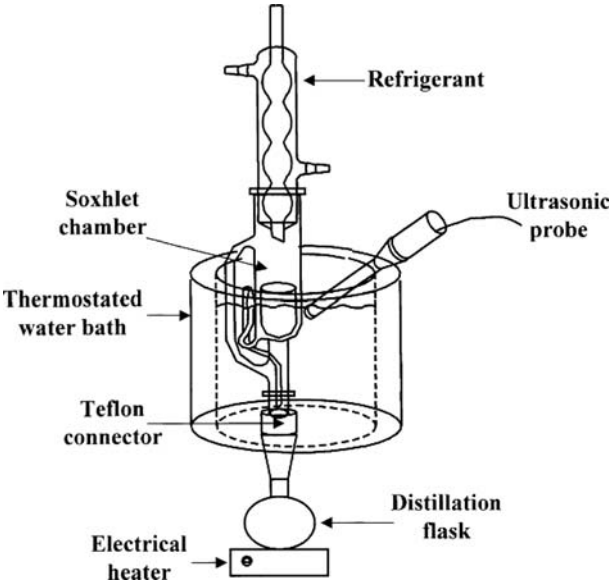

Fig. 7. Schematic of ultrasound-assisted Soxhlet extraction [90]

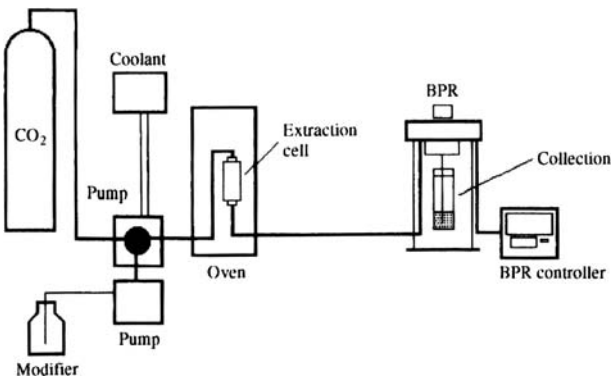

Fig. 8. Schematic of a basic SFE system [41]. BPR, back pressure regulator (with attached controller unit)

After manual agitation the sample was exposed to USE for 3 × 15 min. After each period, extracts were collected by pouring the extractant through a funnel plugged with cotton wool and overlaid with anhydrous sodium sulphate. The final 15-mL extract is evaporated to dryness and redissolved in 200 µL ethyl acetate, and 1 µL was analysed by GC–MS. LODs were in the 0.05–7.0 µg kg^{-1} range. Figure 6 shows a chromatogram of a 50-µg kg^{-1} spiked soil. The procedure is straightforward and analyte detectability is fully satisfactory. However, the total analysis is somewhat time-consuming and includes risky solvent evaporation.

As another example, Zhou et al. [89] used USE for the determination of 4-fluoro-3-phenoxybenzaldehyde cyanohydrin (FPBC) and 4-fluoro-3-phenoxybenzaldehyde (FPB), two degradation products of flumethrin, in honey. A 5-g honey sample, dissolved in acetone–dichloromethane was extracted in a mixture of hexane–dichloromethane using a sonication bath. After clean-up by SPE and concentration, the extract was analysed by GC–ECD; the LODs were 1–2 ng g^{-1} with recoveries of 90–106%. Luque-García et al. [90] combined USE with conventional Soxhlet extraction for the analysis of total fat in oleaginous seeds. A water bath was modified such that the Soxhlet chamber was located in it. The bath was sonicated by a probe to accelerate the extraction process (Fig. 7). The efficiency was similar to, or even better than, those of conventional Soxhlet extraction and the official ISO method, saving both time and sample manipulation. Recently, the twofold application of USE in a single analytical protocol was reported [91]. The main triterpenes—eleanoic acid, ursolic acid, uvaol and eryuthodiol—were quantitatively leached from olive leaves by 20-min USE with ethanol. This compares favourably with the 5 h required by conventional procedures involving maceration. An aliquot of the leachate was silylated prior to GC–MS. Ultrasound-assisted silylation took only 5 min, as against 0.5–3 h for conventional silylation.

Supercritical Fluid Extraction

One area that stimulated an interest in enhanced fluid extractions, was supercritical fluid extraction (SFE). This is a long established method, which has been used industrially for many years. However, it was not until an interest was shown in supercritical fluids as chromatographic media that it started to be seriously studied as an extraction technique on an analytical scale. It has since been the subject of numerous books and reviews (e.g., [4, 101–103]).

Almost all SFE employs carbon dioxide (critical point, 30.9 °C, 73.8 bar) as the supercritical fluid: it is an almost ideal solvent since it combines low viscosity and high analyte diffusivities with a high volatility (which makes analyte recovery very simple and provides solvent-free concentrates), and is inexpensive and environmentally friendly. An important drawback of CO_2 is its non-polar character. In order to widen the application range of the technique to include more polar analytes, the preferred route is to employ polar modifiers such as methanol, ethanol, acetone and acetonitrile (1–10% addition, preferably by means of a separate modifier pump). In addition to a modifier pump, the basic components of an SFE system (Fig. 8) are: a supply of high purity carbon dioxide; a CO_2 pump; an oven for the

extraction vessel; a pressure outlet or restrictor; and a suitable collection vessel for recovery of the extracted analytes. Sample collection can be performed by purging the extract through a solvent or over a suitable adsorbent, such as, Florisil.

SFE comprises two integrated parts, extraction of the analyte from the sample matrix and subsequent collection—or trapping—of the analytes. There are three main collection modes: (1) collection in a vessel containing solvent; (2) trapping on a cartridge packed with an adsorbing or inert solid-phase material and (3) collection in a device that is connected on-line with the chromatographic system. Compared to 'off-line' solvent collection or solid-phase trapping, the on-line technique offers better analyte detectability because the entire extract rather than an aliquot, can be transferred to the chromatographic system. However, sample size should be limited since co-extracted fat or water may easily contaminate the interface used and/or ruin the analytical column. For the rest, it is good to add that all three types of collection require careful optimization, with solvent collection probably being the simplest system to use and the easiest to optimize, and solid-phase trapping offering selectivity by the two-step trapping/elution procedure. On-line collection provides the best sensitivity because the entire extract is introduced into the GC system.

Applications Over the years, SFE has been used for the extraction of PAHs, PCBs and dioxins, aliphatic hydrocarbons and pesticides from soil, sediment and air-borne particulates, in food and fragrance studies, especially for essential oils and fats, for the extraction of polymer additives, natural products, and drugs and their residues. Special attention has always been given to the extraction of thermolabile compounds because the mild conditions of CO_2-based SFE will minimize their degradation. Illustrative examples are summarized in Table 5.

In order to give an impression of the wide variety of analyte/matrix combinations for which SFE has been used as sample-preparation method, three studies included in Table 5 are briefly discussed. The extraction of onion oil from fresh onions by means of SFE was reported by Seangcharoenrat and Guyer [104]. Onions were peeled, cut and juiced. The juice was filtered to separate it from the pulp and fed to an Amberlite XAD-16 polymeric sorbent bed. The onion oil was extracted with supercritical CO_2 (20.7–28.7 MPa, 37–50 °C) in the up-flow direction and, after dilution in dichloromethane, the extract was analysed by GC–MS. Rissato et al. [105] used SFE for the analysis of pesticides in honey. A 5 g honey sample was mixed with 3 mL water and heated at 40 °C to improve handling. After lyophilization, the honey samples were poured into a stainless-steel extraction cell in the sandwich mode, using silanized glass wool at the bottom and top. Extraction was performed with CO_2 with 10 vol% acetone as a modifier, at 200 bar and 60 °C during 5 min. The pesticides were collected on-line on Florisil at 10 °C. After rather time-consuming elution with two 5 mL solvent mixtures, concentration and redissolution in 1 mL acetone, only 1 µL was analysed by GC–ECD (Fig. 9). The LODs were better than 0.01 mg kg^{-1} (recoveries, 75–94%). Compared with conventional LLE, sample contamination was greatly diminished as sample handling was minimized and the use of organic solvents was reduced (consequently, solvent evaporation was much faster). Garrigós et al. [106] used SFE for the analysis of styrene in polystyrene. Styrene was extracted with supercritical CO_2 with collection in dichloromethane. After concentration, the extract was analysed by GC–MS. SFE was found to be more selective than MAE, Soxhlet and HS (less extraction of matrix components) and gave an analyte recovery of about 100%.

The factors that govern the extraction of an analyte from a matrix are the solubility of the analytes in the supercritical fluid, the mass transfer kinetics of the analyte from the matrix to the solution phase, and interactions between the supercritical phase and the matrix (Fig. 10) [107–110]. To put it differently, despite quite a number of promising initial results obtained when CO_2 has been used for the extraction of non-polar micro-contaminants from sediments [111], natural products from biological samples [112] or essential oils from plant material [113], SFE has not become as widely and as easily useful as initially expected. One main reason is that SFE has been found too analyte- and, specifically, too matrix-dependent to be readily and routinely applicable for much work involving complex environmental and food samples. This is especially true for environmental samples where analyte/matrix interactions often become stronger in ageing samples: optimization on the basis of spike recoveries may then lead to quite erroneous results. In addition, method development is rather difficult since quite a number of parameters have to be optimized, and there are often technical problems. In both respects, PLE—another 'modern' compressed-fluid technique—is superior. Moreover, PLE can be used with most conventional solvents and can therefore handle polar as well as non-polar compounds, whereas SFE is preferentially employed for non-polar analytes only. On the other hand, on-line coupling to GC is much easier with SFE [114], it is a solvent-free method and miniaturization should not meet with any problems [4]. Dedicated attention is obviously required to underscore the merits of what is now somewhat of a 'niche' technique [115].

Matrix Solid-Phase Dispersion

The analysis of (semi-) solid environmental, food or biological—sometimes fat-containing—matrices is a challenging problem, with rapid and efficient analyte isolation—and subsequent purification—being of key interest. In 1989, Barker et al. [126] introduced matrix solid-phase dispersion (MSPD) and the technique has since then been discussed in several reviews [127–130]. MSPD involves the direct mechanical blending (for solid samples) or mixing (for semi-solid and liquid samples) with, usually, an alkyl-bonded silica SPE sorbent—but, occasionally, also plain silica, Florisil or sand. The added abrasive promotes the disruption of the gross

Table 5. Selected applications of SFE combined with GC

Analytes	Matrix (g or mL)	Pre-treatment	CO_2 modifier	Temperature (°C)	Extraction time (min)	Pressure (MPa)	Collection mode	Post-treatment	Detector	Recovery (%)	Ref.
Pesticides	Gazpacho (20)	Dry with $MgSO_4$	–	50–90	20	30–50	EtOAc		MS		[116]
Pesticides	Honey (5)		10% Acet	60	20	20	Florisil cartridge		ECD	75–94	[105]
Pesticides	Food (2)	Mix with Hydromatrix	–	50	30	12.3	Stainless-steel balls		ECD, NPD	70–133	[117]
Pesticides	Fish muscle	Freeze-dry	–	36–64	–	10–24	Florisil		ECD		[118]
Pesticides	Baby food (2)	Extrelut to dehydrate	15% MeCN	70	55	17.2	DCM	C_{18}-SPE, conc.	MS	11–37	[119]
Volatiles	*Bunium persicum Boiss.* seed (3) *Mespilus germanica* L. seed (3)	Grind, mix with sand	–	45	35	20	DCM	Conc.	MS		[120]
Volatiles	Wine (170)		–	50		20	EtOH	–	FID		[121]
Essential oils	*Equisetum giganteum* L. (40)	Dry, grind	–	30–40	300	12–30	Flask	–	MS		[122]
Essential oils	*Hypericum perforatum* L. (50)	Grind, filter	–	14–40	150	8–10	–	–	MS		[123]
Essential oils	*Laurus nobilis* L. (60)	Grind, mix with sea sand	4% EtOH	60	75	25	–	–	MS		[113]
Onion oil	Onion	Grind, filter	–	37–50	–	10.3–28.7	–	–	MS		[104]
Cholesterol	Cow brain (0.1)	Freeze-dry, grind	–	60	300	25	–	Deriv.	FID		[112]
FAMEs	Infant powder (2)	–	15% EtOH	100	20	46.5	C_{18}-trap	Deriv.	MS		[124]
Styrene	Polystyrene		–	105	30	48.3	DCM		MS		[106]
Squalene	*Terminalia catappa* leaves and seeds (1)	Freeze-dry, grind	–	40–60	15	13.8–27.6	–	–	MS		[125]

architecture of the sample while, with a bonded silica, sample constituents will dissolve and disperse into the bonded phase, causing a complete disruption of the sample and its dispersion over the surface. When blending or mixing is complete, the homogenized mixture is packed into an empty column or cartridge (with, usually, frits, filters or plugs at both top and bottom). Obviously, there is one main difference here between MSPD and SPE: with the former technique, the sample is distributed throughout the column and not only retained in the first few millimetres. Elution with, preferably, a limited volume of solvent is the final step of the remarkably simple procedure.

The use of small particles for the dispersion sorbent, should be avoided to prevent unduly long elution times or column plugging, and 40 μm or less expensive 40–100 μm particles are used most frequently. The sample/sorbent ratio usually is about 1:4, but may vary up to 1:1. The nature of the sorbent used for a specific application also has to be considered. For example, for analyte extraction from animal tissue, C_{18}-bonded silica is the most popular sorbent, while C_8- and C_{18}-bonded silicas and Florisil are preferred for plant samples. Florisil has been applied successfully also for other types of sample, e.g., fruit juices, soil and honey. A more selective sorbent, cyanopropyl-bonded silica, has been used to isolate polar analytes such as veterinary drugs from biological fluids and tissues. Recent developments include the use of acidic silica, which will strongly retain basic compounds and facilitate basic/acid group separations. After elution of the basic analytes with a non-polar solvent, the latter class of compounds can be eluted with a relatively polar solvent. Silica treated with sulphuric acid has also been used for efficient fat removal. Sand is sometimes selected to allow the early elution of interferences that would not be retained by any sorbent during the elution of the target analytes.

The elution solvent should effect an efficient desorption of the target analytes while the bulk of the remaining matrix components should be retained. In the literature, a wide variety of solvents has been tested, ranging from hexane and toluene, via dichloromethane and ethyl acetate, to alcohols and water at elevated temperatures. Not surprisingly, pesticides are usually eluted with low- or medium-polar solvents, and drugs and naturally occurring compounds with more polar ones. Generally speaking, the nature of the preferred sorbent/solvent combination is mainly determined by the polarity of the target analytes and the type of sample matrix. Keeping this common-sense consideration in mind will facilitate MSPD optimization.

In some cases, eluates from an MSPD column are sufficiently clean to permit direct injection into the GC system [131]. However, more often additional clean-up is required. For some applications, e.g., the analysis of fruits and vegetables, washing the MSPD column with water prior to elution of the analytes generally suffices [131, 132]. Post-MSPD treatment may range from simple filtration or centrifugation, to evaporation-plus-redissolution or aqueous-to-organic extraction, and more versatile SPE. In the last-named case, a suitable sorbent can be packed at the bottom of the MSPD column or the MSPD column can be eluted off- or on-line onto a conventional SPE cartridge or disk. An interesting development is to combine MSPD and PLE, i.e., to increase the speed of the analysis by applying elevated temperatures and pressures, although these should be relatively mild in order to maintain the selectivity of the MSPD procedure [133].

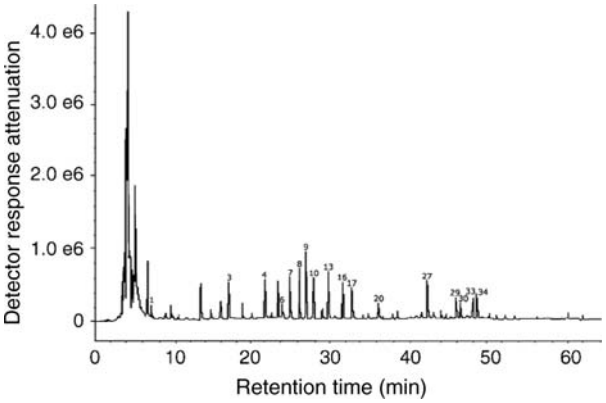

Fig. 9. GC–ECD chromatogram of a honey sample obtained by SFE [105]. **1** = Dichlorvos; **3** = Trifluralin; **4** = Hexachlorobenzene; **5** = Dicloran; **7** = Dimethoate; **8** = Chlorothalonil; **9** = Vinclozolin; **10** = Aldrin; **13** = Chlorpyrifos; **16** = α-Endosulfan; **17** = Hexaconazole; **20** = β-Endosulfan; **27** = Tetradifon; **29** = Cyflutrin I; **30** = Cyflutrin II; **33** = Cypermetryn II; **34** = Cypermytrin III

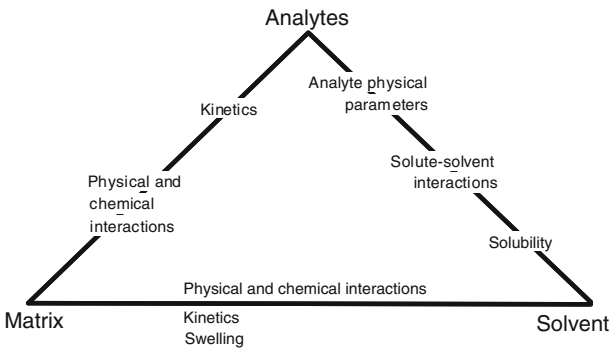

Fig. 10. Factors to be considered when studying an SFE extraction process [108]

Applications Three application areas in which MSPD is frequently used are the determination of drugs, organic microcontaminants and naturally occurring compounds (however, with the last-named group, MSPD is usually combined with LC, not GC). Table 6 summarizes a

Table 6. Selected applications of MSPD combined with GC

Analyte	Sample (g or mL)	Sorbent (g)	Elution solvent (mL)	Pre-treatment	Post-treatment	Detector	LOD (μg kg^{-1} or μg L^{-1})	Recovery (%)	Ref.
PCBs, PBDEs	Biota (0.5)	Florisil (1.5 g)	Hex (20)	Dry 0.5 g sample with 2 g Na_2SO_4	Acid silica, neutral silica with 20 mL hex + 12 mL DCM–hex (20:80)	ECD	0.1		[141]
PCBs	Eggs, clams, mussel, oyster (2)	Florisil (4)	DCM–Pen (15:85), 40 °C, 14 MPa (55)	–	Florisil, conc., Hex	ECD, MS–MS	0.001–0.004/ 0.002–0.07	90–105	[133]
OCPs, PCBs	Chicken egg (1)	Florisil (2)	DCM–Hex (1:1) (10)	Discard shells	Conc., H_2SO_4	ECD/MS	0.2–0.7	80–110	[142]
OCPs	Human serum (1)	Florisil (2)	Hex, DCM	–	Florisil or C_{18}	ECD		0–110	[143]
Fungicides	Fruits, vegetables (0.5)	C_{18} (0.5 g)	EtOAc (10)	–	Silica	NPD, ECD, MS (SIM)	3–30	60–100	[138]
Pesticides (266)	Apple juice (10)	Diatom. earth (20 g)	Hex–DCM (160)	–	Conc.	MS (SIM)	3–18		[135]
Pesticides	Olives (1)	Aminopropyl (2 g)	MeCN	–	Florisil, conc., MeCN–water (1:1) or MeCN	MS	10–60	80–105 75–105	[144]
Halogenated compounds	Aquaculture sample (1.5)	C_{18} (1 g)	Hex (30)	–	Acid silica, alumina, conc.	MS/MS	0.02–0.9	1–8	[145]
OPPs	Fruit juices (1)	Florisil (2)	EtOAc (2 × 5)	Mix 1:1 with MeOH	Filter, conc.	NPD, MS	0.1–0.6	70–110	[146]
OPPs, permethrin	Fruit (0.025)	C_8 (0.025)	EtOAc (0.1)	8 mL water or –	–	MS	4–90	85–120	[131]
OPPs, amidine, carbamate	Honey (1.5)	Florisil + Na_2SO_4 (2.5 + 1)	Hex–EtOAc (9:1) (2 × 5)	–	Filter, conc.	NPD, MS	6–15	80–100, 60	[147]
Insecticides	Honey bees (0.5)	Florisil, silica (1.5)	Hex–diethyl ether (9:1, 8:2, 7:3) + Hex–EtOAc (7:3) (4 × 15)	15 mL Hex	Alumina or silica, conc, hex–acet	NPD/ECD	5–50	70–110	[148]
Insecticides	Fruit juices	Florisil (4)	EtOAc (2 × 5)	–	Conc., Na_2SO_4	ECD, MS	1–5	75–110	[149]
Pesticides	Liver (0.5)	C_{18} (2)	EtOAc (4 + 3+3)		Florisil, conc., cyclohexane	MS/MS	0.01–9	70–115	[150]
Chloramphenicol	Muscle tissue (2)	C_{18} (3)	MeCN–water (1:1) (10)	10 mL Hex + 12 mL MeCN–water (1:1)	C_{18}, LLE EtOAc, conc., deriv.	ECD/MS	1.6	95–100	[151]

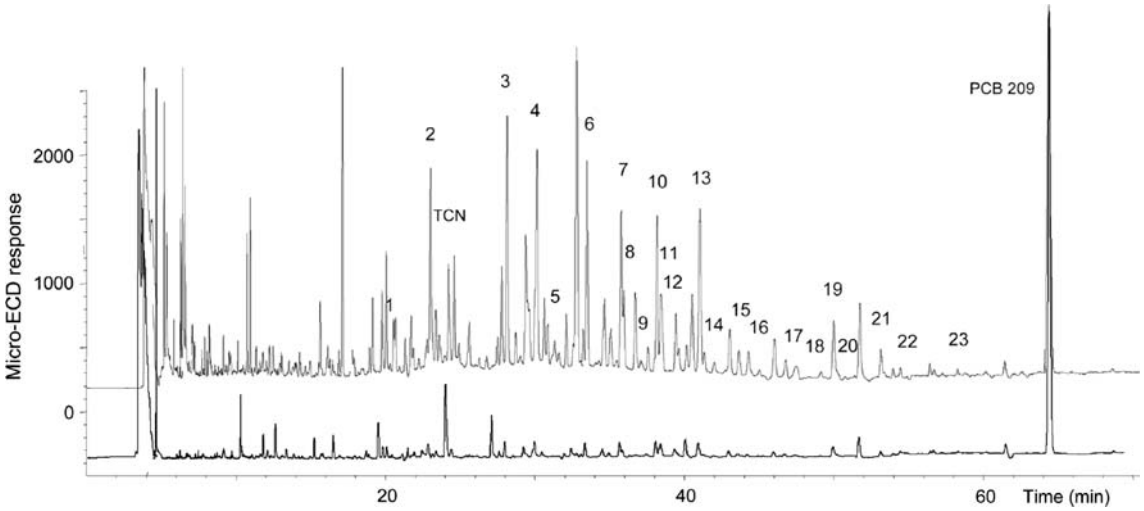

Fig. 11. GC–μECD chromatograms of a non-spiked meat sample (upper trace) and a procedure blank (lower trace) using miniaturized MSPD [136]. Sample size, 0.1 g. Peak identification: **1** = CB 28; **2** = CB 52; **3** = CB 95; **4** = CB 101; **5** = CB 81; **6** = CB 77 + CB 110; **7** = CB 123 + CB 149; **8** = CB 118; **9** = CB 114; **10** = CB 153; **11** = CB 132; **12** = CB 105; **13** = CB 138; **14** = CB 126 + CB 129 + CB 178; **15** = CB 183; **16** = CB 167; **17** = CB 156; **18** = CB 157; **19** = CB 180; **20** = CB 169; **21** = CB 170; **22** = CB 189; **23** = CB 194; **TCN** (1,2,3,4-tetrachloronaphthalene), external standard; **PCB 209**, external standard

number of recent examples of each of these, and provides relevant information on the experimental conditions and analytical performance. In most studies, the amount of sample is seen to be in the 0.5–2 g range. Large glass columns have been used for applications involving high sample amounts in order to determine trace-level concentrations of PCBs and PCDD/Fs [134] and pesticides [135]. In one study, Chu et al. [135] mixed 10 g apple juice with 20 g diatomaceous earth, transferred the mixture to a glass column and leached the pesticide residues with 160 mL hexane–dichloromethane (1:1). The eluent was concentrated to 1 mL and 1 μL was injected to GC–MS in SIM mode. LODs for 266 pesticides were 3–18 μg kg^{-1}, with analyte recoveries close to 100%. There are, on the other hand, also several papers which feature miniaturized MSPD of, typically, some 25–100 mg of sample [131, 136, 137]. To quote an example, Ramos et al. [136] analysed PCBs in freeze-dried meat, where only 0.1 g meat was dispersed with 0.1 g of acid silica. The recoveries were 80–130% and the LODs for ECD detection were below 0.3 ng g^{-1}. Figure 11 shows a GC–μECD chromatogram. The approach merits attention because of (1) its practicality if sample size is limited as, e.g., with single-insect studies [137], and (2) the significantly reduced volume of elution solvent, which facilitates further handling. Actually, with solvent volumes as low as a few millilitres, one would expect on-line coupling of MSPD and GC, or LC, to have been implemented but to the best of our knowledge, no papers dealing with this topic have been published so far.

Navarro et al. [138] compared MSPD and LLE for the analysis of fungicides in vegetables with both techniques using ethyl acetate as solvent. The results showed satisfactory agreement, but the LLE extracts contained much more interfering compounds. Picó et al. devoted two (LC-based) studies [132, 139] to a comparison of MSPD, SBSE and SLE (solid–liquid extraction) for the determination of pesticides in fruit with MS detection. The authors concluded that MSPD should be preferred because it is easier to perform and faster, and shows equal accuracy.

In a comparison of MSPD and MAE for the determination (admittedly, by LC) of 16 PAHs in soil, the analytical performance data of the two techniques were found to be closely similar. As for MSPD, extraction and clean-up of the lyophilized samples were carried out in a single step, using a Florisil/silica sorbent mixture [140].

Direct Thermal Desorption

Thermal desorption (TD) is a valuable alternative to headspace techniques for the isolation of volatile compounds from non-volatile solid, semi-solid and, occasionally, liquid matrices, and a wide variety of applications has been reported in the literature. Although TD is not really a new technique, fully automated systems are only in use for slightly over 10 years. One of the first examples was the use of automated thermal desorption (ATD) for the determination of volatile constituents of plants and food [152]. Typically, a 1–40 mg sample is placed in a desorption cartridge between two glass-wool plugs. By heating the cartridge for a pre-set time, the volatiles are desorbed and, next, adsorbed on a cold Tenax trap. Heating of the trap effects rapid transfer of the analytes to the GC for further analysis. Similarly, TD–GC–MS can be used as a screening method, e.g., for chlorinated hydrocarbon contamination in soil [153]. In this case, a dual-tube system was used to enable focusing of the analytes on a Tenax-plus-carbon trap prior to their release and transfer to the GC system. Total analysis including the sample preparation, required less than 1 h. TD is also used to study the relatively low-molecular-mass components present in (oil-containing)

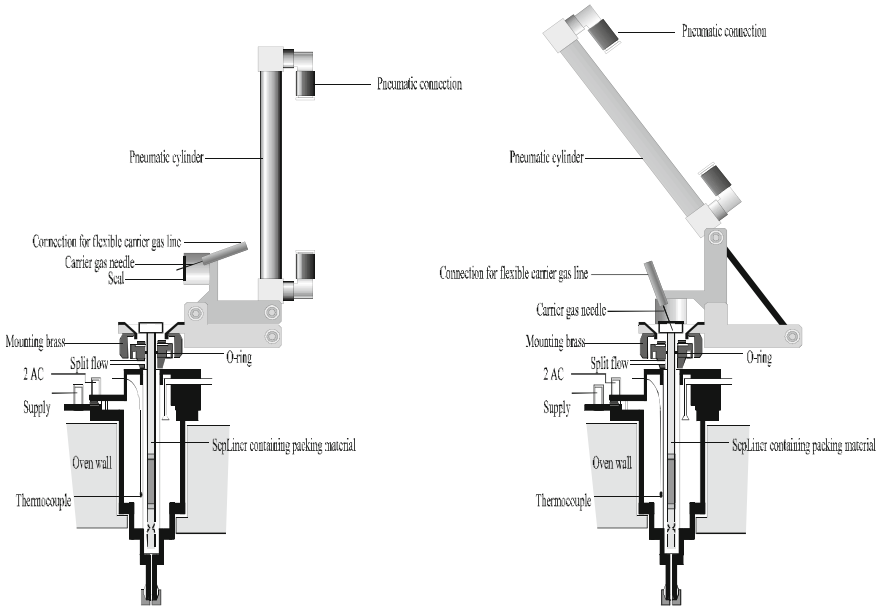

Fig. 12. DTD automated liner exchanging head [163]. Left, open; right, closed

rocks [154, 155]. Pyrolysis techniques are used to study the very-high-molecular-mass structures in such samples which are not directly amenable to GC [156, 157]. An inexpensive and user-friendly system for multi-step TD–pyrolysis–GC for use in geochemical analysis was designed by van Lieshout et al. [158]. Thermal treatment was performed inside a PTV injector which served as both the TD unit and the pyrolyser system. Sample amounts ranging from sub-mg amounts up to 2 g were weighed directly into the liner of the injector. The system was also used for polymer characterization [159].

TD is being increasingly used for the analysis of aerosols (see, e.g., [160, 161]) and, also in this area of application, primarily in order to replace time-consuming procedures involving solvent extraction (and evaporation) by more direct approaches in which (parts of) aerosol-loaded filter material is packed into a GC injector liner and directly subjected to thermal desorption plus instrumental analysis [162]. The main advantages are reduced sample handling and improved analyte detectability (9–500 times better LODs than solvent extraction [162]), while there is no need to modify the GC–MS set-up. The practical usefulness of this, so-called direct thermal desorption (DTD) is discussed in some more detail below.

As indicated above and in the section on applications below, the basic instrumentation needed for (D)TD studies is rather simple. However, because of the (semi-) solid nature of most samples, automation of the sample introduction is difficult. In 2002, de Koning et al. [163] designed a system which features fully automated liner exchange. To this end, a Focus XYZ sample preparation robot was equipped with a newly developed injector head to open and close the Optic 2 (ATAS GL, Veldhoven, The Netherlands) injection interface. In Fig. 12 the injector head is shown in the open (left) and closed (right) position. The specially designed liners, capped with a standard crimp cap, are placed in a sample tray and transported to the thermal desorption device. Both liner transport and liner exchange (which can be performed after each analysis) are automated. Two systems are commercially available today, the ALEX (Automatic Liner EXchange) from Gerstel (Mülheim, Germany) [164] and the LINEX (LINer Exchanger) from ATAS GL [165]. As a first application, the wood preservative *N*-cyclohexyl-diazeniumdioxide (HDO) was quantified in 10 mg of sapwood powder by means of DTD–GC–MS (m/z 114). The reproducibility of the procedure (5–10%) and the LOD (4 mg HDO/kg wood) were fully satisfactory [166].

Applications The number of applications of DTD–GC–MS (and DTD–GC × GC–MS) is still rather limited but, on the other hand, the published examples do show that the approach can be used successfully for a wide range of samples, and yield interesting results (Table 7). Recent work by three groups of authors is briefly discussed below.

Özel and co-workers used DTD combined on-line with GC × GC–ToF MS to analyse the essential oil of pistachio hulls [34] and the volatile components of Cheddar cheese [167]. In both cases, 10 mg of sample were placed in a GC injector liner, glass wool being used to hold the sample in place. After a brief purge at ambient temperature to remove water vapour, the DTD programme was started. The head of the first-dimension GC column was cryo-cooled to ensure trapping of the analytes. With the essential oil, some 100 compounds were identified—with the cheese, some 55.

Zimmermann and his group [168–171] collected particulate matter (PM < 2.5 µm) on quartz fibre filters and placed filter punches representing 1–2.5 m^3 of sampled air into an injector liner together with an IS mixture for quantification. DTD–GC–ToF MS revealed the presence of some 1,500 compounds, out of which some 200 could be (semi-)quantified. When GC × GC was used instead of GC, some 10-fold more, i.e., over 10,000 compounds were detected. An example of a DTD–GC × GC–ToF MS contour plot is given in Fig. 13.

A technique which is strongly related to DTD is DMI (or DSI: difficult matrix/sample introduction) which was first described by Amirav et al. [172, 173]. The authors used an exchangeable micro- or μ-vial which holds the sample and is manually placed in the GC injector using a ChromatoProbe (Varian, Palo Alto, CA, USA) [160, 174]. After purging the injector is heated to evaporate the analytes. At the end of the run, the μ-vial which contains non-volatile sample constituents is removed from the

Table 7. Selected applications of DTD combined with GC

Analytes	Sample (mg or μL)	Pre-treatment	Desorption parameters	Carrier gas	Trap	Detector	LOD	Ref.
DTD								
PAHs	Aerosol filter		25 °C–12°/s–300 °C	20 mL min^{-1}	Glass wool, −100 °C	MS		[183]
PAHs, alkanes	Aerosol filter		100 °C–275 °C (7 min)	55 kPa	No	MS	5–240 ng m^{-3}	[162]
Volatiles	Plant material	Grind, dry	180 °C, 15 min	20 mL min^{-1}	Tenax, −30 °C	MS		[184]
Volatiles	Oak wood (125), plant material (2–15)	Grind, dry	180 °C, 15 min	20, 50 mL min^{-1}	Tenax, −30 °C	MS		[185, 186]
Volatiles	Olive oil (10)		20 °C–30°/min-40 °C (20 min)	100 mL min^{-1}	Cryo, −120 °C	MS		[187]
Volatiles	Plants (5–25)	Dry, grind	180 °C(15 min)	50 mL min^{-1}	Tenax, −30 °C	MS		[152]
Volatiles	Olive oil (5)		40 °C–16°/s−70, 175, 250 or 600 °C (10 min)	210 kPa	Cryo, −150 °C	ToF MS[a]		[188]
Volatiles	Apricot (2–5)	Cut, dry	150 °C (5 min)	–	Carbon black + mol. sieve, −30 °C	ToF MS		[189]
SVOCs	Aerosol filter		50 °C (2 min)–1°/s−320 °C (15 min)	2, 5 mL min^{-1}	–	ToF MS[a]		[168–171]
SVOCs	Aerosol filter		320 °C (15 min)	3 mL min^{-1}	–	MS		[190]
SVOCs	Aerosol filter		120 °C–3°/s−350 °C (3 min)	4.5 mL min^{-1}	–	MS		[191]
Explosives	PTFE wipe		45 °C–40°/min−280 °C (3 min)−80 °C	285 mL min^{-1}	Tenax, 40 °C	ECD	2–3 ng	[192]
Explosives	Wipe		50 °C–30°/min−170 °C (2 min)	6.4 mL min^{-1}	–	ECD, NCI MS	30–350 pg, 0.1–6 ng	[193]
Solvent additives	Waterborne paints (0.3)		60 °C–20°/min−190 °C (solvents) 190 °C–20°/min−280 °C (additives) 550 °C (pyrolysis)	50 mL min^{-1}	Cryo	MS		[194]
Residual solvents	Printed paper		27 °C (1 min)−3 °C/min−40 °C (10 min)	10 mL min^{-1}	–	FID		[195]
Preservatives	Pine sapwood (10)	Grind	45 °C (0.5 min)−10°/s−200 °C (1 min)	128 kPa	–	MS	4 mg kg^{-1}	[166]
Essential oil	Plant material (10)	Dry, grind	40 °C (2 min)−400 °C/min−150 °C (5 min)	255 kPa	Cryo	ToF MS[a]		[34, 167, 196, 197]
DMI								
Pesticides	Tomatoes	Blend with Acet.	90 (1 min, solvent vent 50 mL min^{-1})−300°/min−250 °C (0.5 min)−900 °C	5 mL min^{-1}	–	PFPD		[173]
Fatty acids	Green microalgae (1.8 μg)	TMSH methylation	40 °C (5 s)−16°/s−350 °C	70 kPa	–	MS		[180]
Fatty acids	Aquatic micro-organisms (1.8 μg)	TMSH methylation	40 °C (5 s)−16°/s−350 °C	70 kPa	–	MS		[181]
Pesticides	Food (5)	Extract in EtOAc	50 °C (2 min, solvent vent 1 50 mL min^{-1})−6°/s−280 °C	1 mL min^{-1}	–	ToF MS	1–10 ng g^{-1}	[175]
Pesticides	Food (5)	Extract in EtOAc	70 °C (3.3 min, solvent vent)−4°/s−280 °C	1 mL min^{-1}	–	ToF MS	<10 ng g^{-1}	[176]

[a] GC × GC instead of GC analysis

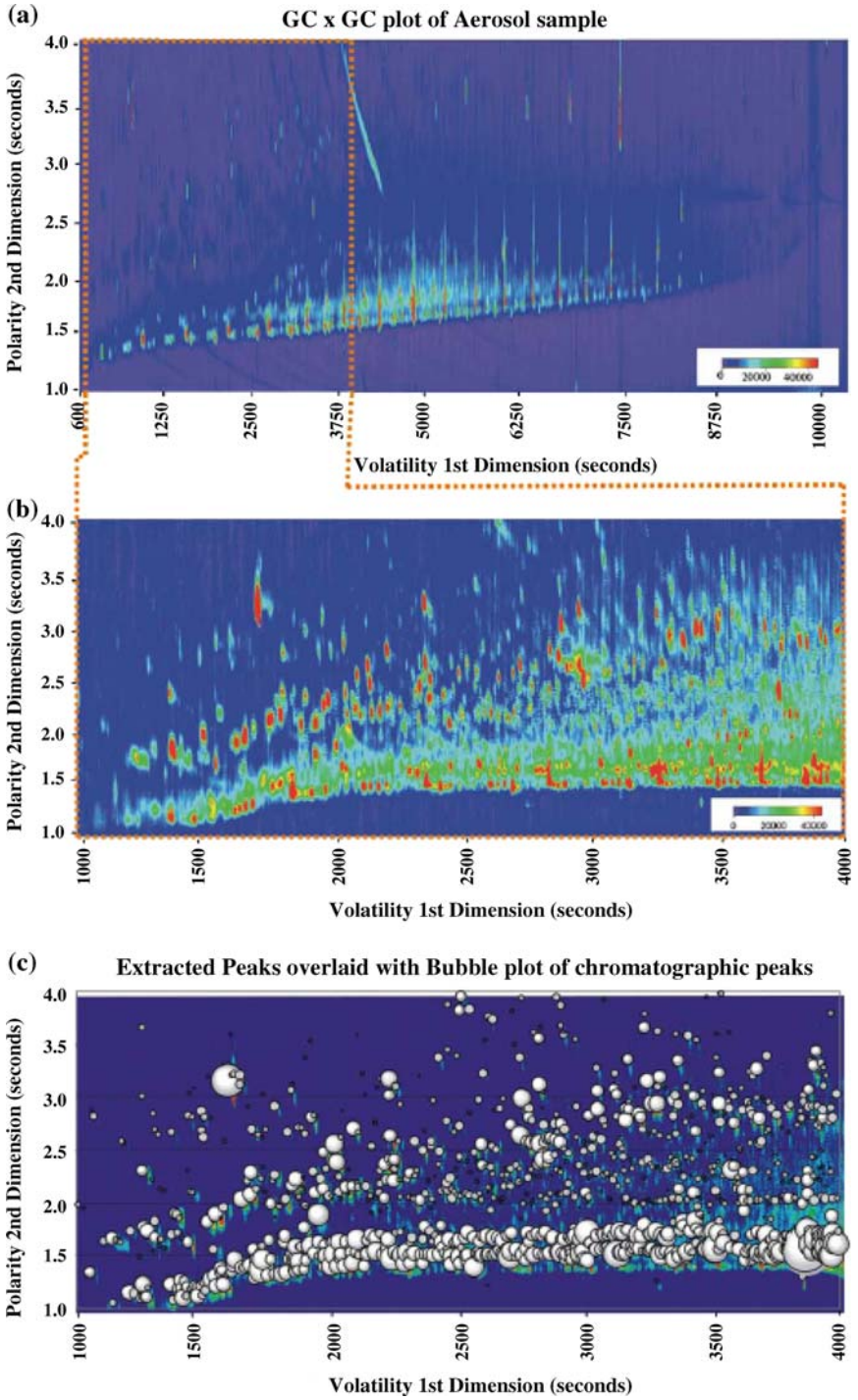

Fig. 13. DTD–GC × GC–ToF MS total ion current contour plot of an aerosol sample: (**a**) shows the full chromatogram of the analysed aerosol and (**b**) the enlargement of a selected section; (**c**) represents this section overlaid with a bubble plot generated from the peak apices of the same section [168]

injector. De Koning et al. [175] included this approach in the liner-exchange set-up discussed above to analyse pesticides in food by GC–ToF MS. The XYZ sample processing robot now holds a tray with a number of sample extracts, while an additional tray contains an equal number of liners containing a μ-vial. Just before analysis, a fresh liner is placed in the injector. After the sample preparation, the robot injects an amount of sample extract in the μ-vial in the liner for GC analysis. The LODs were 1–10 ng g^{-1}, which meets the European directives for baby-food analysis. Patel and co-workers published a related study [176] on the use of DMI in contract laboratories. Silanization of the DTD liners was found to be particularly important to mask active sites present in the frit. Elimination of a commonly employed GPC or SPE clean-up step accelerated sample processing and provided a significant reduction of the solvent usage. Other authors [177–179] combined rapid analyte isolation by means of liquid partitioning plus dispersive SPE (to remove fats and waxes) with DMI to determine pesticide residues in vegetables and fruits. Blokker et al. [180] used the DMI approach to record the fatty acid profiles of microalgae and vegetable oils (which included in-unit transesterification of the target compounds into FAMEs) and the chemical analysis of spores and pollen (which could be carried out with less than ten pollen per analysis). Akoto et al. [181] used the same approach for the fatty acid GC–MS profiling of raw biological samples. The authors stated that up to 18 algal and microbial cell samples could be analysed per day.

Özel et al. [34] compared the performance of DTD, steam distillation (SD) and SHWE for the determination of volatile compounds from plant leaves. The authors concluded that the chemical compositions of the volatile fractions obtained by SD and SHWE were similar, but a greater number of compounds was isolated when using DTD. The conclusion partly agrees with a much earlier study [182] where it was shown that, although the chromatographic profiles of plant volatile fractions obtained by SD and DTD were similar, the recovery of both low-volatile and thermolabile compounds were better using DTD.

Solid-Phase Extraction

In the late 1970s, SPE was introduced for the pre-treatment of aqueous samples. Since that time, off-line and,

specifically, on-line trace enrichment and clean-up by means of SPE using pre-columns or (disposable) cartridges has become a very popular—probably the most popular—column-switching technique in LC. Most techniques and much of the hardware used today for off-line SPE-GC and on-line SPE–GC were adapted from the corresponding LC techniques. In the 1990s, semi- and fully automated systems were designed for both chromatographic techniques, and scores of off-line, at-line and on-line applications were reported. Consequently, many of the more informative reviews [198–200] were published in that period—with environmental applications being the main field of interest for GC-based studies.

SPE cartridges have dimensions of, typically, 10–20 mm length x 1–4.6 mm ID. In most instances the cartridges are packed with 10–30 μm sorbents such as C18- or C8-bonded silica or a styrene–divinylbenzene (SDB) copolymer. These are essentially non-selective sorbents because for many applications the SPE step should primarily guarantee the enrichment of analytes covering a wide range of polarities, with the subsequent chromatographic separation (plus detection) step ensuring the proper recognition of the individual compounds. Since separation-plus-detection is much more powerful in GC than in LC analysis, with the former technique the bonded silicas and the copolymer are virtually the only sorbents used in real-life applications. A typical set-up for SPE–GC is depicted in Fig. 14. After cartridge conditioning, a sample volume of, often, some 10 mL is loaded at a speed of several mL min^{-1}, the cartridge is cleaned with a few millilitres of water, and dried for some 20–30 min with nitrogen at ambient temperature. Next, the enriched analytes are desorbed with as little as 100 μL of an organic solvent—frequently ethyl or methyl acetate—and transferred on-line to the GC part of the system for further analysis. There is abundant experimental evidence [201–203] that with, e.g., GC–MS, GC–NPD or GC–AED as instrumental analytical techniques, LODs of 5–50 ng mL^{-1} can be obtained for a wide variety of micro-contaminants in 10-mL real-life samples.

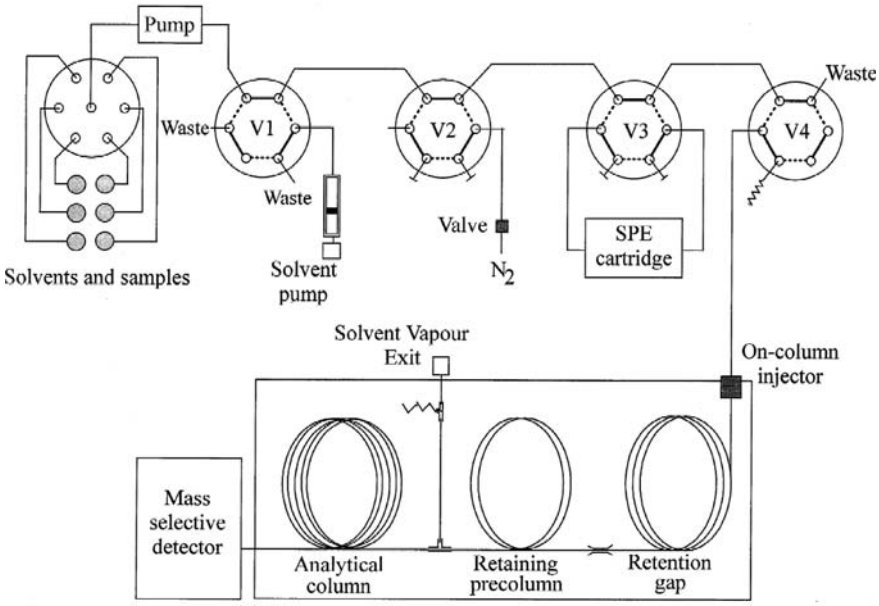

Fig. 14. Scheme of an on-line SPE–GC–MS system [202]

The above conclusion is an important one because (semi-) automated SPE–GC is indeed a very powerful technique but is, at the same time, somewhat more complex than is appreciated by many analysts who, therefore, prefer to use an off-line procedure. The protocol is, then, essentially the same as the one given above and, if desired, the SPE part of the procedure can be carried out fully automatedly on a stand-alone instrument such as the Symbiosis (Spark, Emmen, The Netherlands)—the successor of the highly successful Prospekt—the MPS2-SPE (Gerstel) or the ASPEC XL (Gilson, Middleton, WI, USA). However, the SPE eluate containing the analytes is now collected in a vial and, typically, some 25 μL are injected by means of LVI–GC. In other words, there is a fourfold loss in performance compared with the on-line operation (25 out of 100 μL), which can either be accepted (if analyte detectability does not create problems) or can be compensated by loading a fourfold larger volume (which usually will not cause breakthrough problems: experience shows that these do not tend to occur for sample volumes of less than 100 mL).

One main advantage of the various on-line set-ups briefly referred to above was the substantial sample-volume reduction from the conventional 100–200 mL (combined with classical 1-μL injection volumes) to, typically, 10 and sometimes even 1–2 mL, which could be effected without adversely affecting the analytical performance of the procedures. Here, one should add that SPE also is a rewarding technique when ultra-trace levels of, e.g., 0.01–0.5 ng mL^{-1}, of micro-contaminants have to be determined in marine waters. In such cases, sample volumes typically are as large as 5–20 L and off-line procedures involving the use of 47–90 mm diameter C_{18} or SDB disks or stacked cartridges packed with graphitized black carbon are preferably used.

Applications For the reasons outlined above, most of the selected on-line applications included in Table 8 are from the 1990s rather than the past few years. For readers interested in setting up a system of their own—where aspects such as complete removal of water from the loaded cartridges to prevent GC column problems, re-use of cartridges and complete retention of even volatile analytes are relevant issues—two other papers are recommended [202, 204]. The table also features several very-large-volume applications.

One typical example is described by Hankemeier et al. [202] who used SDB-SPE–GC–MS to analyse 10-mL river water samples (without and with spiking

Table 8. Selected applications of SPE combined with GC

Analyte	Sample (mL or g)	Pre-treatment	Sorbent	Desorption solvent (mL)	Post-treatment	Detector	LOD (ng L^{-1})	Recovery (%)	Ref.
On-line									
Microcontaminants	Water (20)		SDB	EtOAc (0.1)		IR			[213]
Microcontaminants	Water (10)		SDB	EtOAc (0.1)		MS	20–50	70–115	[202]
Microcontaminants	River water (75)	Filter	SDB	EtOAc (0.75)		MS, AED	20–200		[214]
Microcontaminants	Water (50)		SDB	EtOAc (0.1)		MS, AED	20–1,000		[215]
Micropollutants	Water (7.5)		SDB	EtOAc (0.05)		MS (SIM)	0.5–5	75–95	[216]
Pesticides	Water (10)	30% MeOH	SDB	EtOAc (0.1)		MS (SIM)	2–20	15–100	[217]
Pesticides	Water (10–100)		SDB	EtOAc (0.1)		MS/MS	0.01–4		[218]
OPPs	Water (100)		SDB	EtOAc (0.1)		AED	0.5–1.5	60–105	[201]
Endocrine disruptors	Water (15)	Add 50% MeOH	SDB	EtOAc (0.3)		MS	1–35	30–110	[205]
Alkyl-, chloro-, mononitrophenols	Water (10)	Deriv.	SDB	EtOAc (0.1)		MS (SIM)	1–15		[206]
Large-volume									
Micropollutants	Water (50)		SDB	EtOAc (0.3)		MS	1–2		[219]
Pesticides	Sea water (10,000)		SDB	EtOAc (3 × 30) + Hex–EtOAc (4:1) (50)	Conc., silica clean-up, conc.	MS	0.1–0.7	60–130	[220]
Triazines, OPPs, acetanilides, OCPs	Marsh water (10,000)		90 mm C_{18} disk	DCM–Acet (1:1) (40)	Filter, conc.	MS	0.05–2	7–130	[221]
Selective									
Semaridine	Human plasma (0.6)	LLE	MIP	Hep (1.7)	Washing	NPD			[210]
Cholesterol	Yolk (10)	Saponification	MIP	TCM–EtOH–EtAc (3:1:1) (3)	Deriv.	FID			[209]
Organo-S compounds	Water (10)		Pb(II)-loaded cation-exchange	1% CS_2 in toluene		PFPD	500–3,000		[222]
OPPs	River water (1 000)	Filter	MIP	DCM–MeOH (9:1)		NPD	10–30	82–99	[223]
Triazines	Water (10)		IA	Glycine buffer	SPE	FID, NPD	15–25, 1.5–2.5		[212]

of 86 micro-contaminants at the 0.5 μg L^{-1} level). Full-scan MS traces are shown in Fig. 15. LODs were in the 20–50 ng L^{-1} range or lower for essentially all analytes. The identification potential of the procedure is illustrated by *m*/*z* traces of the four characteristic ions of peak 11 (benzaldehyde) in the raw, i.e., non-spiked, water. Its concentration was calculated to be approx. 40 ng L^{-1}. A similar approach was used for the analysis of endocrine disruptors such as atrazine, hexachlorobenzene, DDT and benzo[*a*]pyrene by SPE–GC–MS [205]. In this case the 15-mL water sample contained 50% methanol to prevent sorption problems. 100 μL ethyl acetate were used for analyte desorption. The LODs for the target analytes were 1–40 ng L^{-1}. Jahr [206] used automated SPE–GC–MS to determine 26 alkyl-, chloro-, and nitrophenols (after their in-sample derivatization) in drinking water and river water. Time-scheduled SIM-MS enabled target analysis down to, typically, LODs of 2–10 ng L^{-1}.

So far, no mention has been made of more specialized SPE phases such as restricted-access media (RAM), molecular imprinted polymers (MIP), immunoaffinity extraction (IAE) phases and other class- or compound-selective sorbents. This is because almost all applications which utilize one of these selective types of sorbent use LC for subsequent analysis (see, e.g., [207, 208]). Although this is, therefore, an area largely beyond the scope of the present review, a few pertinent examples are included in Table 8. Shi et al. [209] analysed cholesterol in yolk. After saponication and the addition of water and hexane, 1 mL of the organic phase was loaded on the MISPE cartridge. After repeated washing, elution was done with 3 mL chloroform–ethanol–acetic acid (3:1:1). The eluate was evaporated to dryness and the residue dissolved in pyridine with subsequent derivatization with BSTFA. Analysis by means of GC–FID showed that MISPE created more selectivity than C_{18}-SPE treatment. However, most of the extra clean-up was created in parts of the GC chromatogram far removed from the analyte position. A rather similar conclusion holds for the MISPE-based determination of semaridine in plasma [210]. For the selective extraction of tributylphosphate (TBP) from diesel, Harvey [211] injected 20 μL of diesel on a MIP column (37 × 3.0 mm). After elution, the TBP-containing fraction was analysed by LVI–GC–FID. Figure 16,

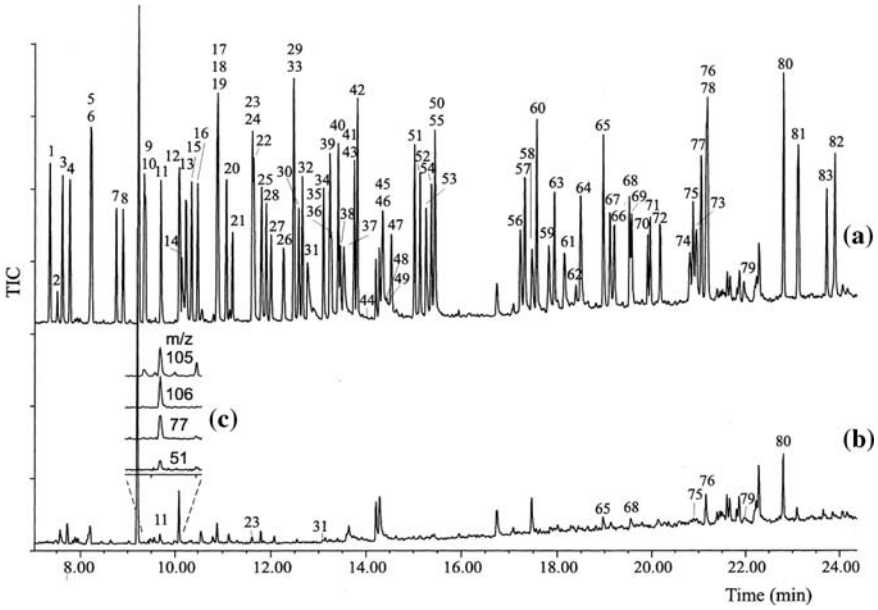

Fig. 15. TIC chromatogram for SPE–GC–MS of 10 mL of river Rhine water (**a**) spiked at the 0.5 μg L^{-1} level with 86 microcontaminants and (**b**) non-spiked. A 50-μL volume of methyl acetate was used as presolvent. For peak assignment, see ref. [202]. The insert (**c**) shows the mass chromatograms of four characteristic masses of benzaldehyde (*m*/*z* 51, 77, 105 and 106). The time scale for the mass chromatogram is twice as large as for the TIC chromatogram

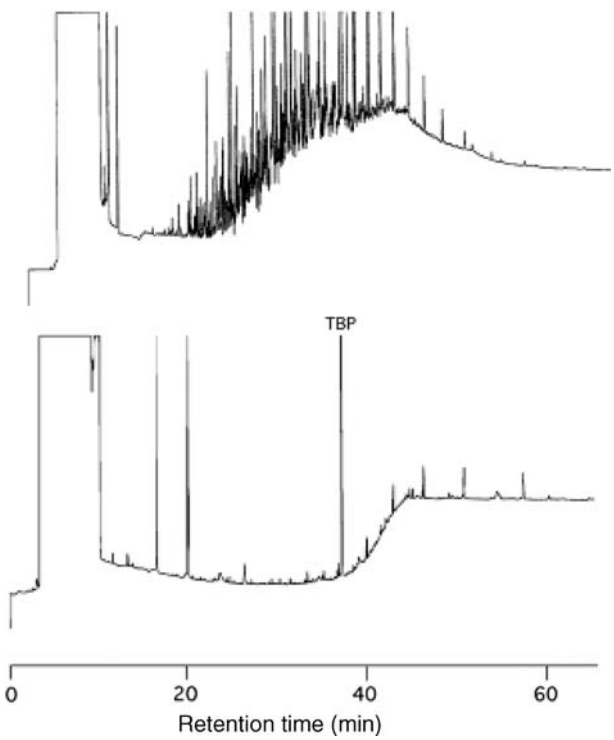

Fig. 16. GC–FID of TBP-spiked diesel sample (top) and the fraction retained by the TBP-specific MIP (bottom) [211]

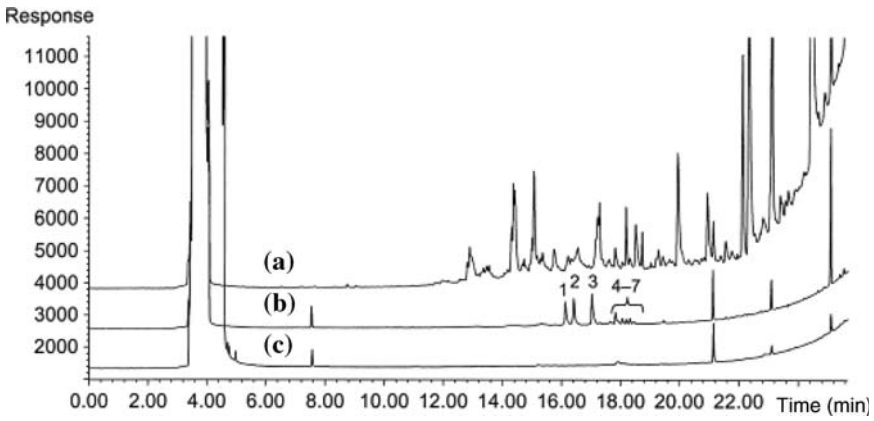

Fig. 17. GC–FID chromatograms of an extract obtained by (**a**) on-line SPE and (**b**) on-line IASPE of 10 mL of municipal waste water, spiked with 1 mg L^{-1} of seven triazines. (**c**) Blank run of IASPE–GC–NPD of 10 mL of HPLC-grade water. **1** = Atrazine; **2** = Terbuthylazine; **3** = Sebuthylazine; **4** = Simetryn; **5** = Prometryn; **6** = Terbutryn; **7** = Dipropetryn [212]

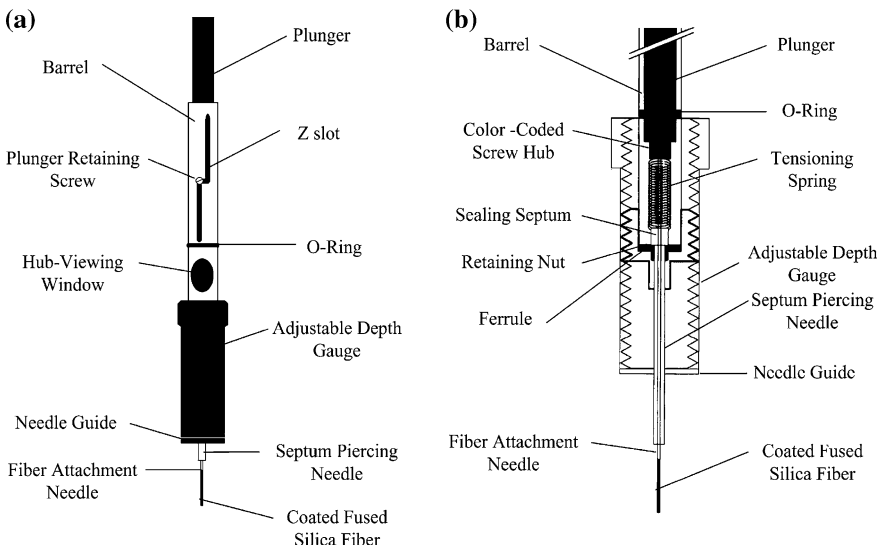

Fig. 18. Commercial SPME device [234]. (**a**) SPME fibre holder; (**b**) section view of SPME holder and fibre assembly

shows the chromatogram of that fraction which is (not surprisingly!) much cleaner than the chromatogram of the original diesel sample.

On-line IASPE–GC–FID/NPD was used to determine triazines in 10-mL water samples [212]. Since the material is not compatible with an organic solvent, after enrichment the analytes were eluted with an aqueous glycine buffer and transferred on-line to an SDB cartridge. After clean-up and drying of the cartridge, the entire extract was desorbed with ethyl acetate and transferred on-line to the GC column. The selectivity was such that a non-selective FID could be used for detection (Fig. 17), with LODs of 15–25 ng L^{-1}. With a selective detector, i.e., an NPD, the LODs could be improved 10-fold.

Solid-Phase Micro-Extraction

In 1990, solid-phase micro-extraction (SPME) was introduced by Arthur and Pawliszyn as an organic-solvent-free extraction technique [224]. The theory and practice of the method have been examined in considerable detail [225–228] and numerous applications have been reported and reviewed [229, 230]. Basically, the technique enables the trace enrichment of analytes by the exposure of a fused-silica fibre coated with an appropriate sorbent layer, for a selected time, to a gas or liquid sample, with the subsequent (rapid) desorption of the target analytes by heating the exposed fibre in the injection port of a GC. A number of fibre coatings, which offer a range of analyte solubilities and porosities, are commercially available. These include the highly popular non-polar polydimethyl siloxane (PDMS) and more polar coatings such as PDMS–divinylbenzene copolymers, polyacrylates and mixtures of carboxen (an inorganic adsorbent) and PDMS or divinylbenzene. Their mutually different physicochemical characteristics help to widen the application range of the technique. Fibre coatings are available in increasing thicknesses from 7–150 µm, which increases the partitioning ratio of the target analytes—and, hence, analyte detectability—but also increases equilibration times.

The schematic of an SPME device is shown in Fig. 18. The fibre is mounted in a syringe-like device for protection and ease of handling. The needle serves to conveniently pierce the septum of a sample vial or the GC injector. That is, during analyte extraction and desorption, the fibre is exposed but during transfer of the sample to the GC injector, it is inside the protective needle. Obviously, this is an elegant approach, and the fact that no solvent is required is a distinct advantage. On the other hand, it is a disadvantage that the fibres are rather fragile, even though they are shielded when out of the sample or injector; they can also be damaged by the build-up of involatile material from the samples. [To improve the robustness of the technique, Lipinski [231] introduced (automated) solid-phase dynamic extraction (SPDE) which uses needles prepared from stainless-steel capillary columns, with PDMS-coated inner walls.]

In a typical SPME experiment, the coated fibre is exposed directly immersed in, or to the headspace of, a small volume of liquid or sample extract, usually some 2–5 mL. The analytes partition into the stationary phase until plateau

conditions are reached, which typically takes 2–60 min. The process can be aided by salting-out (addition of, e.g., 25% NaCl) and/or pH adjustment, sample agitation (to speed up analyte transport from the bulk of the solution to the vicinity of the fibre) and heating [232, 233]. Adverse matrix effects can be avoided by applying a standard addition procedure for quantification or, less frequently, using protective membranes to prevent adsorption of matrix components on the fibre [226].

If selective detection, such as MS in the SIM mode or ECD, is used, LODs for both volatile and semi-volatile analytes typically are in the low-ng mL^{-1}, and sometimes in the ng L^{-1}, range. However, one should consider that SPME (as is also true for e.g., SBSE; see section on SBSE) is an equilibrium technique. That is, although favourable analytes can be extracted essentially quantitatively, there are also many classes of compounds for which this is certainly not true—actually, it is not unusual to find recoveries of less than 10% in the published literature (Table 9). For such classes of compounds, conventional SPE (cf. section on SPE) can always provide (substantially) better analyte detectability. Admittedly, non-equilibrium methods can also be used for SPME—and also for SBSE and HS—but this will decrease method sensitivity and will require highly precise timing procedures.

As already indicated above, there are three modes of SPME, viz. the often applied direct-immersion extraction (DI-SPME) and headspace extraction (HS-SPME) and the rarely used membrane-protected SPME (Fig. 19). It will be clear that DI-SPME is a very straightforward technique which does not require further discussion. However, exposing the fragile fibres to highly complex samples—which, in addition, can contain high NaCl concentrations and/or have a too extreme pH—may well cause damage and, consequently, lead to erroneous results. The increasingly popular HS-SPME mode primarily serves to protect the fibre coating from such damage by high-molecular-mass material such as humic substances or proteins and other non-volatiles present in the sample matrix. Self-evidently, modifying the sample composition now does not create any problems either. One should note that the amounts of analyte extracted into the fibre coating are the same at equilibrium for DI and HS sampling provided the sample vial, and the volumes of the liquid sample and the gaseous headspace are the same. This is due to the fact that the equilibrium concentration is independent of the fibre location in the sample/headspace system. If the above conditions are not satisfied, a significant sensitivity difference between the two approaches exists only for very volatile analytes.

With membrane-protected SPME the main purpose of the barrier also is to protect the fibre against damage, viz. when very dirty samples have to be analysed. In addition, membrane protection can be used for the determination of analytes having volatilities too low for the headspace approach. In principle, a suitable membrane can add a degree of selectivity to the extraction process. However, the analyst should consider that the kinetics of membrane extraction are substantially slower than for direct extraction, because the analytes must diffuse through the membrane before they can reach the coating.

In the literature, rather much attention is devoted to extending the application range of SPME to more polar compounds. Generally speaking, this is an approach which is not to be recommended today, since most classes of polar compounds can be analysed successfully by means of LC–MS techniques (also see section on Stir-Bar Sorptive Extraction). With the LC-based route, the intact compounds can be subjected to analysis and time-consuming derivatization (which, moreover, often generates artefacts and is frequently not successful at the ultra-trace-level) is avoided. There are, however, also instances when the LC route cannot be used and SPME-*cum*-derivatization has to be applied [235]. Derivatization can be performed in different ways, with direct derivatization in the sample matrix [236] and on the fibre [237] being most popular. Derivatization in the GC injection port is also used [238]. As regards on-fibre derivatization, there are two modes of operation, viz. (1) sampling of the target analytes on the fibre with subsequent exposure of the fibre to the HS-derivatizing reagent solution, and (2) exposure of the fibre to the HS analyte solution after it has been exposed to the derivatizing reagent solution. Practical examples of each of these approaches will be given below, in the section on applications.

The SPME technique is marketed by Supelco (Bellefonte, PA, USA). Most reported applications are of the manual type. However, automated analysis can be performed by using systems commercialized by Varian (Palo Alto, CA, USA) [174, 236] and CTC (Zwingen, Switzerland) [239–241]. Recently, Pawliszyn and his group reported the automation of SPME on a 96-well plate format [242], which they claim to be a viable approach compatible with both GC and LC platforms.

Applications In the early years, SPME was used primarily for the determination of relatively volatile compounds of environmental interest [243, 244]. Today, there are also many applications in the biomedical field [245] and for food analysis [246]. Moreover, as was discussed above, the technique is also used for less volatile compounds [234]. A number of relevant applications are listed in Table 9. Some of these are briefly discussed below.

A popular application of SPME is the analysis of aroma compounds in wine. To give an example, Peña et al. [247] determined monoterpenes by adding NaCl to 7 mL of wine to obtain a final salt concentration of 25%. SPME was performed by immersing a 100-μm PDMS-coated fibre for 15 min in the sample, with stirring at 1,100 rpm. With analyte recoveries of 71–91%, the LODs (TIC MS) were 11–25 μg L^{-1}. In the environmental field, HS-SPME was used to determine volatile organochlorines in landfill leachates [248]. 10 mL of sample were put in a 12-mL vial. No salt was added and the sample was kept at room temperature. The HS-SPME procedure, which used a 10-μm PDMS-coated fibre and stirring at 900 rpm, was complete in 2 min. With LODs (SIM MS) of 0.05–0.10 ng mL^{-1} and analyte recoveries of

Table 9. Selected applications of SPME in combination with GC

Analytes	Sample (g or mL)	Pre-treatment	Extraction	Desorption	Detector	LOD (ng mL^{-1} or ng g^{-1})	Recovery (%)	Ref.
Direct immersion								
PAHs	Vegetable oil (0.2)	Dilute with Hex	30 min	Thermal	ToF MS[d]	0.1–1.5		[250]
PAH metabolites	Urine (5)	Enzyme hydrolysis	45 min, 35 °C[a]	Thermal	MS			[237]
PAH metabolites	Water (1)		40 min, 900 rpm	MeCN	ToF MS	0.06–0.2		[242]
Fenitrothion and ist metabolites	Poplar leaves	Liquid extraction	40 min	Thermal	MS (SIM)	0.5–2.5		[251]
Monoterpenes	Wine (7)	25% NaCl	15 min	Thermal	MS	11–25	70–90	[247]
Amphetamines	Urine (1.2)	pH, deriv.[b]	16 min	Thermal	MS	5–15	1.5–10	[236]
Headspace								
PCBs	Water (20)	MAE (30 W)	10 min, 100 °C	Thermal	ECD	0.3–1.5 ng L^{-1}	55–160	[252]
VOCs	River water (20)		30 min, 70 °C	Thermal	ECD	0.2–11 ng L^{-1}	95–110	[253]
VOXs	Landfill leachates (10)		2 min	Thermal	MS (SIM)	0.05–0.10	90–100	[248]
Dichlorvos	Fruits and vegetables (2)	MAE (10 min, 132 W, pH 5)	10 min	Thermal	ECD		105	[254]
Benzenes	Workplace air		10 min	Thermal	MS			[243]
Aroma profile	Wine (20)		15 min, 750 rpm	Thermal	MS			[255]
Amphetamines	Blood (0.5)	1 M NaOH	15 min[c]	Thermal	MS	5–10	2.0–6.5	[238]
Sulphur volatiles	Cheese (2)	Cut in cubes of 0.5 cm	30 min, 50 °C, 250 rpm	Thermal	PFPD			[256]
Volatiles	Ice wine (3)	1 g NaCl	5 min, 45 °C	Thermal	ToF MS			[239]
Phenols, haloanisoles	Wine (5)	0–2 g NaCl	60 min, 70 °C	Thermal	MS/MS	0.01–0.15	95–100	[241]

[a, b, c] Procedure involves on-fibre (a), direct (b) or injection-port (c) derivatization
[d] GC × GC instead of GC analysis

93–100%, the results were closely similar to those found with conventional headspace (HS) analysis. However, HS-SPME was faster than HS (2 min vs. 15 min); on the other hand, HS gave more precise results.

As for derivatization, the direct approach has been used for the automated SPME determination of amphetamines (as carbamates) in buffered urine samples, with propylchloroformate as derivatization agent [236]. Analyte recoveries were less than 10% and the LODs (TIC MS) were somewhat high (5–15 ng mL^{-1}). The same compounds were also analysed in whole blood via HS-SPME and injection-port derivatization with heptafluorobutyric anhydride [238]. Desorption-*cum*-derivatization took only 3 min. Finally, the on-fibre alternative was applied for, e.g., PAH metabolites in urine [237]. SPME with an 85-µm polyacrylate fibre was rather time-consuming, i.e., 45 min at 35 °C under stirring. After extraction, the fibre was placed in the headspace of a vial containing BSTFA; derivatization at 60 °C took 45 min. The fibre was then transferred to the hot injection port of the GC and desorbed for 3 min.

As an alternative to SPME, and also SBSE, Burger et al. [249] introduced the use of a sample-enrichment probe (SEP), which was developed primarily for HS analysis. The SEP consists of a thin rod of an inert material, provided at one end with a short sleeve of PDMS for the high-capacity analyte enrichment. After enrichment, the end of the rod carrying the silicone rubber is introduced into the injector and the analytes are subjected to TD–GC. SEP is similar to SPME, but a main difference is that a much larger mass of the sorptive phase is employed. Results of the two techniques for (semi-) volatile organic compounds are stated to be comparable.

Stir-Bar Sorptive Extraction

In the previous section, the relatively small volume of bound stationary phase used for analyte extraction, was quoted as a main limitation of SPME. This prompted the development of another miniaturized extraction technique by Baltussen et al. [257], stir-bar sorptive extraction (SBSE), marketed as the Twister by Gerstel. The technique has been reviewed in several recent papers [258–261].

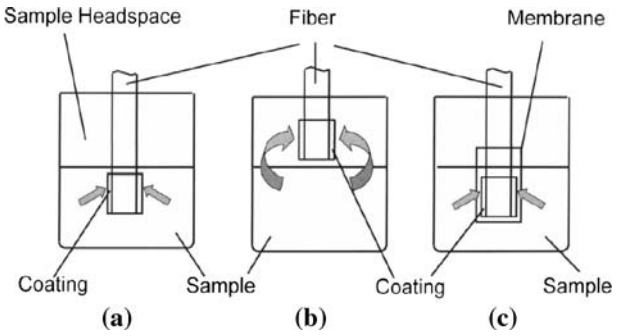

Fig. 19. Modes of SPME operation: (**a**) DI-SPME, (**b**) HS-SPME, (**c**) membrane-protected SPME [226]

In SBSE, a magnetic stir bar of, typically, 10–30 mm length, and coated with 24–47 µL of polymethyldisiloxane (PDMS), is rotated in an aqueous sample at some 1,000–1,500 rpm for a preset time which is often very long, i.e., 60 min or more. After (near-) equilibrium has been reached, the stir bar is removed by hand with tweezers, dipped briefly in distilled water to remove, e.g., absorbed sugars or proteins, placed on tissue paper to remove residual droplets. Rinsing does not cause solute loss, because the adsorbed solutes are present inside the PDMS phase. As an alternative, liquid rinsing with a non-polar solvent such as hexane can be used. Finally, the stir bar is placed in the liner of a thermal desorption system to enable GC analysis [258]. After thermal or liquid desorption, the stir bars can be re-used.

Sample volumes in SBSE typically are on the order of 2–20 mL. There are, however, also several applications which feature sample sizes of 80–200 mL. Since the dimensions of the stir bars selected for analyte extraction are the same as when using more modest volumes, stirring times now frequently are excessive, i.e., 3–15 h [16, 262–264].

As in SPME, analyte extraction from the aqueous phase to the extraction medium is controlled by the partition coefficient between the two phases and, consequently, the $K_{o/w}$. Since the amount of sorbent coated on a stir bar is 50–100-fold larger than on an SPME fibre, there is a higher phase ratio than in SPME and, hence, a higher extraction efficiency, which results in improved analyte detectability. Today, only PDMS is available as an extraction phase on commercially available stir bars and the large majority of applications therefore use this coating. Here one should add that attempts to apply other coatings have failed mainly because of irreproducible coating or excessive bleeding during thermal desorption [258]. In this context, a recent innovation should be mentioned, viz. the introduction of dual-phase twisters which combine the concentrating capabilities of two sampling materials, PDMS and carbon, which operate in different ways, i.e., by sorption and adsorption, respectively [265]. These stir bars consist of an outer PDMS coating holding an activated carbon material inside. Two magnetic stoppers which close off the ends of the PDMS tube, enable stirring. Increasing recoveries were found for very volatile compounds emitted from plant material and for polar solutes in water.

Most applications of SBSE deal with aqueous samples containing low concentrations of organic compounds. Samples containing high concentrations of solvents, detergents, etc. should be diluted before extraction. If very hydrophobic solutes have to be determined, such as, e.g., PAHs and PCBs, some 10 vol% of an organic is added to minimize wall adsorption, as is also done in, e.g., SPE. The negative effect on the partition of the target compounds can be neglected because of their high $K_{o/w}$ values; actually, the overall selectivity of the

procedure will improve because many less hydrophobic compounds will be (partly) flushed to waste. In quite a number of papers, SBSE is combined with in situ derivatization [260, 266–269], especially in order to improve the recoveries of polar analytes with their low $K_{o/w}$ values. Derivatization reactions that can be performed in aqueous media include acylation of phenols using acetic anhydride, esterification of acids, acylation of amines using ethyl chloroformate and oximation of aldehydes and ketones using PFBHA. However, in every single instance the analyst should duly consider whether the time-consuming SBSE-*cum*-derivatization procedure should be used or the intact analytes subjected to an LC-based analysis.

SBSE is also used for headspace sorptive extraction (HSSE). A stir bar is hung in the headspace of a sample, often by attaching the magnetic stir bar to a paper clip, which pierces the septum of a headspace vial, by magnetic force. HSSE has been applied to headspace sampling of a wide variety of interesting sample types. These include aromatic and medicinal plants [270], chiral monoterpenes in essential oils in combination with enantio-MDGC–MS [271], coffee [272] and volatile metabolomics from toxigene fungi [273, 274].

Applications SBSE is mainly used for the GC analysis of biological and food samples (Table 10). Some selected applications are briefly discussed below.

Sandra et al. [275] determined fungicides in wine. The authors poured 10 mL of undiluted wine in a 20-mL headspace vial and used a stir bar containing 24 μL PDMS to stir the sample for 40 min at 1,400 rpm. The absorbed compounds were transferred to the GC–MS system by thermal desorption of the stir bar. Although the recoveries were rather low (7–35%), LODs were in the range of 0.2–2 ng mL^{-1}. In order to determine the seven so-called Ballschmiter PCBs in human sperm, Benijts et al. [276] sonicated 1 mL of sperm to break the membrane of the spermatozoa and diluted the sample with 9 mL water–MeOH (1:1). For SBSE, the resulting solution was rotated for 25 min at 1,000 rpm by a PDMS-coated stir bar. After thermal desorption, GC–MS was performed in the time-scheduled SIM mode. With analyte recoveries of 30–40%, the LODs were 0.1–3 pg mL^{-1}. Kawaguchi et al. [267] applied SBSE for the determination of chlorophenols in 2 mL of human urine. The sample pH was adjusted to 11.5 prior to the addition of the derivatization reagent, acetic acid anhydride. SBSE was performed for 60 min with stirring at 500 rpm. GC–MS in the SIM mode resulted in LODs of 10–20 pg mL^{-1} with quantitative analyte recoveries. The extracted-ion-chromtograms for the studied chlorophenols derivates are shown in Fig. 20. HSSE was the sampling method used by Demyttenaere et al. [273] to monitor the mycotoxin production of fungi. The fungi were cultivated in 22-mL vials, and a PDMS stir bar was held in the headspace for 1 h. The mycotoxins were analysed by thermal desorption–GC–MS. The authors concluded that SPME is faster (30 min extraction) and simpler, because it does not require a special thermal desorption device and, also, because the concentrations of the target analytes were relatively high. Moreover, SPME can easily be automated and used for fast detection.

Membrane Extraction

Separation by means of a membrane can be achieved in many ways and very generally, a membrane can be defined as a selective barrier between two phases. When a driving force is applied across a membrane, transport of matter occurs from the donor to the acceptor phase, giving the so-called flux. Separation is achieved when some species are transported to a larger extent than others and, in the ideal case, components of interest are transferred quantitatively, while all other sample components remain in the donor phase.

Membrane separation processes can be classified by means of the driving forces involved. The most important ones are differences of (1) concentration, which cause a molecular flux (transport of molecules), (2) electric potential, which cause an electrical flux (transport of charge) and (3) pressure, which cause a volume flux (transport of bulk liquid or gas). Very often, more than one driving force is present in a membrane separation process.

A wide variety of membrane materials can be used. In many cases, a membrane is a porous network of a synthetic polymer, such as polypropylene, polysulphone or a cellulose derivative. Separation is based only on size-exclusion: sufficiently small molecules can permeate through the pores but larger ones cannot. More selectivity can be obtained with, e.g., ion-exchange membranes, which have positively or negatively charged groups covalently attached to the polymeric membrane material. Separation is now based on both size and charge differences of the various solutes. Non-porous membranes are a rather different class: they consist of a liquid or polymer film, into which a molecule must actually dissolve in order to be able to pass through. For a particular compound, the efficiency of membrane transport now largely depends on its partition coefficients between the different parts of the membrane separation system. Only compounds which are easily extracted from the donor phase into the membrane and, in addition, easily extracted from the membrane into the acceptor phase will be transported. Separation is therefore based on the same principle as in LLE with a subsequent back-extraction and analytes with different physicochemical properties will be extracted to a different extent even if they are of equal size.

Four membrane separation techniques are frequently used for sample preparation. Three of these—dialysis (concentration-driven), electrodialysis (electrically driven) and filtration (pressure-driven)—utilize porous membranes and are combined (mainly) with LC [289, 290]. They are therefore beyond the scope of this review. One technique, so-called membrane extraction, uses non-porous membranes and is combined with LC as well as GC.

The most frequently used membrane-extraction system, referred to as supported liquid membrane (SLM), consists of a porous membrane support impreg-

Table 10. Selected applications of SBSE combined with GC[a]

Analytes	Sample (mL or g)	Pre-treatment	Stirring	Detector	LOD	Recovery (%)	Ref.
SBSE							
PCBs	Human sperm (3)	Dilute 1:9 (water/MeOH 1:1)	45 min, 1,000 rpm	MS (SIM)	3 pg mL^{-1}	30–40	[276]
25 PCBs	Water (8)	2 mL MeOH	120 min, 1,000 rpm	MS (SIM)	0.05–0.2 ng L^{-1}	75–95	[277]
PBDEs	Water (100)	20% MeOH	25 h, 900 rpm	MS	0.3–10 ng L^{-1}	95–105	[278]
Pesticides	Brewed green tea (20)	Tea brewing (1.25 g/200 mL), centrifuge, 30% NaCl	60 min, 1,500 rpm	MS	0.6–110 ng L^{-1}	10–70	[279]
Pesticides	Food (15)	Homogenize, USE with MeOH, centrifuge, dilute with water	60 min, 1,000 rpm	MS	Low ng g^{-1}	–	[280]
OCPs, chlorobenzenes	Soil (10)	SHWE (water:MeCN 75:25, 130 °C, 100 bar, 3 × 10 min)	180 min, 1,000 rpm	MS	0.002–5 ng g^{-1}	60–130	[16]
OPPs	Cucumber, potato (10)	SLE with Acet, centrifuge, dilute 1:10, 30% NaCl	30 min, 600 rpm	TSD	0.003–0.2 ng g^{-1}	95–105	[281]
Fungicides	Wine (10)		40 min, 1,400 rpm	MS	0.2–2 μg L^{-1}	10–35	[275]
Volatiles	Wine (25)	–	90 min, 700 rpm, 60 °C	MS	0.001–6 μg L^{-1}	–	[282]
35 SVOCs	Water (100)	Add 20% NaCl	240 min, 1,400 rpm	MS	0.04–10 ng L^{-1}	–	[263]
Phenols	Wine (25)	Dilute with water	60 min, 900 rpm	MS (SIM)	6–375 μg L^{-1}	90–100	[283]
Chlorophenols	Water (10)	pH 11.5, deriv.	240 min, 500 rpm	MS (SIM)	1–2 pg mL^{-1}	95–105	[267]
Chlorophenols	Human urine (2)	pH 11.5, deriv.	240 min, 500 rpm	MS	10–20 pg mL^{-1}	95–110	[267]
Nonylphenols, octylphenols	Water (2)	–	60 min, 500 rpm	MS	0.002–0.02 μg L^{-1}	95–105	[268]
Estrogens	River water (10, 50)	pH 11.5, deriv.	240 min, 500 rpm	MS	0.2–5 pg mL^{-1}	95–105	[266]
Phenolic xenoestrogens	River water (10)	pH 10.5, deriv.	90 min, 1,000 rpm	MS (SIM)	0.5–2 pg mL^{-1}	95–115	[284]
Aroma profile	Wine (20)	Dilute with water	60 min, 800 rpm	MS	–	–	[255]
Explosives	Water (10)	–	30 min, 4,000 rpm	IMS[b]	0.1–2 ng mL^{-1}	–	[285]
Aromatic hydrocarbons	Sea water (200)	–	60 min, 900 rpm	MS	0.1–1 ng L^{-1}	–	[286]
24 organic pollutants	Water (100)	10 g NaCl	12 h, 800 rpm, 21 °C	MS	0.1–5 ng L^{-1}	90–110	[264]
HSSE							
PBDEs	Water (80)	Add 30% NaCl	14 h, 95 °C	μECD	0.1–2 pg mL^{-1}	85–90	[262]
Volatiles	Coffee powder (0.050)	–	60 min, 50 °C	MS	–	–	[265]
Halophenols, haloanisoles	Cork	–	60 min, 100 °C	MS	3–30 ng g^{-1}	70–115	[287]
Mycotoxins	Fungi	–	60 min, 25 °C	MS	–	–	[273]
Sesquiterpene hydrocarbons	Fungi	–	30 min, 25 °C	MS	–	–	[274]
Sevoflurane	Urine (1)	Add 1.5 mL 10 M H_2SO_4	60 min, 100 °C	MS (SIM)	1 μg L^{-1}	–	[288]

[a] For almost all applications: stir bar: 10–30 mm, 24–47 μL PDMS; post-treatment: (wash) + dry; desorption: splitless, 250–280 °C
[b] IMS, ion-mobility spectroscopy

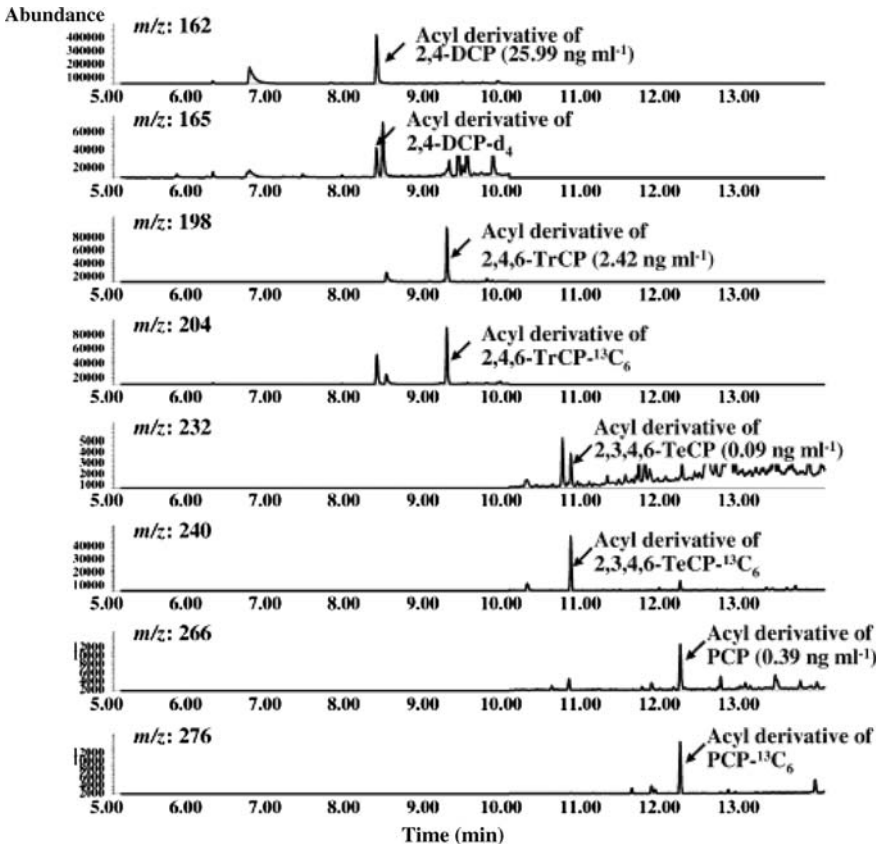

Fig. 20. Chromatograms of chlorophenols and surrogate standards in human urine sample [267]. **DCP**, dichlorophenol; **TrCP**, trichlorophenol; **TeCP**, tetrachlorophenol; **PCP**, pentachlorophenol

nated with a water-immiscible organic solvent, which is present in the membrane pores. In another approach, non-porous silicone rubber is used as the membrane material. In both cases, the membrane separates two aqueous phases and the sample pH (donor channel) is adjusted to ensure that the analytes of interest are not charged and are easily extracted into the membrane liquid or the silicone polymer film. The acceptor phase has the proper pH to effect ionization of the analytes immediately after their passing the membrane to prevent back-extraction. With the silicone membranes one can also add an organic solvent to the acceptor phase to improve the trapping of neutral compounds. The third mode of membrane extraction uses a porous membrane with an organic solvent, both in the membrane pores and in the acceptor channel. Both flat-sheet and hollow-fibre membrane units can be applied. With this technique, microporous membrane LLE (MMLLE), larger extraction surfaces can be achieved with the hollow fibres, which leads to improved extraction efficiency. Counter-current donor/acceptor solvent flow is usually applied in order to create optimum conditions [21, 291]. MMLLE differs from the other two in that it can be compared to a single LLE step rather than to LLE plus a back-extraction. A common characteristic of all three techniques is that selectivity is obtained because sample components which do not readily dissolve in the membrane liquid, are retained in the donor channel.

When using a stagnant acceptor phase and a flowing donor phase (the most common way of membrane extraction), the donor phase flow-rate will have a distinct influence on the membrane-extraction performance. If low detection limits are required and there are no sample-volume limitations (e.g., with natural waters), the best option is to use a large sample and apply a relatively high donor flow-rate of, often, 1–2 mL min^{-1} [292]. If sample volume is a limiting factor, such as for plasma, the sample is either kept stagnant in the donor channel or pumped at a low flow-rate of typically 25–50 μL min^{-1} [293]. Alternatively, a sample can be passed through the membrane device several times to obtain a better recovery.

Also for membrane extractions, there are some practical limitations and aspects worth taking into account. A problem is the incomplete transfer of analytes from the membrane to the acceptor phase during the sample preparation process. This leads to a decrease in the recovery and, more seriously, to carry-over effects for sequential analyses. Thorough rinsing of the acceptor channel is therefore essential. In general, if analytes are easily extracted into the membrane, they also show large carry-over effects obviously because they have a high affinity for the membrane material and are not readily released into the acceptor phase. Since for MMLLE there is no distinction between the membrane solvent and the acceptor phase, there are no problems of slow mass transfer to the acceptor phase or serious carry-over effects with this technique. Leakage of the membrane liquid adversely affects the extraction performance and should be avoided as much as possible. Membranes impregnated with non-polar solvents which are insoluble in water, are generally stable for several weeks without any regeneration. Obviously, with silicone membranes there is no leakage of the membrane material and they are, indeed, quite stable. The continuous use of a single silicone membrane for a period of more than 2 months has been reported [294].

The application of membranes for on-line sample preparation was a trend in the 1990s, where the coupling to an LC system is most straightforward: transferring (part of) the acceptor phase to an injection loop and injecting it is in principle sufficient. In order to couple an SLM and a capillary GC system on-line, pure water is used as the acceptor phase. The analytes are trapped on a polymer sorbent, which is dried with nitrogen

prior to desorption with an organic solvent, e.g., ethyl acetate. On-line injection to a GC is performed via LVI (also see section on SPE). More suitable for direct coupling to GC is the use of an entirely organic acceptor phase, which has been performed with silicone membranes [295] and MMLLE [296, 297]. Another automated technique of membrane extraction is membrane-assisted solvent extraction (MASE), which was first described by Hauser and Popp [298]. The extraction cell consists of a conventional 20-mL headspace vial with a membrane insert. Membrane bags are made from dense polypropylene, attached to a stainless-steel funnel and fixed with a PTFE ring. The funnel is suspended in the opening of the vial, which is closed with a crimp cap. The vial contains an aqueous sample, typically 15 mL, and the bag 100–800 µL organic solvent. After agitation an aliquot of the organic solvent is analysed by LVI–GC. An automated device is manufactured by Gerstel.

The membrane techniques mentioned so far are all characterized by liquid donor as well as acceptor phases. However, for best compatibility with GC a gaseous acceptor phase is the more convenient. This is the approach used in membrane extraction with a sorbent interface (MESI) [300]. The membrane is a polymeric hollow fibre, and the analytes are extracted from the surrounding liquid or gaseous sample (see Fig. 21 for different configurations). A gas inside the hollow fibre transports the analyte molecules into a cold sorbent tube where they are trapped. Next, the analytes are thermally desorbed from the sorbent and guided into the GC. One can also use a catalytic reaction to trap the extracted analytes directly in the gas phase [301]. In an integrated instrument set-up, the GC carrier gas passes through the membrane fibre and the sorbent trap [300]. However, one can also use the technique off-line, e.g., in field sampling. The sorbent trap is then later connected to the GC and desorbed in a separate step [302, 303]. To quote an example of MESI, Brown et al. [304] described the monitoring of trihalomethanes in drinking water. The water was sampled at a flow rate of 2.5 mL min^{-1}. Analytes

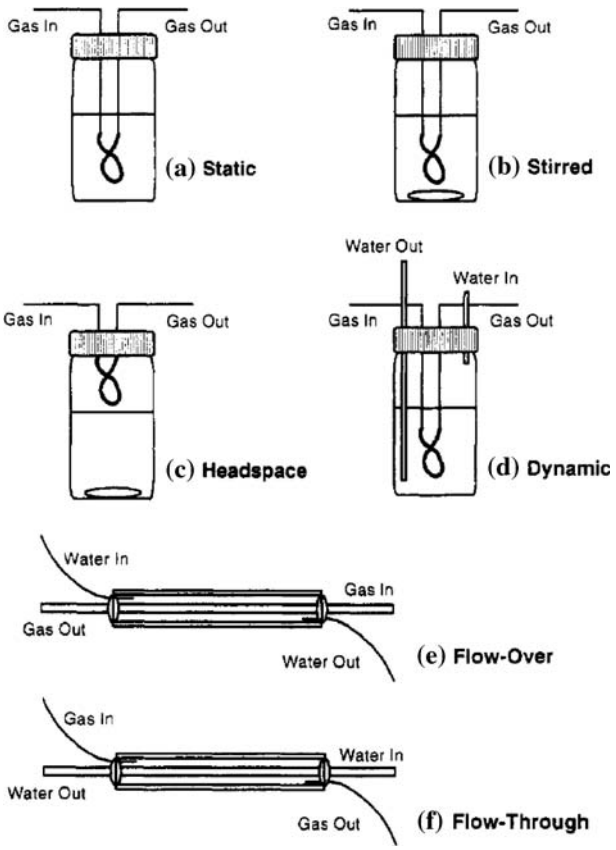

Fig. 21. Different configurations for MESI [299]

were extracted in a helium gas stream of 30 mL min^{-1} and trapped on Tenax. Next, the trap was heated and the analytes were transferred to a GC–ECD system. LODs of trihalomethanes were 0.1–1 µg L^{-1}.

Applications A list of selected applications for the isolation of a range of compounds from a variety of matrices is shown in Table 11. This list is restricted to GC applications only. An equally long, if not longer, list could also be compiled for LC. It was stated above that SLM can be combined with GC; however, no recent applications are reported. MASE, MMLLE and MIMS (membrane introduction mass spectrometry) are mainly used for environmental (air, water), and food and beverage (juice, wine) samples; an example of each of these techniques is briefly discussed below. Rodil et al. [305] determined PAHs in water and beverages by means of MASE combined with LVI–GC–MS. A 20-mL headspace vial was filled with 15 mL of a river water, apple juice, or red wine sample. A polypropylene membrane bag containing 400 µL of ethyl acetate, was hung in the sample and the vial closed. After 60 min of agitation, 100 µL of the ethyl acetate extract were analysed by PTV–GC–MS (SIM). The LODs were 3–40 ng L^{-1}. On-line MMLLE–GC–MS of PAHs in red wine was reported by Hyötyläinen et al. [296]. The MMLLE unit consisted of two PTFE blocks, both with 11-µL grooves. The grooves were separated by a porous polypropylene membrane wetted with the acceptor solvent, toluene. Extraction at a donor flow rate of 0.2 mL min^{-1} took 40 min. The acceptor phase was pumped to a loop in a GC transfer valve. The whole content of the loop was injected into the GC to ensure transfer of the entire extract. The LODs of analytes such as quinalphos and isoproturon for MS detection (scan mode) were in the range of 0.03–0.4 µg L^{-1}. Figure 22 shows the chro-

Table 11. Selected applications of membrane extraction combined with GC

Analytes	Matrix (mL, g)	Pre-treatment	Membrane	Acceptor (μL)	Extraction time (min)	Detector	LOD	Recovery (%)	Ref.
MASE									
PCBs	River water, white wine, apple juice (15)	–	PP bag	Cyclohex (800)	30	MS(SIM)	2–10 ng L^{-1}	88–114	[307]
PAHs	River water, red wine, apple juice (15)	10% MeOH	PP bag	EtOAc (400)	60	MS(SIM)	3–40 ng L^{-1}	70–136	[305]
Pesticides	Waste water, bacterial culture (15)	–	PP bag	Cyclohex (1,000)	30	MS(SIM)	2–50 ng L^{-1}	–	[308]
VOCs	River water (15)	–	PP bag	Cyclopen (100)	30	ECD	5–50 ng L^{-1}	40–96	[309]
Phenols	Ground water (15)	Sat. NaCl, pH 2	PP bag	EtOAc (800)	60	MS(SIM)	9–600 ng L^{-1}	10–98	[310]
MESI									
Trihalomethanes	Water		Silicone flat sheet	Helium	0.9	ECD	0.1–1 μg L^{-1}	110–128	[304]
VOCs	Water		PDMS-BAPC[a] flat sheet	Hydrogen	0.5	TCD	25–90 ng L^{-1}	–	[311]
Biogenic emissions	Eucalyptus leaves		PDMS flat sheet	Helium		MS			[312, 313]
MIMS									
(S)VOCs	Air, water	–	PDMS-coated PP hollow fibre	Helium	–	MS	30–540 μg L^{-1}	–	[314]
Volatiles	Microbiol. system	–	Silicone flat-sheet, silicone hollow fibre	Vacuum	–	MS	–	–	[315]
BTEX	Water	–	Silicone hollow fibre	Vacuum	0.16	ToF MS	0.03–1 ng L^{-1}	–	[306]
Alcohols, organic acids, aromas	Beer	–	–	Vacuum	8	MS	0.3–30 mg L^{-1}	–	[316]
MMLLE									
PBDEs	Water (100, flowing)	–	PP hollow fibre	Undecane (10, stagnant)	60	MS(SIM)	0.3–1 ng L^{-1}	85–110	[317]
PAHs	Sediment (0.010), Soil (0.005)	SHWE (30 min, 300 °C)	PP hollow fibre	Cyclohex (30, stagnant)	30	MS(SIM)	0.1–1 μg g^{-1}	–	[291]
PAHs	Soil (–)	SHWE (50 min, 300 °C)	PTFE flat sheet, PP flat sheet	Isooctane (125, stagnant)	50	FID	0.7–2 μg g^{-1}	–	[21]
Pesticides	Wine (6, flowing)	Dilute	PP flat sheet	Cyclohex (150, stagnant)	30	FID	1–370 μg L^{-1}	9–35	[318]
Pesticides	Wine (8, flowing)		PP flat sheet	Tol (11, stagnant)	40	MS	0.03–0.4 μg L^{-1}	–	[296]

[a] BAPC, bisphenol A polycarbonate

matograms of a blank wine, a spiked red wine and a positive red wine. Direct combination of membrane extraction with MS, so without a GC in between, is possible. Continuous BTEX screening by means of MIMS was described by Oser et al. [306]. A constant flow of water was pumped through a silicone membrane tube. As the sample passes across the inner surface of the membrane, the analytes diffuse through the membrane and evaporate into the MS ion source. LODs obtained by ToF MS were 0.03–1 ng L^{-1}.

Single-Drop Micro-Extraction

In 1996, Liu and Dasgupta [319], and Jeannot and Cantwell [320] introduced the concept of using a small drop for sample preparation, so-called single-drop micro-extraction (SDME), which combines analyte extraction and pre-concentration prior to instrumental analysis. For reviews on SDME, the reader should consult refs. [321–325].

Liu and Dasgupta reported a 'drop-in-drop' configuration in which a 1.3-µL organic drop, suspended in a larger aqueous drop, extracts the analyte of interest. The system has the advantages of low consumption of organic solvent and the facility of automated backwash. Jeannot and Cantwell introduced a technique where an 8-µL drop of organic solvent containing an internal standard is left suspended at the end of a PTFE rod immersed in a stirred aqueous sample solution. After sampling, the rod is withdrawn from the solution and, with the help of a micro-syringe, an aliquot of the drop is injected into a GC system. As a more convenient alternative, micro-extraction can be performed by suspending a 1-µL drop directly from the tip of a microsyringe needle immersed in a stirred aqueous sample. After extraction, the microdrop is retracted back into the needle and, next, transferred to the GC [326, 327]. Figure 23 shows the schematic of an SDME system. Since droplet instability at high stirring speeds can cause problems, while such high speeds are usually beneficial because

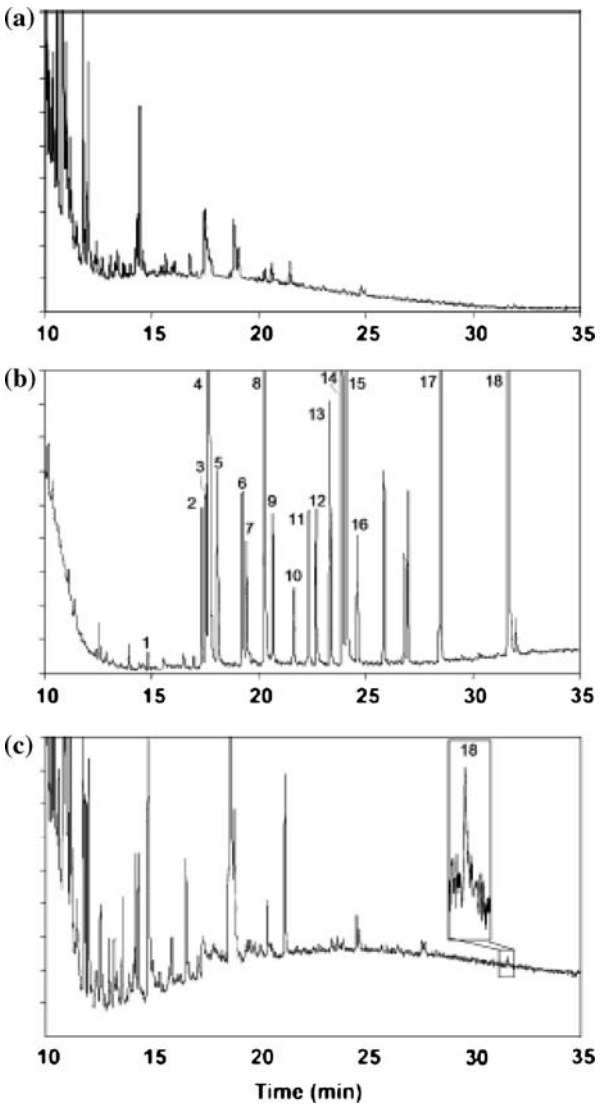

Fig. 22. MMLLE–GC–FID analysis of (**a**) blank wine, (**b**) MMLLE extract of a spiked red wine (c = 0.05 mg L^{-1}) and (**c**) MMLLE extract of an Italian red wine containing tetradifon. Peak identification: **1** = Aldicarb; **2** = Diphenylamine (ISTD); **3** = Simazine; **4** = Atrazine; **5** = Lindane; **6** = Terbuthylazine; **7** = Metoxuron; **8** = Metobromuron; **9** = Vinclozolin; **10** = Isoproturon; **11** = Chlortoluron; **12** = Metazachlor; **13** = Quinalphos; **14** = Procymidone; **15** = Endosulfan I; **16** = Endosulfan II; **17** = Endosulfan sulphate; **18** = Tetradifon [296]

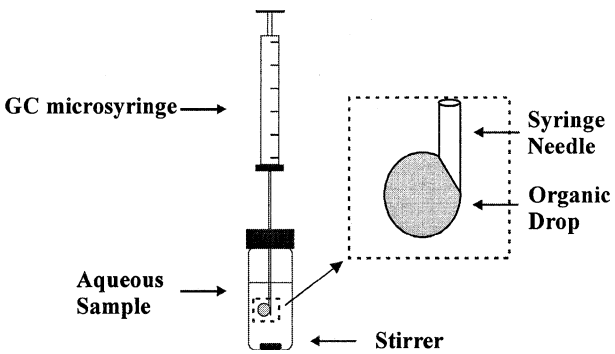

Fig. 23. Schematic of an SDME system [325]

they enhance extraction, the use of a modified tip design was recommended in recent work [328].

The similarity of SDME and SPME operations suggests that autosamplers that can be used for SPME should also work with SDME. First results using a 2-μL drop of hexadecane for BTEX analysis [333] using a CombiPAL (CTC, Zwingen, Switzerland) autosampler, and a standard 10-μL microsyringe confirmed this supposition. A single magnet mixer was used to permit temperature-controlled extractions while stirring the sample.

In order to improve the extraction efficiency, He and Lee [327] developed dynamic LPME (with P for 'phase' because there is no 'D for drop' configuration). With this technique, extraction occurs by withdrawing an aqueous sample into a microsyringe already containing an organic solvent. After a dwell time of a few seconds to allow extraction of the analytes into a thin film of organic solvent adhering to the wall of the barrel as the bulk of the solvent is withdrawn back up, the aqueous phase is pushed out. The cycle has to be repeated quite a number of times (20 in the quoted example) before the analyte-enriched organic phase is subjected to GC analysis. In subsequent studies, a programmable syringe pump was used to automate the repetitive sample withdrawal/expelling process.

In continuous-flow micro-extraction (CFME), which evolved from conventional SDME [329], an aqueous sample is pumped continuously into a ca. 0.5-mL glass chamber via a piece of PEEK tubing which serves for both sample delivery and the introduction of the organic solvent. Once the glass chamber is filled with the aqueous sample, the required volume of the extractant is introduced through an injector and moved, together with the sample solution, towards the glass chamber. When it reaches the end of the PEEK tubing, a microdrop is formed which is virtually immobilized near the outlet of the tubing. Since the aqueous sample solution is continuously pumped around the drop of extractant, high enrichment factors can be obtained. After a preset time of extraction, the drop is withdrawn with a microsyringe and transferred to the injector of a GC system.

Another recent addition to the list of drop-type extraction techniques is headspace SDME (HS-SDME) [330]. The technique is rather similar to HS-SPME, the only difference being that the fibre used in SPME is replaced by a liquid microdrop. In the three-phase system, aqueous-phase mass transfer is the rate-determining step, and a high stirring speed is therefore indicated. Compared with HS-SPME, HS-SDME appears to have similar capabilities in terms of precision and speed of analysis; however, it offers two distinct advantages. Firstly, intuitively, the choice of solvents is wider, if not virtually unlimited, as compared to the limited number of phases currently available for SPME. Solvents can have boiling point below or above the compounds of interest and can cover a wide range of polarities. Secondly, the cost of solvent is negligible compared to that of commercially available SPME fibres. However, the use of SDME for headspace analysis seems relatively difficult, because solvents with relatively low vapour pressures would be preferred. Yet, the most suitable solvents for GC would have relatively high vapour pressures. The difficulty with the latter solvents is clear: they would evaporate too quickly in the headspace during extraction. Thus, in reality, the choice of suitable solvents is fairly limited. In the recent literature, several attempts to improve the evaporation situation by means of semi- or fully automated dynamic HS-SDME were reported [331, 332]. One interesting solution may be the use of the same solvent as sample solvent and drop of extractant [333].

Theoretical considerations concerning the nature and dynamic characteristics of the various micro-extraction processes, and discussions of the influence of various parameters—e.g., drop size, sampling time, solvent selection, salt addition, dwell time—are presented in several of the reviews and papers cited above, notably in [322].

Applications In the literature, some 50 applications of SDME-type sample preparation combined with GC have been reported. The main application areas are environmental, bio and food analysis, and a wide variety of analytes has been determined (Table 12). Several selected applications are briefly discussed below.

In an interesting study, HS-SDME and simultaneous derivatization were applied for the determination of acetone in human blood as a diabetes biomarker [334]. A 1-mL blood sample was introduced in a headspace vial. Derivatization and extraction of acetone were performed by using 2 μL *n*-decane containing PFBHA, at an extraction temperature of 25 °C and an extraction time of 4 min. Analyte recovery was 88% and the LOD for MS detection was 2 nM. In another study, OPPs were determined in orange juice [335]. 5% NaCl was added to 5 mL of orange juice for salting out the analytes of interest. SDME was performed by immersing the syringe needle in the sample, exposing a 1.6-μL drop of toluene during 15 min (stirring at 400 rpm). With analyte recoveries of 76–108%, the LODs for FPD detection were below 5 μg L^{-1}. A third example shows that even SDME can be miniaturized [336]. In so-called drop-to-drop solvent micro-extraction (DDSME), the extraction of methoxyacetophenone isomers from water was performed in a 100-μL vial containing one drop (7 μL) of water. A 0.5-μL drop of toluene was exposed to the sample for 5-min extraction (stirring at 360 rpm and room temperature). The extractant was directly injected into a GC–MS system and LODs of 1 ng mL^{-1} were obtained for all isomers.

Since SDME is strongly related to SPME, the two techniques are frequently compared. To quote an example, Palit et al. [337] studied the use of SDME and SPME for the analysis of chemical warfare agents such as dimethyl methylphosphonate, sesquimustard and Sarin in water. Under optimized SDME conditions, LODs with MS detection were in the range of 10–75 μg L^{-1}. SDME was found to extract analytes of diverse structure, while SPME was not effective in the case of polar analytes. The authors also preferred SDME with regard to, e.g., cost, time of analysis and versatility.

Table 12. Selected applications of SDME and LPME combined with GC

Analytes	Sample (mL or g)	Pre-treatment	Solvent (μL)	Extraction	Detector	LOD (μg L^{-1}, mg kg^{-1})	Recovery (%)	Ref.
SDME								
OPPs	Orange juice (5)	NaCl 5% *w*/*v*	Tol (1.6)	15 min	FPD	1.0–1.6	76–108	[335]
OPPs	Water (2), juice (2)	pH 5–6	Tol (1.5)	20 min	FPD	0.2–0.6	77–114	[339]
Fungicides	Water, wine (5)		Xyl (1.6)	15 min	μECD	0.0006–0.001	80–102	[340]
Anisaldehyde	Urine, serum (20)		Tol (0.5)	25 °C, 5 min	MS	2–5	82–98	[341]
Chemical warfare agents	Water (1.8)		DCM–Tetra (3:1) (1)	30 min	MS	10–75		[337]
Dialkyl phthalate esters	Food simulant (10)		DCM–Hex–Tol (7:3:0.5) (2)	50 °C, 25 min	FID	0.03–0.4		[342]
Amphetamines	Urine (2)	pH 10.5, filter	TCM (2)	8 min	PDHID	15–50		[343]
Methoxyacetophenone	Water (7 μL)		Tol (0.5)	Room temp., 5 min	MS	1		[336]
Amino acids	Urine (1)	Deriv., 50 mg NaCl, 200 rpm, 2 min	TCM–tol (3:1) (1.5)	5 min	MS	0.3–60	92–101	[344]
Solvent residues	Edible oils (4–5)		Benzyl alcohol (2)	60 °C, 6–15 min	FID, ECD	0.11–0.37 (FID) 0.001–0.05 (ECD)		[338]
HS-SDME								
Organotins	Water (5), sediment (0.5)	Deriv.	Dec (2)	1 min	MS			[345]
BTEX	Water (1.5)		Hexadecane (1)	23 °C, 6 min	FID	0.7–5		[346]
BTEX	Engine oil (0.5)		Hexadecane (1)	50 °C, 3 min	FID			[347]
Cancer biomarkers	Human blood (1)	60 °C, 240 min, 1,300 rpm	Dec + PFBHA (2)	40 °C, 6 min, drop deriv.	MS	0.1–0.2 nM	86–90	[348]
Alcohols	Beer (5)		Ethylene glycol (1)	60 °C, 15 min	FID	0.004–0.05		[349]
LPME								
Bisphenol A	Water (10)	1 mL 1 M NaOH, deriv.	Tol (4)	Room temp., 90 min	MS	0.002		[350]
HS-LPME								
Volatile solvents	Pharmaceutical product (0.5)	5 mL 10% NaCl	Octanol (3)	20 min	FID	4–400 mg g^{-1}		[351]
Acetone	Blood (1)	40 °C, 10 min, 1,100 rpm, deriv.	Tol (2)	40 °C, 50 s	MS	6 nM	87	[352]
Fatty acids	Blood plasma (0.5)	0.3 g NaCl, pH 1.0, dilute to 1 mL	Butyl phthalate (2)	60 °C, 45 min	FID	20–80	70–87	[353]
Alcohols	Beer (2)	60 °C, 10 min, 1,500 rpm	Octanol (0.8)	60 °C, 9.5 min	MS	1–100	90–114	[331]

Michulec and Wardencki [338] used SDME–GC–ECD and –FID to determine (chlorinated) hydrocarbon solvent residues in edible and pharmaceutical oils. SDME was found to be as rapid and precise as SPME. On the other hand, the linear range was much narrower, and the LODs were higher than for SPME procedures. However, the LODs easily met the requirements for the quoted applications. In such cases, it is a clear advantage that SDME requires no special equipment.

Headspace and Purge-and-Trap

Headspace techniques are well suited for sample preparation prior to the GC determination of volatiles in liquid and (semi-)solid samples. Instead of direct sampling, a gas phase in equilibrium with the sample material is sampled and analysed. In most instances, a considerable enrichment of the analytes can also be obtained in the gas phase, which improves analyte detectability. Moreover, because only the gas phase in equilibrium with the sample is injected, contamination issues are absent, even for very 'dirty' samples. The practicability of the method drew much attention after the first publication in 1958 [354], and instruments for fully automated headspace sampling in combination with GC were marketed soon after by Perkin Elmer (Shelton, CT, USA). Today, there is hardly an adequately equipped laboratory in the environmental, food or drugs area which is without a headspace instrument. The state of the art of headspace analysis is documented in book chapters and reviews, which also discuss a wide variety of applications (see, e.g., [355–360]). The main variable is the distribution constant of an analyte between the gas phase and the liquid or solid phase; the more the equilibrium is shifted to the gas phase, the more sensitive the analyte can be determined. The distribution constant, in its turn, primarily depends on the vapour pressure of the analyte and the activity coefficient of the analyte in the matrix.

There are two experimental approaches in headspace analysis. If the sample is in equilibrium with the gas phase in a closed vessel, then the method of analysis is referred to as static headspace, or HS. If a carrier gas is passed over, or through, the sample and the extracted volatile compounds accumulated in a cryogenic or sorbent trap, then the method is generally referred to as dynamic headspace, gas-phase stripping or purge-and-trap, with P&T as the common acronym.

HS Analysis

In HS analysis, the volatiles in the sample material are equilibrated with a gas phase above the sample in a closed vial. After a predetermined equilibration time, part of the gas phase is (automatedly) withdrawn from the vessel, and injected into a GC system. For compounds which, because of low distribution constants, largely remain in the liquid or solid matrix, an obvious way to enhance the analyte concentration in the gas phase is to increase their vapour pressure by increasing the equilibration temperature or to decrease the activity coefficient by, e.g., increasing the ionic strength of the solution ('salting out'). In liquids, analyte diffusion generally is fast enough for equilibrium to be reached in a short time and many HS systems have stirring facilities to aid this. In (semi-)solids, however, diffusion is often very slow and procedures such as grinding of the sample are used to speed up the analysis.

After equilibrium has been established in the carefully thermostated vial, the gas phase is sampled using a syringe for manual procedures or automatically using commercially available pneumatic headspace analysers. Pneumatic sampling ensures that both the pressure and volume of the headspace sampled are identical for all samples and standards. A constant pressure is obtained by pressurizing the headspace vials with an inert gas to a pressure at least equal to the column inlet pressure. The sample is then either expanded directly into the column or to a sample loop of a thermostated gas-sampling valve. Instead of first filling a loop, a pressurized headspace gas can also be expanded directly into the GC column by using a so-called balanced sampling system [357, 361].

Another procedure to collect the static headspace from a sample is the use of a sorbent. The adsorbent is allowed to stay in the headspace for a specific period of time and at a constant temperature. After equilibrium has been reached, (an aliquot of) the solid sorbent is transferred to a thermal desorber. In the past this procedure was often performed using small paperbags ('teabags') filled with Tenax or another polymer sorbent. Today, an SPME fibre is typically used (HS-SPME; see section on SPME). However, one has to be aware that, with this technique, the distribution is between the fibre and the matrix. Consequently, even though raising the temperature increases the analyte concentration in the headspace, it reduces the deposition on the fibre because the vapour concentration of the analyte increases above the sample, but also above the fibre. HS-SPME can therefore give a selectivity which markedly differs from that of HS analysis: HS will favour the volatile analytes, but HS-SPME the less volatile compounds.

Finally, one should keep in mind the overriding importance of rigorously controlling the temperature both during analysis, from sample to sample, and from sample to standard, in order to ensure reliable quantification and adequate repeatability/reproducibility. Meeting these demands is facilitated by using automated HS samplers.

P&T Analysis

In P&T analysis, a sample is continuously purged with an inert gas (commonly helium) and volatiles are transported from the sample to a trap with sufficiently high retention power (e.g., Tenax, activated carbon or silica) for the analytes to be collected without the risk of breakthrough. After purging, the trap is heated and the trapped volatiles are released onto a GC column, usually via a cold trap (Fig. 24). P&T—which, in principle, enables quantitative analyte isolation—is an effective way of achieving much better analyte detect-

ability than equilibrium-type HS: under favourable conditions low- and sub-ng L^{-1} LODs can be obtained for many VOCs. The key parameters in P&T optimization are purge time, flow rate and temperature. Extending the purge time will, generally speaking, enhance the recovery of the analytes of interest. However, highly volatile compounds may be (partly) lost if purge times are too prolonged and/or the trap displays insufficient retention. As for the purge temperature, since less volatile and/or more water-soluble analytes will be removed only partly even under optimized conditions, careful control of the temperature of the sample vessel is required for precise quantification. For the rest, for obvious reasons elevated temperatures will enhance analyte recovery. However, the disadvantage is that more water vapour will be carried over into the trap and the GC analytical system. Actually, water management is a serious problem in P&T (much more than in HS sampling where the gas volumes are relatively small) because a large amount of water vapour from the liquid sample matrix is also transported by the inert gas. Since cold traps, which are frequently used to collect the analytes, easily become blocked through the large amount of vapour, it is important to remove the moisture from the purge gas before it enters the cold trap. Inorganic desiccants, water condensers, pre-separation on a column packed with Tenax or another such sorbent, or selective permeation through a polymeric (often a Nafion) membrane are all used to this end. However, each of these alternatives unfortunately, has specific disadvantages which invariably cause the uncontrollable loss of particular classes of analytes. For details, the reader should consult the literature [362].

Vendors of HS and P&T systems are Perkin Elmer which markets the LSC 2000 and LSC 3000, Tekmar (Mason, OH, USA) with the Tekmar-3000, Stratum PTC and Velocity XPT, and Quma (Wuppertal, Germany) with the QHSS 20/40/100/111.

Applications Over the years, a large number of mutually divergent applications have been published which use HS or P&T for sample preparation. A selection of recent contributions to this field is summarized in Tables 13 and 14, respectively.

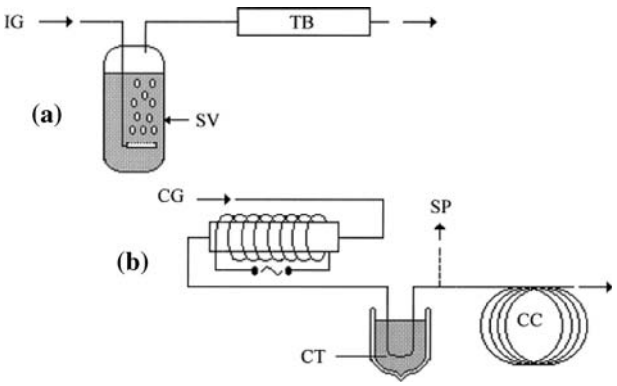

Fig. 24. Schematic of P&T with cryogenic trapping. (**a**) Sample purge and collection of the stripped volatiles in a trap and (**b**) desorption from the trap and introduction into the gas chromatograph. **IG**, inert purge gas; **CG**, carrier gas; **TB**, adsorbent tube; **SV**, sample vessel; **CT**, cryogenic trap; **SP**, split (optional); **CC**, capillary column. [361]

In an interesting study, Cudjoe et al. [363] identified pheromones in ladybugs that can affect the bouquet and taste of wine, using HS–GC–MS in the SIM mode. For this analysis, five ladybugs were placed in a headspace vial that was equilibrated for 20 min at 95 °C. The headspace gas was transferred by balanced sampling with an injection time of 30 s. *Hippodemia convergens* posed the highest threat to wine production due to the high levels of methoxypyrazines found in them. In another paper, P&T sampling was used to determine volatiles in fruits [364]. 15 mL of fruit pulp were equilibrated at 80 °C and subjected to a 35-min purge with helium. The extracted volatiles were trapped on a mixture of Tenax/silica/charcoal kept at 30 °C. After purging, the trap was heated to 180 °C, to transfer the analytes to a GC–MS system. In general it was concluded that in the total volatile profile, the compounds belonging to the terpene and alcohol classes decrease during maturation of the fruit from the half-ripe to the ripe stage.

In environmental analysis, Huybrechts et al. [365] determined 27 VOCs in marine water. P&T of a 60-mL sample (45 °C, 20 min) was used to trap the analytes on a multibed sorbent. After desorption at 275 °C, the analytes were refocused on a cryotrap (−150 °C), and, next, rapidly desorbed at 260 °C. LODs for GC–MS (SIM) analysis were 0.2–7 ng L^{-1} for 23 of the target VOCs. For dichloromethane, chloroform, benzene and 1,4-dichlorobenzene, the LODs were 20–40 ng L^{-1}. Finally, Roose et al. [366] determined VOCs in eel samples by means of on-line P&T–GC–MS. 15 g of sample were homogenized with a blender and transferred to a sample vial containing 25 mL of water. The volatiles were forced out by purging the sample for 34 min at 70 °C. The trapped analytes were desorbed in the backflush mode into the cryofocusing module and, next, released by rapidly heating this module from −120 to 200 °C. Analytical performance was fully satisfactory with analyte recoveries of 80–99% and LODs of 0.003–0.2 ng g^{-1} (when using full-scan MS). A typical chromatogram is shown in Fig. 25.

Conclusions

Essentially all modern reviewers emphasize that sample treatment is a key aspect of trace-level organic analysis and that it is often the most time-consuming and least sophisticated step. It is also recognized that, even though state-of-the-art instrumental chromatographic techniques are sufficiently mature to enable hyphenation with powerful (usually MS-based) detectors that provide high information density, sample preparation is still necessary in most instances. This

Table 13. Selected applications of HS combined with GC

Analytes	Sample (g or mL)	Pre-treatment	Equilibration time (min)	Temperature (°C)	Sampling	Transfer line (°C)	Detector	LOD	Ref.
BTEX	Olive oil (10)	–	25	95	Loop/110 °C/ 3 mL	120	MS	3–9 ng mL^{-1}	[367]
BTEX	Water (15)	2.2 g KCl, 300 µL 5 M HNO_3	20	70	Loop/110 °C/ 3 mL	120	MS	–	[368]
VOXs	Landfill leachates (5)	–	15	75	Loop/110 °C/ 1 mL	110	MS	0.05 ng mL^{-1}	[248]
Volatiles	Bacterial biodegradation	–	20	80	Syringe/81 °C/ 0.4 mL	–	MS	–	[369]
Residual solvents	Pharmaceutical drugs (0.2)	–	60	80	Loop/85 °C/ 1 mL	85	FID	0.3–8 µg mL^{-1}	[370]
Aldehydes	Wodka (5)	Deriv.	30	70	Balanced pressure/ 0.5 min	90	ECD	0.02–4 µg L^{-1}	[371]
TATP	Post-explosion debris	–	30	90	Syringe/1 mL	–	MS	0.1 ng	[372]
Epichlorohydrin	Drinking water (5)	300 g NaCl L^{-1}	22	80	Loop	–	ECD	40 µg L^{-1}	[373]
Pheromones	Ladybugs (5)	–	20	90	Balanced pressure/ 0.5 min	95	MS(SIM)	–	[363]

is true, not only because many solid and semi-solid matrices cannot be handled directly anyway, but also because (1) analyte enrichment is required to reach concentration levels in the final extract that permit reliable compound identification and quantification, and (2) removal of interfering sample constituents (e.g., fat, proteins, sulphur, grit or strongly adsorbing materials) is often needed to maintain the performance of the analytical set-up over prolonged periods of time. Another conclusion, frequently to be read between the lines—i.e., in the applications which are discussed and in information provided in the tables which are included—is that for a large majority of all challenging analytical problems detection is done with an MS instrument, with ToF MS and ion-trap MS/MS gradually coming into their own next to quadrupole MS. One major exception is the use of selective and, more so, highly sensitive ECD detection for, specifically, aromatic organohalogen micro-contaminants.

To phrase things differently, many workers state that, since there is an obvious need for faster, more cost-effective and environmentally friendly analytical methods, there is also a clear need to improve the performance provided by the classical methods of sample preparation. In the past two decades, several tens of newly designed and, also, upgraded older methods have been reported and the progress made in this area is continually being reviewed. One striking general observation is that, despite the improved performance of the (GC) separation plus (MS) detection step effected in the past 10 or so years, sample preparation is, in many instances, as extensive today as it was in the 1990s. This is especially remarkable because, in the same period of time, comprehensive 2D-GC, or GC × GC, with its considerably improved overall chromatographic resolution, has arrived on the scene to facilitate the analysis of highly complex samples [390]. The obvious conclusion is that much of the steps forward made in the fields of sample preparation and instrumental analysis have been used not to simplify the procedures, but to enhance the quality of the information.

To our opinion, conclusions such as those given above, are more relevant than a detailed discussion of the characteristics of the individual sample-preparation techniques. Moreover, an interesting comparison of many of the techniques included in the present review has recently been given by Hyötyläinen and Riekkola [391]. Nevertheless, some brief comments should be presented also here.

As regards solid and semi-solid samples, PLE is a promising technique, and features short extraction times and low solvent consumption. SFE and PLE share several beneficial characteristics but, because PLE can be used with all conventional solvents, its application range is distinctly wider than that of SFE with (modified) CO_2. SFE moreover has a matrix-dependent extraction mechanism and optimization is rather demanding. On the other hand, SFE typically is the method of choice for thermolabile compounds.

With MAE, proper solvent selection is the key to a successful—and, often rapid—extraction; hexane–acetone (1:1) has been shown to be a fairly ideal 'general purpose' mixture. The technique offers little selectivity and clean-up after extraction is needed in most instances. Almost all MAE applications involve off-line procedures since operation of the technique as part of a dynamic system is difficult. The beneficial role of ultrasound assistance in USE, but also to accelerate digestion, sample dissolution or enhance reaction kinetics, is well documented [80, 81]. In many instances, USE and US leaching are efficient alternatives to more

Table 14. Selected applications of P&T combined with GC

Analytes	Sample (g or mL)	Pre-treatment	Temp. (°C)	Purge time (min)	Purge flow (mL min^{-1})	Analyte trap	Desorption temp. (°C)	Desorption time (min)	Cryo trap	Detector	LOD (ng g^{-1}, ng mL^{-1})	Ref.
VOCs	Marine organisms (10–15)	Ultra-turrax, ultrasonic bath	70	34	20	Vocarb 4000	250	–	−120 °C	MS	0.003–0.2	[374, 375]
VOCs	Sediments (30)	Dilute with water	70	30	20	Vocarb 4000	250	–	−120 °C	MS	0.003–0.2	[376]
VOCs	Water (60)	–	45	20	50	Tenax TA, Carboxen 1000 and 1001	275	15	−150 °C	MS (SIM)	0.001–0.03	[377, 378]
VOCs	Water (13)	–	25	11	35	Tenax	225	3	–	MS (SIM)	2–115	[379]
VHOCs	Soil (5)	SLE	25	9	40	Tenax GC, silica, activated carbon	260	4	–	AED	3–40	[380]
VHOCs	Water (5), beverages (5)	–	30	9	40	Tenax GC, silica, activated carbon	260	4	–	AED	0.05–0.5	[381]
VHOCs	Water (10)	–	25	10	10	–	–	–	−100 °C	MS(SIM)	–	[382]
Volatiles	Grape must (2)	–	30	15	30	Tenax	180	10	–	MS	–	[383]
Volatiles	*Spondias sp.* (15)	–	80	35	40	Tenax/silica/charcoal	180	20	–	MS	–	[364]
Trihalomethanes	Drinking water (45)	–	65	15	30	Tenax	220	–	–	ECD	0.2–0.8	[304]
MTBE	Water (44)	–	40	10		Tenax TA	220	10	–	MS	–	[384]
Epichlorohydrin	Drinking water (5)	300 g NaCl L^{-1}	80	70	60	Tenax/silica/carbon/ mol. sieve	180	1	–	ECD	0.01	[373]
Chloroform, trichloroacetic acid, trichloroethanol	Blood (1), urine (0.3–0.5)	–	40	16	65	Vocarb 3000	250	2	−110 °C	MS(SIM)	0.300–2	[385]
1,2-Dichloroethane, 1,4-dichlorobenzene, naphthalene	Honey (10)	Pre-heating, 40 °C	40	40	40	Tenax	180	6	–	MS	0.05–0.8	[386]
2,4,6-Trichloroanisol	Cork, wine (25)	USE or LLE, conc. in water	25	10	40	Carbopack B, Carboxen 1000 and 1001	240	5	–	AED	0.03, 5	[387]
Esters	Cider (5)	–	20	30	50	Tenax	230	10	–	MS(SIM)	5–120	[388]
Benzene, toluene	Human milk (5)	–	30	11		HP BTEX trap	220	8	−150 °C	MS(SIM)	-	[389]

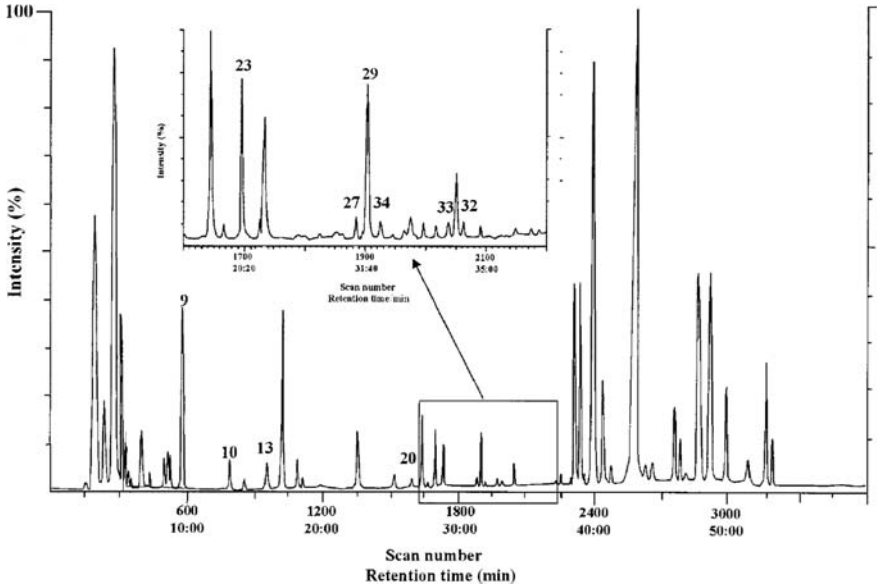

Fig. 25. P&T–GC–MS chromatogram of 15 g of eel from the river Scheldt: **9** = Chloroform; **10** = 1,1,1-Trichloroethane; **13** = Benzene; **20** = Toluene; **23** = Tetrachloroethene; **27** = Chlorobenzene; **29** = Ethylbenzene; **32** = *o*-Xylene; **33** = Styrene; **34** = Bromoform [366]

conventional approaches, and quantification is fully satisfactory if a probe device rather than an ultrasound bath is used. Because of the low overall temperature during the operation, analyte thermolability is no serious problem. The inherent advantage of dynamic/continuous systems merits more attention. USE is often compared with MAE. It is simpler and, sometimes, also faster than that technique. On the other hand, USE is considered less robust and particle size can be a critical factor.

MSPD is a technique designed to simultaneously disrupt and disperse a sample over a properly selected solid support. The combination of extraction and clean-up, short extraction times, small sample size and use of little sorbent and solvent(s) are main advantages. The very simplicity of MSPD explains why additional treatment will usually be required prior to GC analysis. If, however, such treatment comprises three, four or even more steps (Table 6), one may seriously doubt the cost-, and time-, effectiveness of the approach.

DTD is a recently introduced sample-preparation technique which has been applied already to a variety of difficult matrices and can be fully automated, although at considerable cost. The extracts are rather clean and rewarding results are obtained for very small samples such as a few pollen [163] or small pieces of cheese [167]. The main limitations are the determination of thermolabile and very high-boiling compounds.

For the analysis of aqueous/liquid samples, SPE is no doubt the most efficient and flexible technique. This is also frequently indicated by other reviewers. If combined with GC analysis, non-selective sorbents are preferred because collecting a wide (polarity) range of analytes is more important than creating selectivity. In other words, using a commercial copolymer sorbent is, generally speaking, a better approach than designing another MISPE material. A variety of SPE formats for off-line, on-line and semi- or fully automated operation is (commercially) available and for miniaturized (ca. 1 mL), conventional-size (ca. 100 mL) and large-scale (1 L and over) applications. Compared with other—frequently equilibrium-type—techniques, a much larger analyte enrichment can usually be achieved with exhaustively extracting SPE. From among the equilibrium techniques, SPME and SBSE are probably best known. One main advantage is that they are both solvent-free. On the other hand, for a fair number of applications, reaching equilibrium conditions is time-consuming. This is especially true for SBSE, which has the additional disadvantage that quite some manual handling is required and automation is essentially impossible. Generally speaking, this makes SPME—for which fully automated systems are commercially available—a much more attractive option, even though its application range is relatively limited [258]. Recently introduced SDME is an inexpensive equilibrium-type alternative, with 'drop-size' extraction volumes as an attractive feature. Unfortunately, the prolonged extraction times needed to reach equilibrium may cause drop dissolution. If sample agitation is used to enhance extraction, proper procedures have to be used to prevent drop dislodgement. In summary, SDME is not without its technical problems.

There are several more points which briefly require our attention. For example, from among the goals mentioned in the introductory text of this section, environmental friendliness is repeatedly emphasized in the published literature and solvent-free techniques are therefore recommended. On the other hand, despite all the emphasis frequently given to high sample throughput, speed is often given insufficient attention. In addition, designing sample-preparation methods that are easily coupled on-line to the GC–MS system usually has no high priority and the substantial gain that can be effected by injecting the entire (on-line) instead of a minor aliquot of (off-line) sample extract is often overlooked. The obvious disadvantages of equilibrium methods—i.e., the risk of low analyte recovery and the problem of long analyte-extraction times if the application range of the method is unduly expanded—usually are insufficiently considered. On the positive side, several of the more recently developed methods, notably DTD and SDME—and also SPME—enable miniaturization or are, in essence, micro methods. It is also

good that reviewers such as Smith [392] and Kristensson [393] emphasize that derivatization and/or analyte labelling should be avoided whenever possible. The additional, often multi-step, procedures adversely affect sample throughput and cost of analysis. Artefacts are often created and the application is not always validated at the ultra-trace level. With many LC–MS techniques being available to study the intact analytes—a distinct advantage when identification is a primary goal—derivatization is an acceptable approach only in cases such as, for example, the methylation of fatty acids and transesterification of lipids, the silylation of selected steroids or the acylation of amines.

One aspect that is not always given due attention is distinguishing target-compound monitoring and profiling entire samples (see, e.g., [391]). In the former case, in which the search is limited to specific, pre-identified compounds, proper optimization of the sample preparation to create a suitably *selective* procedure may be useful, although it will often be superfluous because of the selectivity inherent in the GC–MS part of the analysis. In the much more challenging profiling situation, in which all constituents of a sample are regarded as analytes, non-selective and (close to) exhaustive analyte extraction are key issues. [If necessary, a straightforward LC-type fractionation may be included as a first step.] Equilibrium methods such as SBSE, SPME and MMLLE should not be selected for such studies, specifically not because the extraction behaviour of the unknown compounds cannot be predicted. Instead, robust non-selective SPE should be used. Similarly, with volatile organic compounds, P&T is a more powerful—i.e., much more sensitive, and automatable—technique than HS-SPME, although one may argue that the difference is not too large in this case because the focus on volatile analytes creates a situation in between target monitoring and profiling. Finally, one should take into account that there is an increasing use of GC × GC instead of GC. This significantly helps to unravel the composition of many food, fish and biota as well as soil, sediment and aerosol samples: applying the comprehensive technique should be seriously considered whenever profiling of such samples is required.

In summary, the developments described in this chapter demonstrate that in the field of sample preparation, a variety of approach routes is continually being opened, optimized and, next, often modified. They serve many different purposes such as, e.g., simplifying the overall analytical procedure and/or enhancing its performance, increasing sample throughput, facilitating analyte identification or enabling more reliable quantification. Or, as a young scientist wrote in 2005 [393]:

> Actually, as is increasingly being said by experts in the field, we are rapidly creating conditions in which it is *not* performing the analyses and handing in the results, but the subsequent data handling and data interpretation which will become the stumbling block. In other words, while still working on solving the analytical problems of the present generation, those of the next generation are already looming on the horizon.

This statement is still valid today or, in other words, the efforts of the ''next generation'' are still urgently required.

Glossary

Acet	Acetone
AED	Atomic emission detector
ASE	Accelerated solvent extraction
ATD	Automated thermal desorption
Benz	Benzene
BSTFA	*N*,*O*-bis(Trimethylsilyl) trifluoroacetamide
BTEX	Benzene, toluene, ethylbenzene, and xylenes
ButOAc	Butyl acetate
CFME	Continuous-flow micro-extraction
Conc.	Concentrate
CTME	*cis*/*trans* Methyl ester
Cyclohex	Cyclohexane
Cyclopen	Cyclopentane
DCM	Dichloromethane
DDSME	Drop-to-drop solvent micro-extraction
Dec	Decane
Deriv.	Derivatization
DI-SPME	Direct-immersion solid-phase micro-extraction
DMAE	Dynamic microwave-assisted extraction
DMI	Difficult/dirty matrix introduction
DSI	Difficult sample introduction
DTD	Direct thermal desorption
DUSE	Dynamic ultrasound-assisted extraction
ECD	Electron-capture detector
EPA	Environmental Protection Agency
EtAc	Acetic acid
EtOAc	Ethyl acetate
EtOH	Ethanol
FAME	Fatty acid methyl ester
FID	Flame ionization detector
FMAE	Focused microwave-assisted extraction
FPD	Flame photometric detector
GC	Gas chromatography
GC×GC	Comprehensive two-dimensional gas chromatography
GPC	Gel permeation chromatography
Hep	Heptane
Hex	Hexane
HexOAc	Hexyl acetate
HRMS	High-resolution mass spectrometry
HS	Headspace
HS-LPME	Headspace liquid-phase micro-extraction
HS-SDME	Headspace single-drop micro-extraction
HS-SPME	Headspace solid-phase micro-extraction
HSSE	Headspace sorptive extraction
IAE	Immunoaffinity extraction
IASPE	Immunoaffinity-based solid-phase extraction
IMS	Ion mobility spectrometry
IR	Infra red
ISTD	Internal standard
$K_{o/w}$	Octanol–water distribution coefficient
LC	Column liquid chromatography
LOD	Limit of detection
LLE	Liquid–liquid extraction
LPME	Liquid-phase micro-extraction
LVI	Large-volume injection
MAE	Microwave-assisted extraction
MASE	Membrane-assisted solvent extraction
MeCN	Acetonitrile
MeOH	Methanol
MESI	Membrane-extraction sorbent interface
MIMS	Membrane-introduction mass spectrometry
MIP	Molecularly imprinted polymer
MISPE	Molecularly imprinted solid-phase extraction
MMLLE	Microporous membrane liquid–liquid extraction

MS	Mass spectrometer
MSPD	Matrix solid-phase dispersion
MTBE	Methyl *tert*-butyl ether
NPD	Nitrogen phosphorus detector
NPLC	Normal-phase liquid chromatography
OCP	Organochlorine pesticide
OPP	Organophosphorus pesticides
P&T	Purge & trap
PAH	Polycyclic aromatic hydrocarbons
PBDE	Polybrominated diphenyl ether
PCB	Polychlorinated biphenyl
PCDD/F	Polychlorinated dibenzo-*p*-dioxin/furane
PDHID	Pulsed-discharge helium ionization detector
PDMS	Polydimethylsiloxane
PEEK	Polyetheretherketone
Pen	Pentane
PFBHA	*O*-(2,3,4,5,6-Pentafuorobenzyl) hydroxylamine hydrochloride
PFE	Pressurized fluid extraction
PFPD	Pulsed flame photometric detector
PHWE	Pressurized hot-water extraction
PID	Photoionization detector
PLE	Pressurized liquid extraction
PMAE	Pressurized microwave-assisted extraction
POP	Persistent organic pollutant
PP	Polypropylene
PTFE	Polytetrafluoroethylene (Teflon)
PTV	Programmed temperatue vaporizer
QqQ	Triple quadrupole
RAM	Restricted-access media
RSD	Relative standard deviation
Sat.	Saturated
SBSE	Stir-bar sorptive extraction
SCD	Sulphur chemiluminescence detector
SD	Steam distillation
SDB	Styrene–divinylbenzene
SDME	Single-drop micro-extraction
SEP	Sample-enrichment probe
SFE	Supercritical fluid extraction
SHWE	Subcritical hot-water extraction
SIM	Single ion monitoring
SLE	Solid–liquid extraction
SLM	Supported liquid membrane
SPE	Solid-phase extraction
SPDE	Solid-phase dynamic extraction
SPME	Solid-phase micro-extraction
SVOC	Semi-volatile organic compound
TATP	Triacetone triperoxide
TCD	Thermal conductivity detector
TCM	Chloroform
TD	Thermal desorption
Tetra	Tetrachloromethane
TIC	Total ion current
TMSH	Trimethylsulphonium hydroxide
ToF MS	Time-of-flight mass spectrometry
Tol	Toluene
TSD	Thermionic specific detector
USE	Ultrasound-assisted extraction
VHOC	Volatile halogenated organic compound
VOC	Volatile organic compound
VOX	Volatile organic halogens
Xyl	Xylene

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