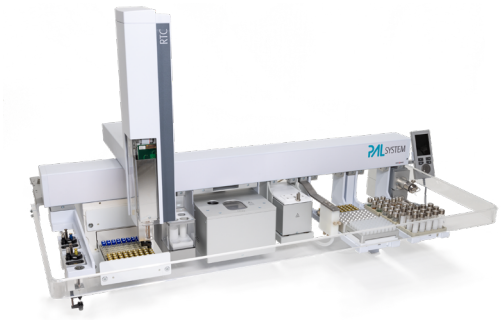
PAL SYSTEM
Ingenious sample handling



Static and Dynamic Headspace Analysis - The PAL Compendium

Why Do Headspace Analysis?

Volatile compounds enrich our life with wonderful flavors from fruits, breads or perfumes, but also can pose a threat to our health and wellbeing from hazardous or malodorous components. The chemical analysis of this wide range of analytes drives quality control, product development and safety, and environmental monitoring likewise.

The volatile organic compounds (VOCs) of interest are characterized in common by their low vapor pressure at ambient temperature. Depending on their distribution between the sample material and surrounding air, the concentration in the gas phase can vary significantly. Typical samples analyzed are water, beverages or perfumes, also solid samples like food and food packaging material, soils and sediments, household, technical products, and more. In general, everything our nose can smell, and even beyond, the headspace analysis can detect and quantify.

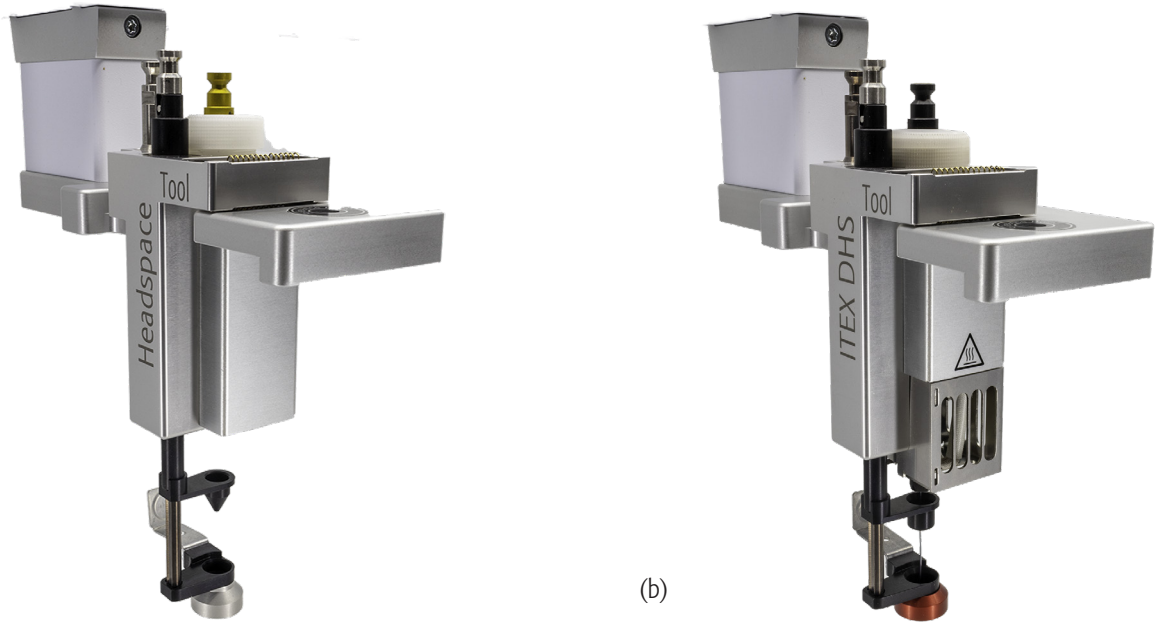
Analysis methods are the direct sampling of an aliquot of the sample headspace (static headspace analysis), or if the concentration of the compounds is low or less volatile (semi volatile organic carbons, SVOCs), a concentration of the analytes before measurement (dynamic headspace analysis). While the static headspace analysis takes an aliquot of gas after a sample/headspace equilibrium is reached, the dynamic method collects as much as possible of the analytes of interest before injection. Both methods required in the past technically different, complex, and separate instrumentation with space-consuming and costly equipment. In common for both methods is the way of analysis by GC or GC-MS. Usually, one dedicated headspace or purge & trap unit was required for each of the static and dynamic headspace analyses.

On the PAL System, both of the headspace analysis modes offer the easiest approach from sample to results for a wide variety of volatile compounds. No wet chemical sample preparation or extraction or clean-up is required. Test portions of the sample go directly into sample vials for automated analysis of large sample series on the PAL System with unmatched sample capacity. The proprietary prep-ahead and overlapping features of the PAL System deliver results faster and more reproducible than any other instrumentation.

PAL System for static and dynamic headspace analysis with incubator, ambient and temperature-controlled sample racks, and automated tool change

The PAL Solution

Headspace analysis with the PAL System delivers many strong benefits to the laboratory. The best benefit is the unique tool-based solution. No additional instrument is needed, no additional bench covered, and no re-routing of gas lines from the GC is necessary. For static and for dynamic headspace analysis only a dedicated tool is inserted into the PAL System and can be used immediately. Even all other tools for liquid injection or solid-phase microextraction (SPME) can still be used for additional methods without any change of the hardware making the PAL System a real multi-method device for any kind of samples and sample preparation methods for GC and GC-MS analysis. All workflows for static and dynamic headspace as well as other automated sample preparation methods are fully integrated into the chromatography data systems of the leading manufacturers.



(a) (b)

Figure 1: (a) Static headspace tool. (b) Dynamic headspace tool (ITEX-DHS)

Static Headspace Analysis

The static headspace analysis is the easiest method. Only little sample preparation with homogenization is required, then adding the liquid or solid sample to 10 or 20 mL headspace vials, weighing, and placing the well-capped vials into the racks of the PAL System. The PAL headspace workflow takes over and injects finally into the GC or GC-MS system. The static headspace analysis is applicable to all analytes with significant vapor pressure. Typically, volatile organic substances (VOCs) analytes are understood with boiling points up to 250°C, covering analytes of natural and anthropogenic sources. The United States EPA method 5021A lists more than 70 compounds, mainly solvents of environmental importance, that are included in this standard method [1].

Static headspace analysis is an equilibrium technique. The extraction of the analytes is based on the partition of the very and moderately volatile analytes between the matrix and the gas phase above the sample. After the partition equilibrium is reached the gas phase in the incubated vial contains a qualitatively and quantitatively representative gaseous sample. All involatile components remain in the vial and are not analyzed.

For taking an aliquot of the sample headspace the vial is pressurized with the same gas volume which is required to fill the syringe. A few plunger strokes homogenize the gas volume taken. After adjustment of the analysis volume, the next step is the GC injection and chromatographic analysis. Very well-known examples are the analysis for residual solvents in packaging materials or pharmaceutical products, or the BTEX analysis from environmental samples.

The PAL headspace tool shown in **Figure 1a** is heated to a constant temperature and carries headspace syringes from 1000 µL to 5000 µL volume, as commanded by the required application. Samples get incubated in an agitator to a constant temperature. For liquid samples, it allows shaking of the sample at different speeds according to the sample viscosity. The headspace workflow allows the overlapped sample incubation during GC analysis runtimes so that all samples are treated equally with the identical incubation time and injected right at the end for the highest reproducibility. The heated syringe can be flushed with a flow of inert gas through a side hole of the syringe as part of the workflow, managed by the PAL System before and after each analysis.

Full Evaporation Technique

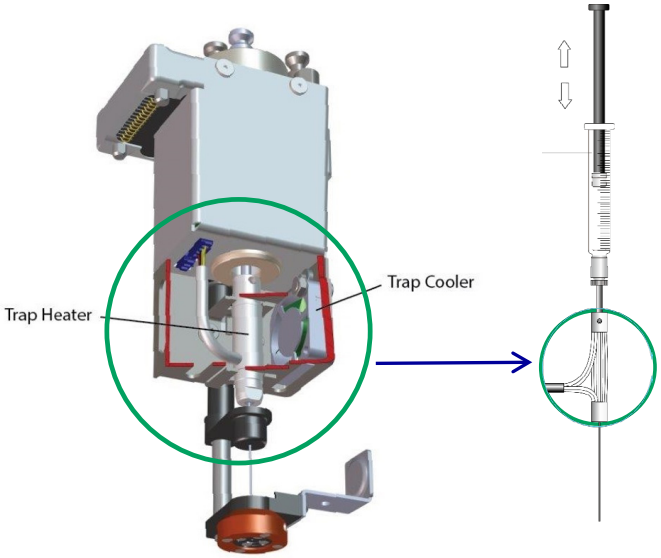
The PAL System also offers the use of the full evaporation technique (FET) of a sample. The FET technique is a proven means of eliminating matrix influences from liquid and solid matrices. The VOCs transfer fully into the gas phase. There is no equilibrium between the matrix and the gas phase anymore. For full evaporation, the sample size is adjusted to milligram amounts of solid samples, or low microliter volumes of liquid samples to avoid a gas phase saturation. The incubation/evaporation and the syringe temperature is set above the analyte boiling points [2].

The FET technique offers quick and easy sample handling and finds its application in the fast determination for instance for monomer control in polymers, residual solvents in pharmaceuticals, fermentation, or cardboard products. Also, it is used for online sampling and is well suited to prepare vapor standards of liquids for calibration.

Dynamic Headspace Analysis

In case the peaks of the compounds of interest are smaller than required, a switch to the dynamic headspace method is recommended. With the PAL System the ITEX DHS dynamic headspace tool is used. The workflow can automatically switch between static and dynamic headspace analysis, as demonstrated below with the trace analysis of volatile sulfur compounds. No different sample preparation or additional instrumentation is required.

The dynamic headspace analysis extends the range of analytes to those with low vapor pressure and higher boiling points [3]. In contrast to the static method, which just uses an equilibrium between the sample and the headspace above, the dynamic method is an exhaustive procedure. The analytes of interest are continuously driven out of the sample and collected until analysis. Only the PAL System runs static and dynamic methods on one and the same instrument. Previous instrumental solutions required two dedicated and space-consuming equipment.



ITEX DHS offers the dynamic headspace enrichment of volatile & semi-volatile compounds from solid, liquid and gaseous samples.

The sorbent material is embedded in the upper part of a syringe needle.The analyte trap is temperature controlled by the trap flash heater and an integrated cooling fan.

Figure 2: ITEX DHS tool with the dedicated syringe and trap heater/cooler

The PAL System uses for dynamic headspace the so-called in-tube extraction tool (ITEX-DHS), shown in **Figure 1b** and **Figure 2**. The ITEX-DHS tool features a sorbent trap connected to the heated syringe, ending in a regular syringe needle with a conical tip. As in all headspace methods, the sample is incubated in the agitator at a constant temperature. Upon penetrating the sample vial septum, the plunger of the syringe pumps the sample headspace through the sorbent trap which is held at room temperature while the sample is continuously replenishing analytes to the headspace. The collection of analytes proceeds until exhaustive extraction or until enough of the analytes of interest are collected for a fit-for-purpose analysis. In the next step, the ITEX-DHS tool moves to the GC for injection. The previously cooled sorbent trap gets quickly heated for a sharp release of the trapped analytes into the GC column. The GC conditions are the same as used for static headspace analysis. As a workflow safety measure, after injection, the syringe and trap can be flushed with inert gas before the next analysis.

As sorbent phase Tenax™ is most used and typically applied in the ITEX DHS trap. Tenax TA and the graphitized Tenax GR are most suitable for the widest range of VOCs and SVOCs. The analytical advantage is the low affinity for water vapor. A short

drying step can be added to the workflow. In addition, other stronger sorbents for instance trapping very volatile organic compounds (VVOCs) like small fluorinated compounds are available for the trap with graphitized carbon black or molecular sieve materials.

The big practical benefit of the PAL System dynamic headspace is the closed system with syringe and sorbent trap. Each sample is analyzed in its individual vial, no carryover can occur. A drying step of the sorbent material can be added to the workflow easily. Also, foaming samples are handled without trouble. No breakthrough can occur, no loss of analytes. And, in a case of high concentrated samples, only the trap and syringe need cleaning, not a complete complex purge unit.

The PAL System dynamic headspace facilitates low-level volatile analysis greatly. Just by adding the ITEX DHS tool, every PAL System can be employed for dynamic headspace analysis. Many applications in different areas are published. All published analytical results are well comparable to previous data achieved with all-glass-sparger units (aka purge & trap).

How to Increase Sensitivity?

Volatiles evaporate from the surface of the sample. Replenishing a liquid surface like water or beverages requires the continuous shaking of the vial. It is important to consider the viscosity of the liquid. High frequencies of the shaker do not affect a viscous liquid much. Solid samples need to be ground to powder to achieve a higher surface area before adding to the headspace vials or using a solvent as a mediator.

For sure the temperature plays a key role for the migration and volatilization of the analytes. Caution must be taken with water as excess water vapor needs to be avoided for GC injection. With aqueous samples, temperatures in the range of 60°C to 80°C are most suitable for both static and dynamic extractions. Also, stronger pressurization in the static mode shows beneficial effects in reducing the extracted water vapor.

For aqueous samples increasing the ionic strength with the so-called “salting-out effect” is a common measure. Also, the salt serves in the standardization of the sample matrix. About 2 g of sodium chloride, or a saturated NaCl solution, is prepared into standard headspace vials before the aqueous sample is added [4,5]. NH_4Cl and K_2CO_3 increase the efficiency of the extraction as well [6]. A pH adjustment needs to be considered for the analysis of basic or acidic analytes reducing the dissociation in the aqueous phase.

All measures support the static as well as the dynamic headspace methods.

Analyzing both, the main compounds and important low-level analytes, for instance, the strong sulfur compounds, the workflow of the PAL System automatically runs samples with static and dynamic headspace analysis to provide a full picture of the flavor or mal-odor profile of a sample. A highly beneficial and unique feature of the PAL System.

With the dynamic headspace analysis using the ITEX-DHS tool, the most important parameter besides the above measures is the number of extraction strokes to concentrate the analytes on the sorbent trap. Fifty or more plunger strokes are often used for trace analyses using the available GC runtime for the exhaustive sample extraction in the unique prep-ahead mode of the PAL System [7].

Reducing the pressure in the sample vial is a known means to reduce boiling points and increase analyte vapor pressure, also called ‚vacuum headspace‘. Applying vacuum during the dynamic headspace sampling significantly increases the yield of analytes in the trap, in particular of the SVOC compounds. A vacuum line gets connected to the side port of the ITEX DHS syringe via the internal gas lines of the PAL System. Upon piercing the incubated sample vial pulling the plunger of the ITEX DHS syringe into the upper position the sample headspace gets continuously extracted through the sorbent trap. The reported signals are up more than 100fold compared to SPME and ITEX-DHS techniques [8].

How Does Quantitation with Headspace Analysis Work?

Headspace quantitation is known to be affected by different matrices, which is called the ‚matrix effect'. The sample matrix influences the equilibrium concentration between the sample and the headspace above, expressed as the K-factor with $c_{sample}/c_{headspace}$.

With the PAL System two analytical approaches are available for correct quantitation in the automated processing: standard addition and multiple headspace extraction. Both quantitation concepts are based on a calibration in the particular matrix of a sample. Both procedures are available for automated headspace analysis on PAL Systems.

Standard Addition Calibration

The calibration by standard addition is of general use for precise quantification methods, not limited to headspace analysis. In particular, when using HS for solid samples like soils or sediments the matrix needs to be compensated as calibration standards cannot be created with the same matrix interactions.

Using a PAL System for static headspace analysis the addition of standards into a series of vials with the same sample can be achieved fully unattended. Several vials are prepared from the same sample. One vial is kept without standard, the other vials get a standard solution in different known amounts or concentrations forming a calibration curve. All vials are treated with the identical incubation and measurement workflow. The resulting peak areas form a calibration function proportional to the added amount, see **Table 1**. The regression line cuts the x-axis on the negative side of the abscissa. The concentration in the sample is expressed by the absolute value of the point of intersection with the negative abscissa.

The precision of the results by extrapolation of the standard addition calibration line is strongly dependent on the quality expressed as R^2 of the regression line of the measured data points. For high sample throughput at least one standard addition is required forming the regression line with the peak area of the unaltered sample. Additional data points define the linear regression more precisely, a typical task of the automated procedure using the PAL System. For the discussion on the precision of the extended calibration line see the publication by Graham R. Bruce and Paramjit S. Gill [9]. An example of the standard addition method is illustrated with the experimental data of **Table 1** and the resulting graph in **Figure 3**.

Standard addition #	Added concentration [mg/kg]	Signal [cts]
no addition	0.0	1.5
1	1.5	2.5
2	3.0	3.3
3	4.5	4.4
4	6.0	5.5

Table 1: Standard addition experiment with 4 addition steps

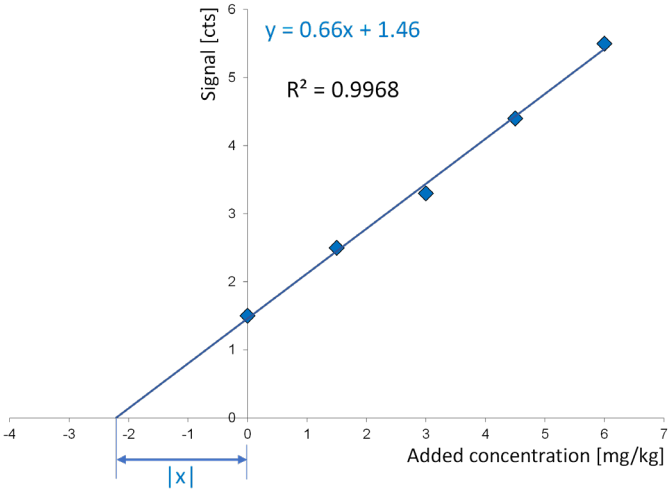


Figure 3: Standard addition graph from Table 1 with |x| the absolute amount of analyte in the sample portion

From the standard addition experiment in **Table 1** with the response data registered from the sample without addition and four addition steps with increasing concentration the graph in **Figure 3** can be generated. The signal axis can be the direct detector response in counts or, in case an internal standard is used, the relative response. The signal of the unaltered sample is the data point at zero concentration added. The regression line is calculated with good precision expressed with R^2 0.9968. The result with the concentration in the unaltered sample can be read from the intercept of the regression line with the abscissa. The absolute value |x| is used. From the given equation of the regression line in **Figure 3** the result |x| can be calculated for y = 0 from the height of the signal axis intercept 1.46 divided by the slope 0.66: |x| = 1.46 / 0.66 = 2.21 [mg/kg].

Multiple Headspace Extraction

The multiple headspace extraction procedure (MHE) is known and used for decades for the matrix independent quantitation in HS analyses [10, 11]. MHE uses stepwise a series of static headspace measurements from the same sample vial. Important here, the partition coefficient *K* is kept constant as matrix and incubation conditions are kept constant. However, the amount of analytes injected is lower with each consecutive step. The specific decline of an analyte peak area is used to interpolate the total amount of analyte in the sample. This eliminates the effect of the matrix in the MHE method [12].

The workflow on the PAL System runs several consecutive static headspace measurements from the same sample vial. After each sampling, the vial pressure is released to atmosphere using the MHE tool. After a new equilibration using identical conditions, the next headspace measurement is performed. The resulting peak areas of the sequential runs show an exponential decline. A linear regression on the logarithmic relation delivers the final concentration result in the sample [13] . In the simplest approach only two measurements are required to calculate the analyte concentration in the sample. In case all samples come with the same matrix only one run is necessary if the slope of the regression is known.

Internal Standard Use

The application of internal standards follows the same rules and requirements as in liquid extraction methods. The standard compound itself must not be present in the sample, should be added in the expected concentration range, and behave to matrix absorption as similar as possible compared to the analyte(s). Preferably a similar distribution coefficient *K* should be achieved. Mass spectrometry allows the use of isotopically labeled standards. A big benefit for sample throughput is that only one measurement of the sample is required. The manual time-consuming addition of the ISTD to the sample vial can be accomplished automatically by the PAL System. Internal standards can be used on the PAL System for relative response calibrations, standard addition or MHE methods, as described above.

How to perform the GC Injection?

The injection of the aliquot taken by static headspace or the thermal desorption of the collected volatiles by the ITEX dynamic headspace follows the same rules and considerations. Any GC injector type can be used, with a recommended setting to a high temperature to avoid potential losses due to condensation in cold areas. This is also valid for the temperature programmable injectors keeping it at a constant high temperature. Injecting a gaseous sample into GC is comparable to liquid injections, but in this case, the sample reaches the inlet from the syringe already vaporized. The inlet liner volume, flow into the column and oven temperature need to be considered for optimum conditions.

For sure, for the gaseous sample volume to be injected appropriate measures must be taken to focus the analytes at the beginning of the GC column to achieve sharp peaks for good separation and sensitivity. Without column focusing the injected peak would become several minutes wide, or, with a large split ratio used, reduced in intensity as the injection volume onto the column is dramatically down to microliters only. Available measures for column focusing are the use of thick film GC columns using a suitable GC oven temperature, or the additional installation of cryofocusing devices in the GC oven.

The right choice of the inlet liner affects the performance of the chromatographic headspace analysis. Ideally, a dilution of the gaseous sample with carrier gas is avoided as much as possible to keep the sample plug entering concentrated the GC column. A large buffer volume in the liner to expand a liquid sample to its vapor volume is not needed as the sample enters the injector from static as well as from ITEX dynamic headspace already gaseous. Small inlet liner diameters of for instance 1 mm ID support narrow peak widths during the injection step.

Analyte re-focusing on the beginning of the GC column assures optimum chromatographic separation and sensitivity with sharp analyte peaks. The analyte focusing is easily achieved when using thick-film capillary columns by setting the start temperature of the oven program during the injection step below the actual boiling point of the analytes to be analyzed. The condensation of the injected vapors in the GC column leads, due to the volume reduction, to a strong suction effect pulling the injected vapors from the inlet liner into the column. In the column the well-known ‚solvent effect' described by Koni Grob more than 40 years ago delivers sharp peak bands before the oven temperature ramp starts.

The re-focusing of the volatiles is working well with the typical thick film capillary columns for VOC analysis, for instance with 1.4 µm film thickness for 0.25 mm ID, and 1.8 µm for 0.32 mm ID columns in GC-MS applications. Typical GC column flows of up to 2 mL/min, for instance, used with a typical volatile analytical column like the Restek Rxi-624Sil MS column of 30 m length, 0.32 mm ID, and 1.8 µm film thickness. These column types allow quick injection speeds from the static headspace tools, also with the ITEX dynamic headspace in the range of 200 µL/s and above.

For the ITEX dynamic headspace it should be noted that the desorption of the trapped analytes takes place during the aspiration flow phase with the needle already penetrated the injector body and with at this point heated sorbent trap. The ITEX DHS operation steps are illustrated in **Figure 4**. The aspiration flow speed is set to default 10 µL/s and should not be increased to allow quantitative desorption and avoid split peaks during the injection. GC injector split flows of 5 to 20 mL/min with resulting split ratios of up to 1:10 can be used depending on sensitivity requirements.

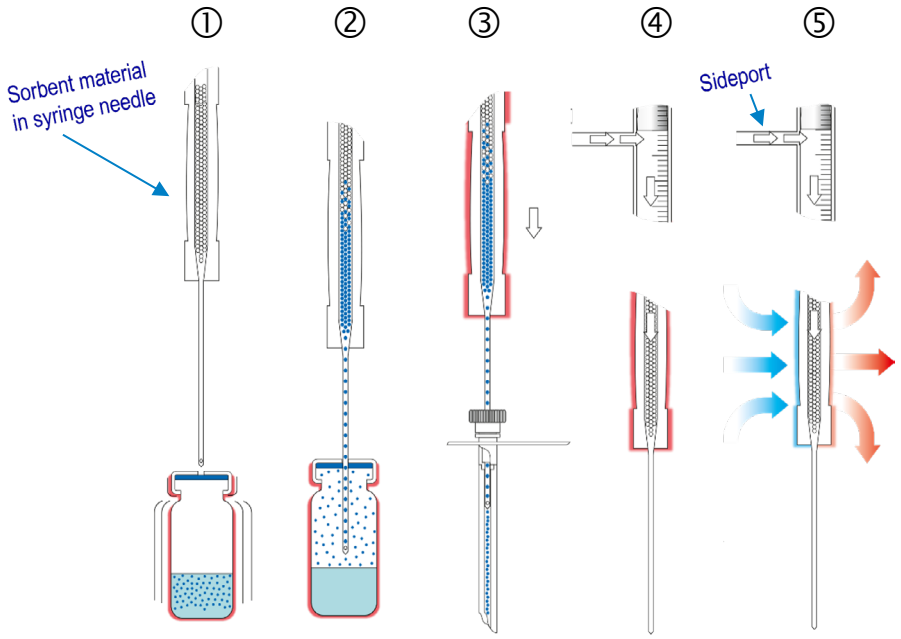


Figure 4: ITEX DHS sample absorption, GC injection, and final cleaning steps:

1. The sample is incubated and agitated in a sealed sample vial.
2. The ITEX DHS trap needle pierces the sample vial and the heated gas-tight syringe pumps with repeated strokes the sample headspace through the sorbent trap.
3. The loaded ITEX trap moves to the GC injector penetrating the septum and is flash heated up to 350 °C. Aspiration of carrier gas desorbs the analytes before injection of the analyte plug into the hot GC Injector
4. After injection, the heated trap is cleaned with inert gas from the syringe sideport.
5. Active cooling allows short cycle times.

The Unique Advantages of the PAL System for Headspace Analysis

- Unattended processing of large sample series
- Temperature controlled sample storage
- Significantly improved data quality and precision
- Open access with different vial sizes, also customized vial sizes
- Static headspace and dynamic headspace methods on one PAL System
- Automated change of static to dynamic method
- Prep-ahead mode for faster results
- Low risk of system contamination from exceeding sample concentrations
- One PAL – Multiple HS methods
- Standards dilution and addition automated and integrated additionally
- Multiple injector and multiple GC column use
- Space-saving, cost-saving – instrument top installation, no bench space occupied
- Fits any GC or GC-MS system
- Lower cost per sample
- Additional automated sample preparation and liquid handling capabilities

Proven Application Examples – The Most Popular PAL Turnkey Headspace Solutions

Residual Solvents in Pharmaceuticals as of Method USP <467>

LIFE SCIENCE FOOD SAFETY

The United States Pharmacopeial Convention defined the residual solvents in pharmaceuticals as volatile organic chemicals that are used or produced in the manufacturing of drug substances, excipients, or dietary ingredients, or the preparation of drug products or dietary supplement products [14]. The residual solvents were evaluated for their potential risk to human health and are classified based on their toxicity and environmental impact data into Class 1 (to be avoided), Class 2 (to be limited), and Class 3 (of low toxic potential). For classes 1 and 2 maximum concentration limits are given in ppm. For class 3 it is considered that concentrations below 5000 ppm are acceptable without justification. The classification and maximum limits are subject to change. The last update became official on December 1, 2020.

While the United States Pharmacopeial Convention document does not state a precision requirement [14], the European Pharmacopeia requires a precision of better than 15 % RSD within three repetitive measurements [15]. In general, in repeat PAL System suitability tests a method precision of better than 2.5 % on average, expressed as the relative standard deviation, is achieved. Exceptions are typically those compounds of high polarity (high *K* factor) and low concentration limits.

PAL System Configuration

The described experiments demonstrate the PAL RTC System performance installed in the identical configuration as shown in **Figure 5** and with **Table 2** on two different brand GC-FID and GC-MS systems, namely Agilent Technologies GC 7890B with FID and Thermo Fisher Scientific TRACE Trace 1300 GC with ISQ single quadrupole mass spectrometer. Both GCs were equipped with the same GC column type, length, ID, and film thickness. The operational parameter for the GC-FID and GC-MS systems are provided in **Table 3**.

PAL Systems: Agilent PAL RTC /Thermo Fisher Scientific TriPlus RSH System	
1	PAL RTC 85/120
2	Park Station
3	Agitator
4	Tray Holder
5	Rack VT15
6	Headspace Tool
6	with a 2.5 mL Headspace Syringe (P/N: SH2500-65-T-23-SP)
System A: GC-FID	
A	PAL RTC system with headspace capability on Agilent 7890B GC-FID. GC Column: Restek Rxi-624Sil MS Column (30 m x 0.32 mm ID x 1.8 µm)
System B: GC-MS	
B	Thermo Scientific TriPlus RSH for headspace injection on Thermo Trace 1300 GC-ISQ. GC Column: Restek Rxi-624Sil MS Column (30 m x 0.32 mm ID x 1.8 µm)

Table 2: GC-FID/MS configurations for USP <467> residual solvent analysis.

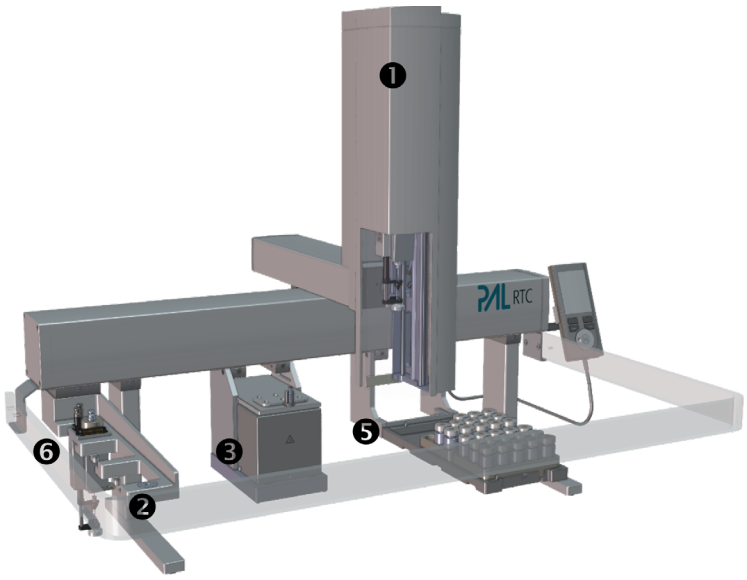


Figure 5: PAL RTC System configured for USP <467> analysis, to be installed GC top.

PAL System Workflow

The workflow executed by the PAL System is illustrated in **Figure 6**. Agitator and headspace syringe tool are heated to the set temperature before the workflow starts. Before taking the sample headspace the vial is pressurized, and several plunger strokes are used for equilibration with the syringe. The PAL System workflow operates in an overlapping mode for large sample series to make efficient use of the six vial positions in the Agitator. The incubation time is scheduled with the GC runtime to be ready for injection at the time the GC *Ready* signal is expected. Both, overlapping and prep-ahead modes significantly increase the sample throughput and guarantee the best usage of the GC-FID/MS measurement time (duty cycle).
The PAL System workflow can be created in minutes by using the PAL Method Composer (PMC) software. The PMC offers a graphical user interface by pulling the desired steps into sequence and adding the given parameters like temperatures or times. The completed PMC workflow is used in the manufacturer sequence table for controlling the PAL workflow.

Analysis

6 mL of a test solution was placed in 20 mL headspace vials and analyzed by System A und B using the instrumental parameters listed in **Table 3**.

Results

Typical chromatograms obtained from a residual solvent standard mix for Class 2 are shown for GC-FID with **Figure 7** and GC-MS with **Figure 8**. Both chromatograms show the typical dynamic with small and very high peak intensities resulting from the different concentrations in the reference mix from 1.63 ppm of o-xylene to 25.02 ppm with methanol. On top of that, the different response factors of the included hydrocarbons and the oxygenates and halogenates like dioxane or methylchloride need to be considered. Areas of low peak intensity are zoomed and show even for the low response compounds a solid peak integration for both, GC-FID and GC-MS data.
The precision of analysis using the PAL System headspace workflow is excellent for both GC-FID and GC-MS systems with an average below 5 % RSD from 20 consecutive measurements (see **Table 4**).

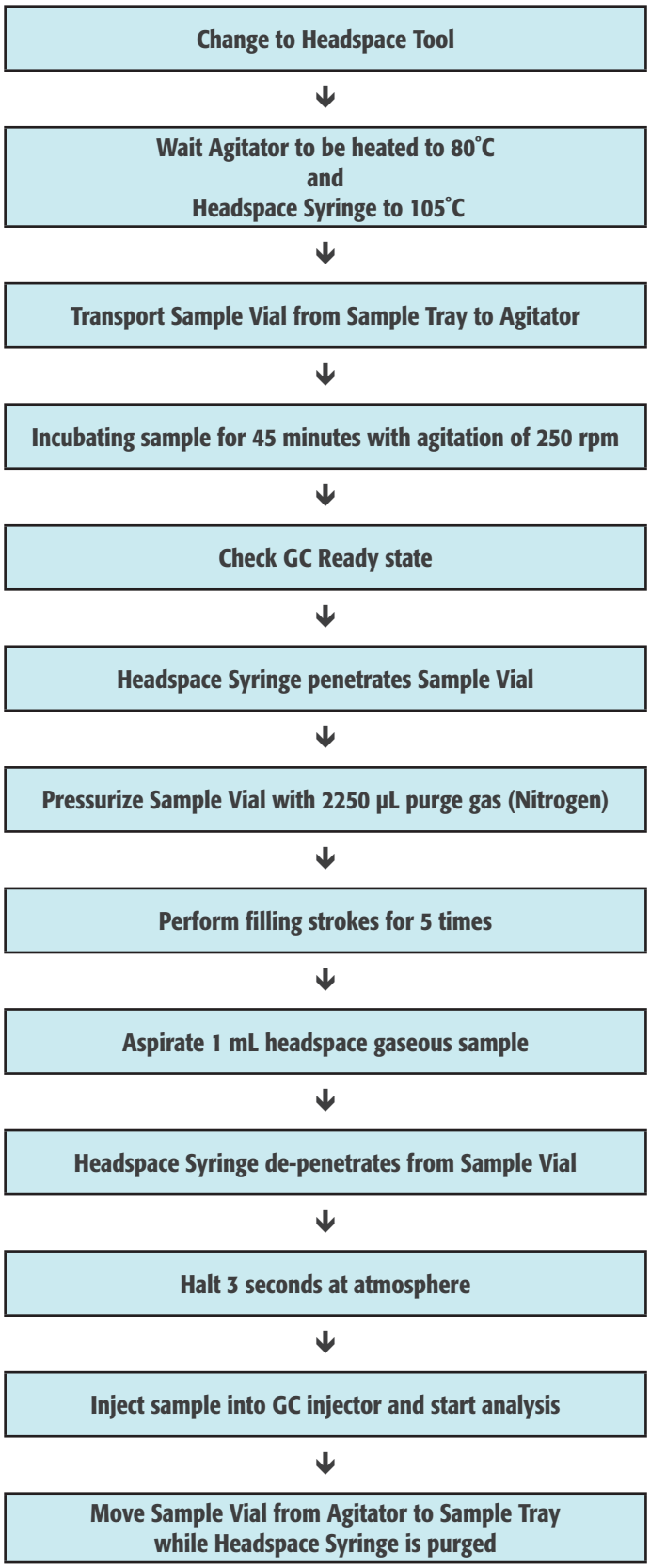


Figure 6: PAL RTC workflow for USP <467> analysis

Analysis Parameters

	GC-FID (System A)	GC-MS (System B)
Instrument Type	**PAL3-RTC**	**TriPlus RSH**
Agitator Temperature	80 °C	80 °C
Syringe Temperature	105 °C	105 °C
Purge Gas Regulator Pressure	1.6 Bar	1.6 Bar
Sample Incubation Time	45 minutes	45 minutes
Pre-Filling	Enable (volume = 2.25 mL)	Enable (volume = 2.25 mL)
Filling Stroke	5 times (volume = 1.2 mL)	5 times (volume = 1.2 mL)
Filling Stroke Delay	30 seconds	30 seconds
Sample Vial Penetration Depth	25 mm	25 mm
Sample Aspiration Speed	6 mL/min	6 mL/min
GC Injector Penetration Depth	45 mm	45 mm
Sample Injection Speed	25 mL/min	25 mL/min
Pre-Injection Dwell Time	3 seconds	3 seconds
Post-Injection Dwell Time	10 seconds	10 seconds
Pre-Injection Purge	Off	Off
Post-Injection Purge	60 seconds	60 seconds

Instrument Type	**7890B GC**	**Trace 1300 GC**
GC Inlet Temperature	200 °C	140 °C
GC Carrier Gas	Helium	Helium
GC Column Flow	2.2 mL/min (constant fow)	2.2 mL/min (constant flow)
Inlet Split Ratio	5:1	20:1
GC Oven Program	Initial 40 °C hold for 20 minutes; Ramp 10 °C/min to 240 °C, hold for 20 minutes	Initial 40 °C hold for 20 minutes; Ramp 10 °C/min to 240 °C, hold for 20 minutes

Instrumetn Type	7890B FID	
FID Temperature	280°C	
		ISQ MS
EI Source		70 eV
Transfer Line Temperature		250 °C
Ion Source Temperature		250 °C
Scan Range		m/z 29 - 150

Table 3: Analysis parameter for GC-FID and GC-MS

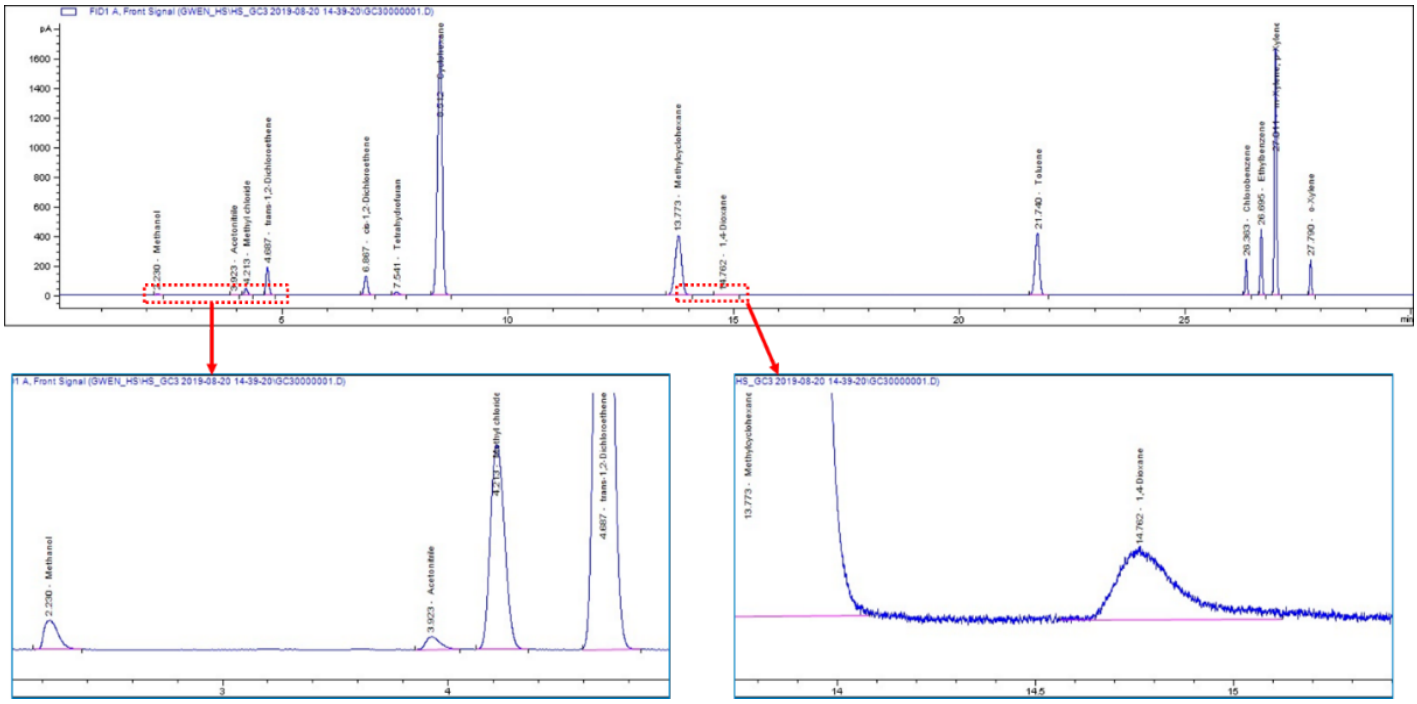


Figure 7: FID chromatogram obtained from residual solvents Class 2 - Mix A diluted with water; concentration: Methanol 25.02 ppm, Acetonitrile 3.42 ppm, Methyl chloride 5.00 ppm, trans-1,2-Dichloroethene 7.83 ppm, cis-1,2-Dichloroethene 7.87 ppm, Tetrahydrofuran 5.75 ppm, Cyclohexane 32.37 ppm, Methylcyclohexane 9.83 ppm, 1,4-Dioxane 3.17 ppm, Toluene 7.42 ppm, Chlorobenzene 3.00 ppm, Ethylbenzene 3.08 ppm, m-Xylene 10.85 ppm, p-Xylene 2.55 ppm, and o-Xylene 1.63 ppm.

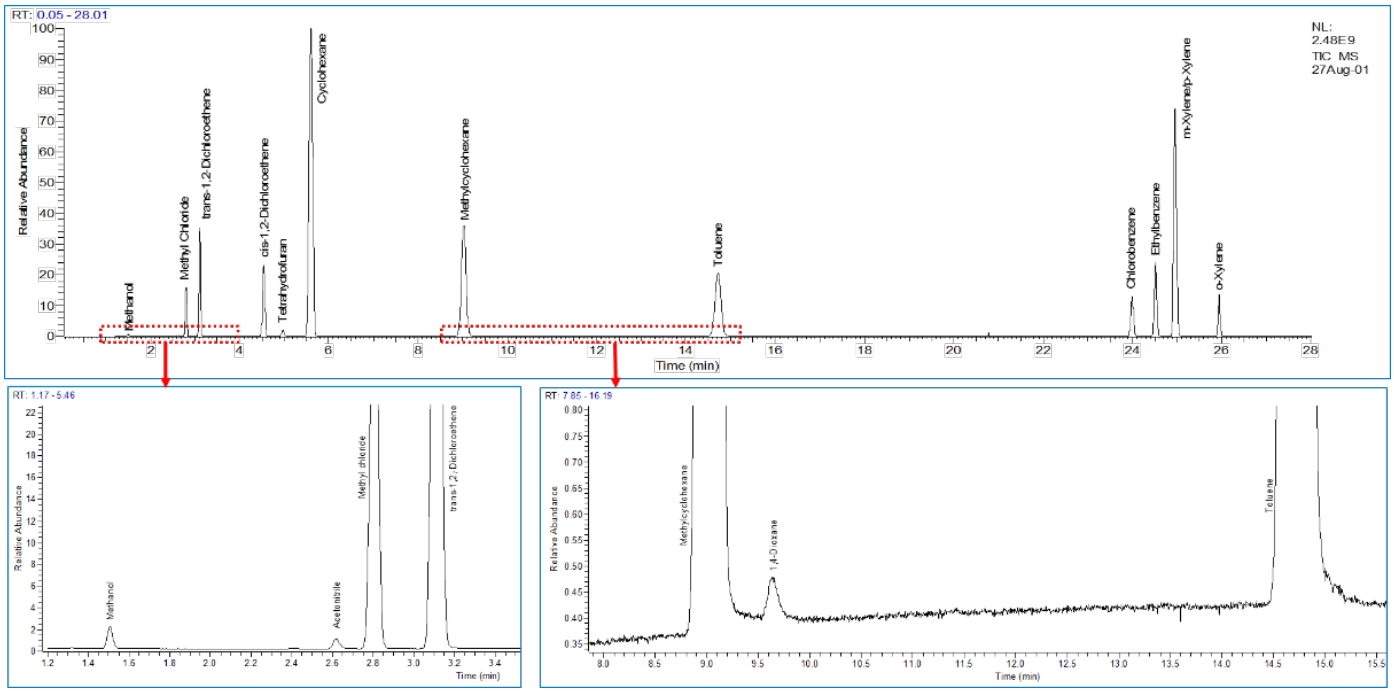


Figure 8: GC-MS TIC chromatogram obtained from residual solvents Class 2 - Mix A diluted with water; concentration: Methanol 8.34 ppm, Acetonitrile 1.14 ppm, Methyl chloride 1.67 ppm, trans-1,2-Dichloroethene 2.61 ppm, cis-1,2-Dichloroethene 2.62 ppm, Tetrahydrofuran 1.92 ppm, Cyclohexane 10.79 ppm, Methylcyclohexane 3.28 ppm, 1,4-Dioxane 1.06 ppm, Toluene 2.47 ppm, Chlorobenzene 1.00 ppm, Ethylbenzene 1.03 ppm, m-Xylene 3.62 ppm, p-Xylene 0.85 ppm, and o-Xylene 0.54 ppm.

Compound Name	System A		System B	
	Retention Time, min	%RSD (n=20)	Retention Time, min	%RSD (n=20)
Methanol	2.230	4.47	1.503	5.91
Acetonitrile	3.923	4.30	2.609	4.44
Methyl chloride	4.213	4.38	2.792	3.53
trans-1,2-Dichloroethene	4.687	4.73	3.099	4.26
cis-1,2-Dichloroethene	6.867	4.51	4.517	3.70
Tetrahydrofuran	7.541	4.14	4.949	4.26
Cyclohexane	8.512	4.70	5.568	4.09
Methylcyclohexane	13.773	4.71	8.972	3.97
1,4-Dioxane	14.762	7.73	9.601	3.88
Toluene	21.740	4.55	14.632	3.78
Chlorobenzene	26.363	4.49	23.954	4.27
Ethylbenzene	26.695	4.59	24.488	4.27
m-Xylene & p-Xylene	27.011	4.60	24.920	4.51
o-Xylene	27.790	4.51	25.916	3.91

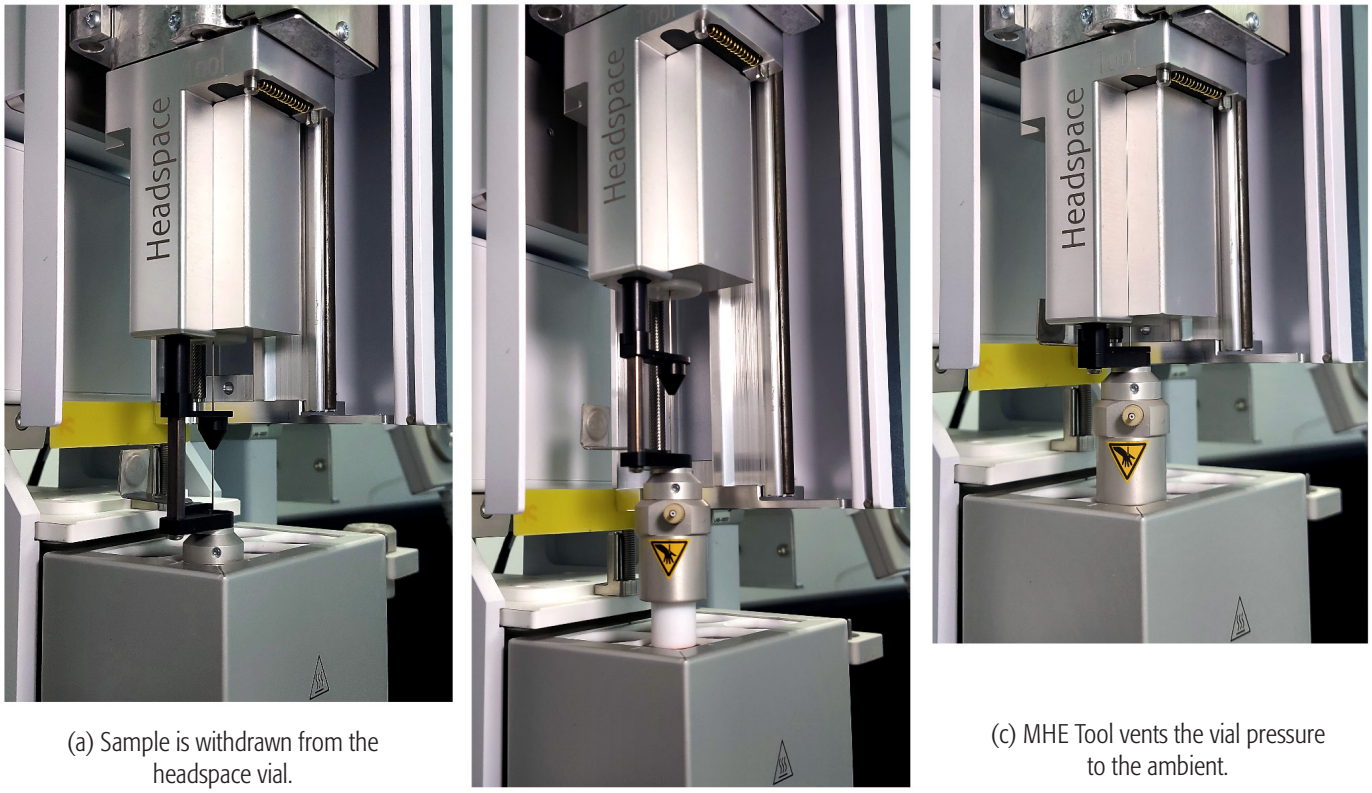
Table 4: Retention time and precision data for 20 replicate analyses using GC-FID and GC-MS systems.

Quantitation by Multiple Headspace Analysis

The fastest and matrix independent quantitative analysis of volatile compounds is achieved by multiple headspace extraction (MHE) [6].

The MHE procedure involves an automated sequence of pressurizing, sampling and venting from the sample for consecutive extraction steps from the same sample vial. Together with the heated headspace syringe, an MHE tool allows the controlled venting of the pressurized sample vial after each sample extraction step as illustrated in **Figure 9** .

The below described application determines residual solvents acetone and 2-propanol in a pharmaceutically active agent 5-aminosalicylic acid (5-ASA), also known as Mesalazine, and commercialized under different brand names [17]. The MHE procedure shown demonstrates the method development with the final workflow of two HS injections only for quantification of the residual solvents in the final pharmaceutical product.



(a) Sample is withdrawn from the headspace vial.

(b) MHE Tool is positioned above the headspace vial.

(c) MHE Tool vents the vial pressure to the ambient.

Figure 9: MHE extraction sequence with (a) initial sampling from the incubated vial with the heated HS syringe, and analysis; (b) positioning of the MHE tool above the sample vial; (c) venting the sample vial to atmosphere, prepares for the next sampling step.

About MHE Headspace Analysis

The concentration of a VOC analyte in a sample c_{sample} is to be determined. Multiple headspace runs with extraction (MHE) from the same sample vial are conducted, with pressure equilibration to atmosphere after each injection. After each run the remaining analyte concentration in the headspace depends on the initial concentration c_0 in the sample, expressed in the first analysis as the peak area A_1 in the first chromatogram. The peak areas from subsequent runs decrease exponentially. So, the total concentration in the sample c can be expressed by c_0 times an exponential factor with a negative exponent describing the duration of extraction, equivalent to the number *i* of MHE steps, times an analyte-specific constant *q*:

(1) $A_i = A_1 \cdot e^{-q(i-1)}$ with A_i the required total area of the analyte in the sample.

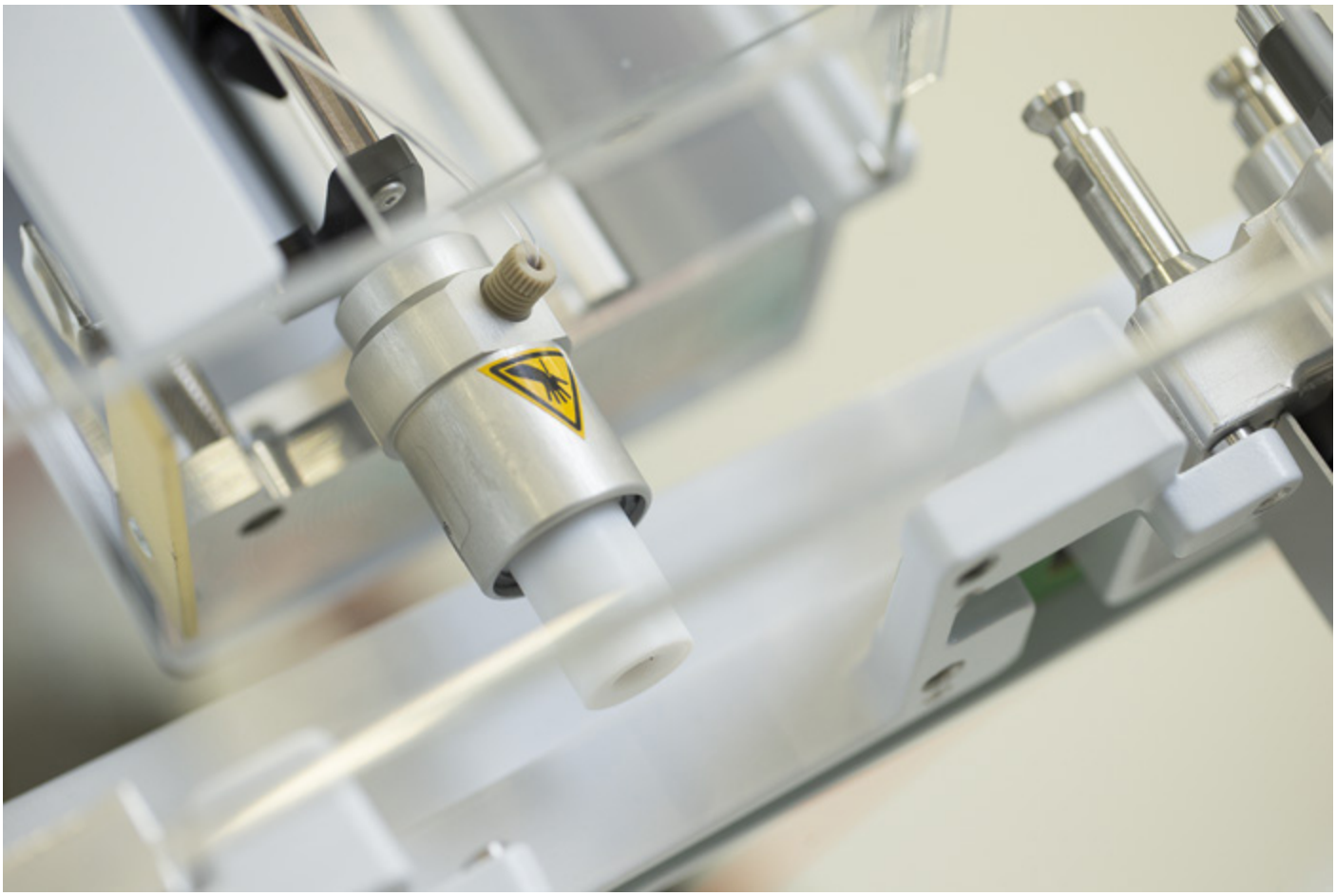
A linear relationship of the measured areas *Ai* vs. the number of runs *i* is expressed by plotting the areas logarithmic against the extraction number *i,* which allows the calculation of the wanted total area of the analyte in the sample by determination of the slope *q* of the straight line:

(2) $\ln A_i = \ln A_1 - q(i-1)$

The required total area *A* is achieved by integration of all potential areas A_i which is reduced to the following equation only using the first peak area A_1 and the slope *q*:

(3) $$A = \sum_{i=1}^{\infty} A_i = \frac{A_1}{1 - e^q}$$

For the practical use two scenarios are possible. Only one measurement is required if the slope of the graph for an analyte is known from previous experiments and the matrix is constant over the series of measurements. Two measurements are required if the slope of the decrease is not known which is probably the most probable situation with real life samples of different matrices. The final concentration in the sample is calculated by multiplication of the received area A_i with the specific response factor of the analyte.



Sample Preparation

50 mg polyvinyl pyrrolidone-bound 5-amino salicylic acid (5-ASA) granulates are placed into a 10 mL headspace vial, spiked with 10 µg acetone and 10 µg 2-propanol. The sample vials were incubated at 80 °C for 20 minutes prior to MHE headspace analyses.

Determination of the Sample Concentration

The following calculations are shown for the analyte acetone (similar to 2-propanol, not shown). Below **Table 5** shows acetone peak area from the five successive extractions of the same sample vial with the calculated natural logarithm of the peak areas. **Figure 10** illustrates graphically the exponential decline with the subsequent MHE measurements from the same vial.

Extraction Number	**Acetone Peak Area (cts)**	**Natural Logarithm ln (Acetone Peak Area)**
1	53.690	3.983227
2	25.480	3.237894
3	11.610	2.451867
4	5.400	1.686399
5	2.440	0.891998

Table 5: Peak area data of 5 MHE runs

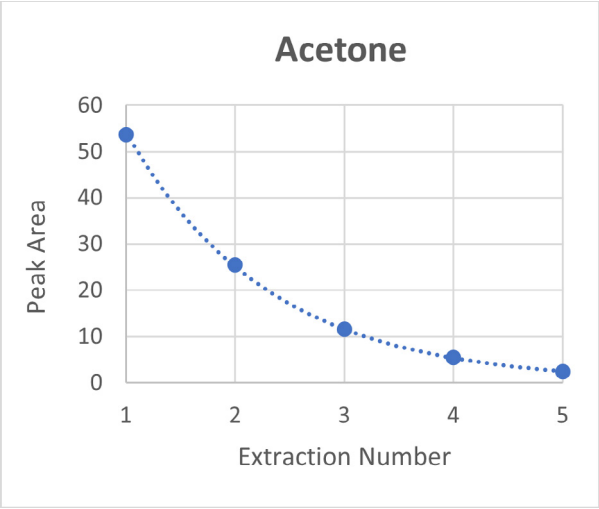


Figure 10: Acetone peak area vs. extraction number showing the exponential decline.

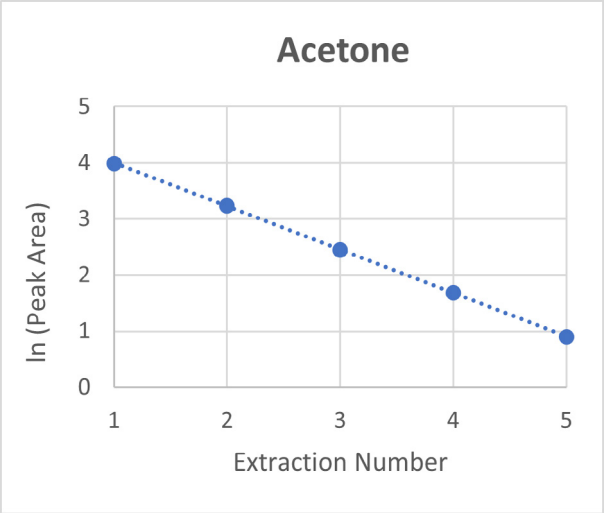


Figure 11: Linear relationship of ln(peak area).

Figure 11 shows the natural logarithm of the measured analyte areas as of **Table 5** plotted against the extraction number. Typically, this graph shows good linearity. The 'validity' of the MHE procedure can be judged from the curve fit. If equilibrium was established, the graph will be linear, and the MHE procedure works as expected.

From the logarithmic plot in **Figure 11**, the linear slope q is calculated as -0.7734. With formula (3) by using just the first headspace measurement with area A_1 the calculated total area A for the concentration in the sample is 99.69 cts which is converted to the concentration in the sample c_{sample} by multiplication with the specific response factor of the used detector for the analyte.

Sulfur Compounds in Tropical Fruits

FOOD SAFETY ENVIRONMENTAL

Tropical fruits become increasingly popular for consumers globally. Besides the different varieties, the degree of ripeness is most important for the aroma profile and finally the customer sensation, and price. "The volatile sulfur compounds (VSCs) are often responsible for the juicy, fresh aroma of tropical fruits" [18] . This „poses a challenge for analytical chemists to identify these compounds as most often VSCs are found at low concentrations in most tropical fruits" [19] . Durian, the 'King of the Fruits' is the most popular fruit in south-east Asian countries available in different varieties. High demand, also due to significant export, leads to steadily increasing prices. Profiling of Durian varieties becomes an increasingly important analytical task, requesting fast and routine-proof analytical methods. The Mao Shan Wang Durian, a premium Durian variety, known for its bright yellow flesh, bitter and sweet taste and creamy texture, was used as a typical sample.

The goal of the described analytical solution is the analysis for both, of the major components, and the low-level characteristic VSC aroma profile in one automated workflow. The PAL System allows the simultaneous extraction of samples by static and dynamic headspace techniques.

A PAL System equipped for static and dynamic headspace analysis is used. A headspace tool with a heated 2500 µL syringe is applied for static, the ITEX DHS tool for dynamic HS operation. The use of static and dynamic headspace is combined in one workflow and provides chromatograms of the major and low-level compounds from the same sample.

Initial Manual Durian Preparation

After opening the fruit, the yellow flesh around the Durian seed was put into a beaker and homogenized. 3 g of the Durian sample were placed into a 20 mL headspace vial, and 1 mL of water added. The headspace vials were closed with magnetic screw caps and prepared into two batches, then placed into the trayholder racks.

Automated Workflow

One batch is undergoing the automated static headspace extraction (Part A, **Figure 12**). The other batch of Durian samples is undergoing dynamic headspace extraction (Part B, **Figure 13**). Part A of the workflow focuses on the extraction of the major volatile organic compounds. Part B uses the ITEX DHS tool for the dynamic headspace extraction of the VSC trace concentrations from the Durian sample. Part A and B are combined in one workflow using the prep-ahead function and sequential GC-MS injection. The extracted components by both techniques were analyzed under the same GC-MS full scan conditions. **Table 6** provides the conditions of analysis for the static headspace (Part A) and the dynamic headspace (Part B) analysis.

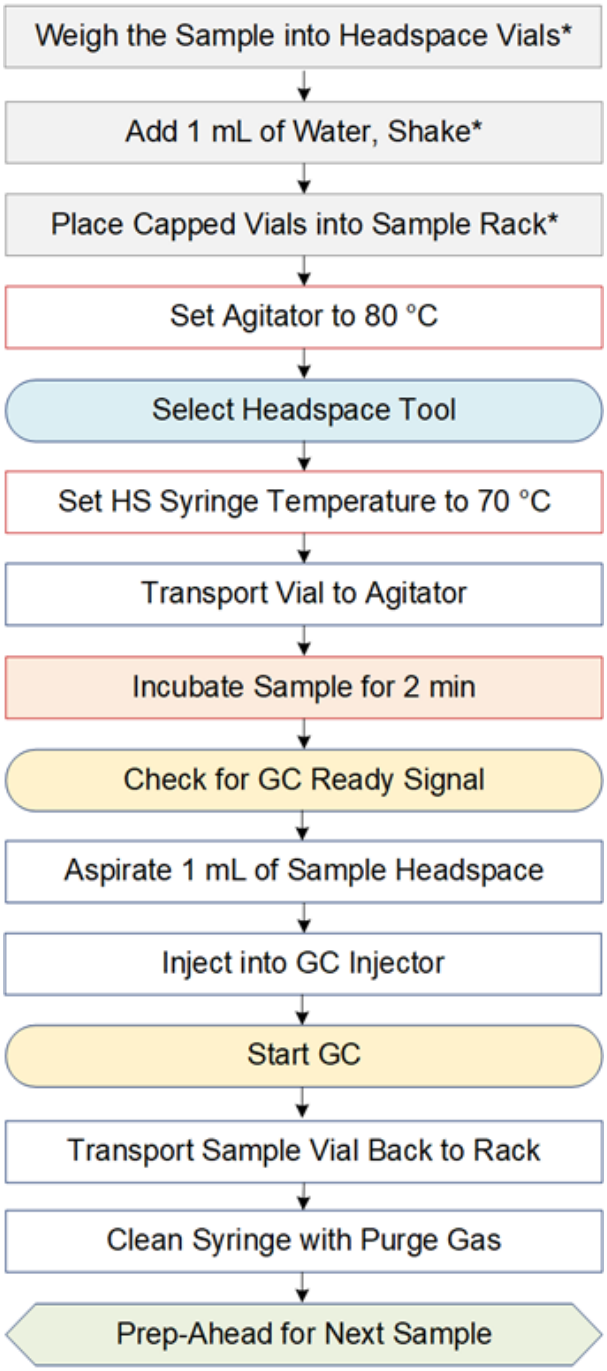


Figure 12: Part A – Automated workflow for static headspace analysis (*initial manual steps).

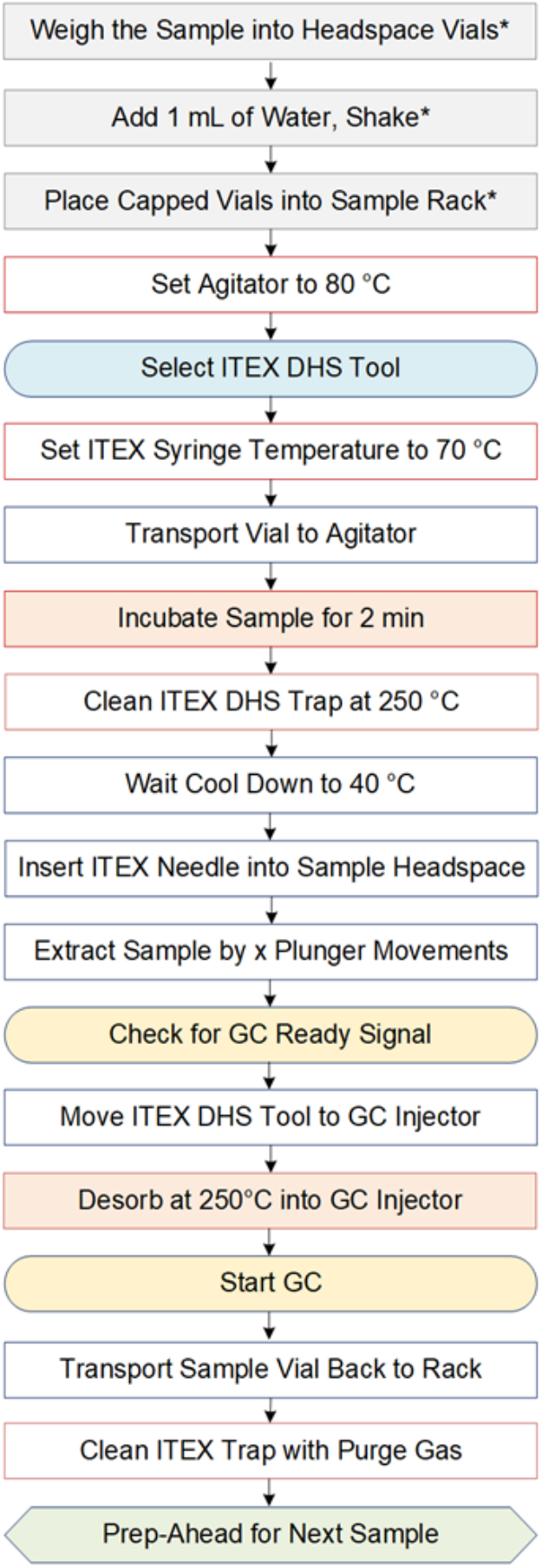


Figure 13: Part B - Automated workflow for dynamic headspace analysis (*initial manual steps).

	Part A - HS GC-MS	Part B - ITEX-DHS GC-MS
	To extract major compounds	To extract minor compounds
Headspace Extraction		
Incubation		
Incubation Temperature	80 °C	80 °C
Incubation Time	2 min	2 min
Agitator Speed	700 rpm	700 rpm
Extraction		
Extraction Strokes	Not applicable	20
Trap Extract Temperature	Not applicable	40 °C
Syringe Temperature	70 °C	70 °C
Trap Desorption		
Desorb Temperature	Not applicable	250 °C
GC		
Column	Rtx – VMS (60 m x 0.32 mm ID x 1.8 µm)	
Inlet Temperature	240 °C	
Inlet Mode	Split	
Split Ratio	10	
Oven Temperature	35 °C (10 min) -> 3 °C/min -> 60 °C -> 5 °C/min -> 130 °C -> 30 °C/min -> 240 °C (2 min)	
MS		
Interface Temperature	240 °C	
Scan m/z	20 - 400	
Scan Time	0.3 s	
Source Temperature	240 °C	

Table 6: Selected important analysis parameters by static and dynamic headspace techniques

Results

The distinctive fruity and onion-like odorous compounds of the Durian fruit were analyzed by both static and dynamic headspace techniques in a combined automated workflow.

In Part A with the static headspace extraction technique, fourteen major volatile organic compounds were detected and identified by GC-MS and NIST11 library search. The detected compounds were mainly from the thio-, alcohol, ester, and sulfide families. The ethanethiol peak #4 was detected with the highest intensity, shown in **Figure 14**. In part B a total of 58 low-level compounds were extracted by the dynamic headspace technique. Of those 45 additional compounds were only detected by the ITEX dynamic headspace in addition to the major compounds from Part A. The total ion chromatogram (TIC) of the ITEX dynamic HS extraction is shown in **Figure 15**.

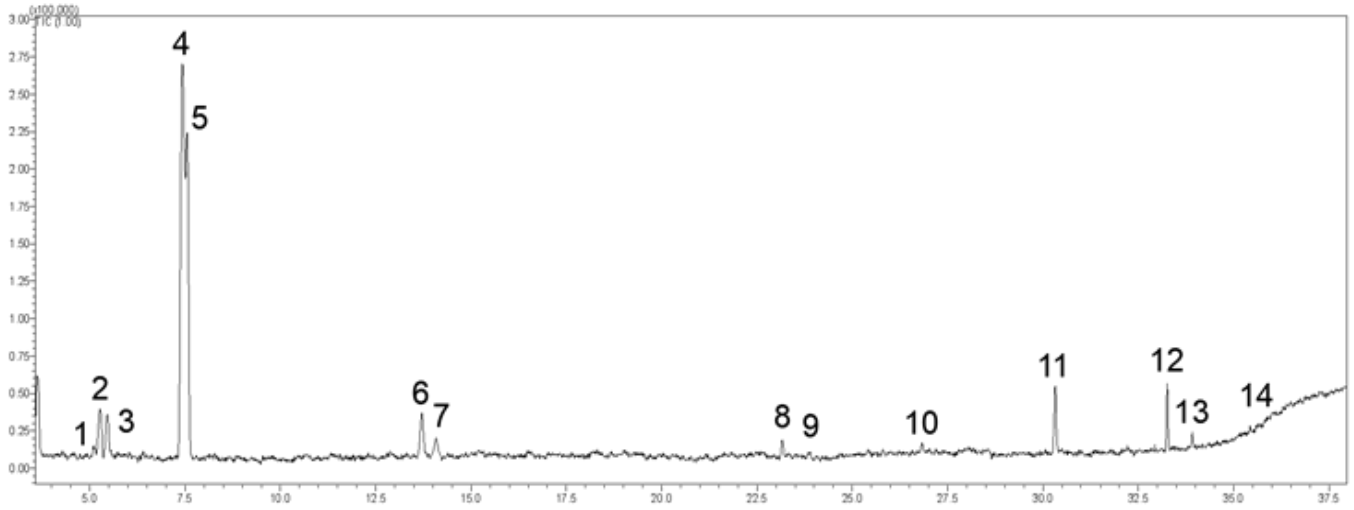


Figure 14: GC-MS full scan total ion chromatogram of the major VSCs by static headspace extraction.

Peak No.	RetentionTime (min)	Compound Name
1	5.04	Methanethiol
2	5.20	Acetaldehyde
3	5.40	Methyl Alcohol
4	7.34	Ethanethiol
5	7.57	Ethanol
6	13.64	Propyl mercaptan
7	14.03	1-Propanol
8	23.14	Propanoic acid, ethyl ester
9	23.88	Butanoic acid, 2-methyl, methyl ester
10	26.81	Butanoic acid, 2-methyl-, ethyl ester
11	30.41	Not identified by library search
12	33.26	Diethyl disulfide
13	33.91	Butanoic acid, 2-methyl - propylester
14	35.42	Disulfide, ethyl 1-methylethyl

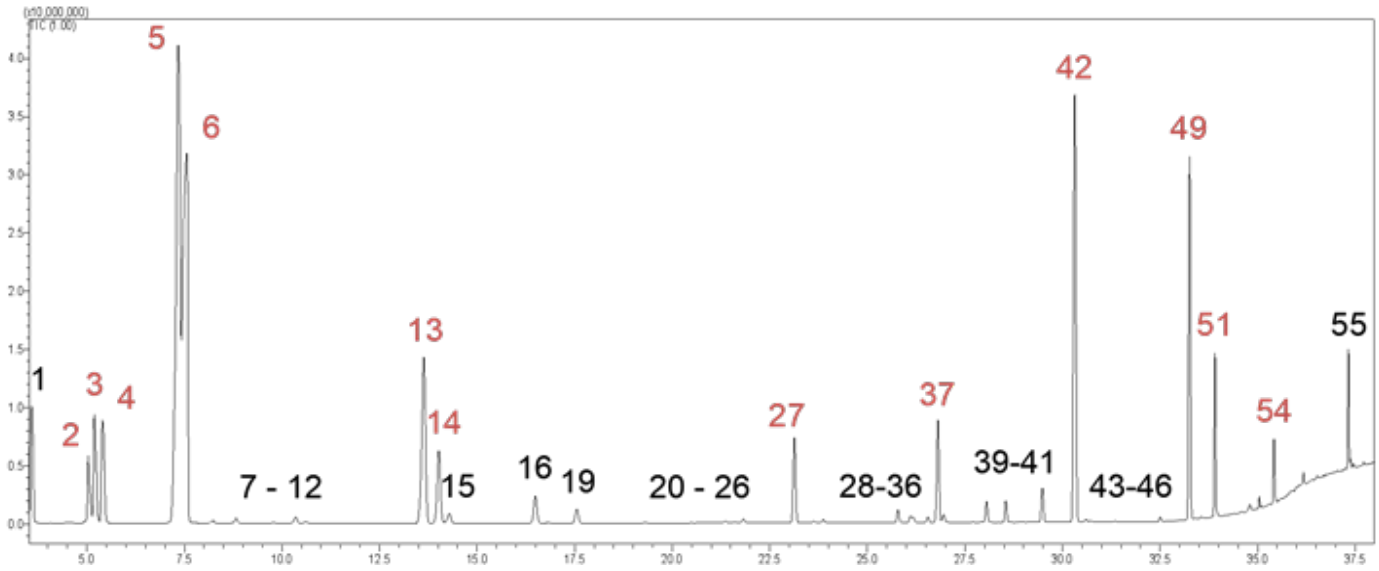


Figure 15: GC-MS full scan total ion chromatogram of the trace VSCs by ITEX dynamic headspace extraction. The major compounds also extracted by static HS technique are labelled in red.

Peak No.	Retention Time (min)	Compound Name
1	3.59	Hydrogen sulfide
2	5.04	Methanethiol
3	5.20	Acetaldehyde
4	5.40	Methyl alcohol
5	7.34	Ethanethiol
6	7.57	Ethanol
7	8.24	Dimethyl sulfide
8	8.83	Propanal
9	9.79	Acetone
10	10.36	Acetic acid, methyl ester
11	10.62	n-Hexane
12	12.99	Propanal, 2-methyl-
13	13.62	Propyl mercaptan
14	14.00	1-Propanol
15	14.29	Ethane, (methylthio)-
16	16.52	Ethyl acetate
17	16.83	2-Butanone, 3-methyl-
18	17.10	2-Butanone
19	17.57	Methyl propionate
20	19.32	1-Propanol, 2-methyl
21	21.30	Propanoic acid, 2-methyl-, methyl ester
22	21.60	1 - Butanethiol
23	21.84	1 - Butanol
24	21.95	2 - Propanal, 2-methyl
25	22.26	Methyl thiolacetate
26	22.60	1-Penten-3-ol
27	23.14	Propanoic acid, ethyl ester
28	23.53	2 - Pentanone
29	23.61	n-Propyl acetate
30	23.80	Butanoic acid, methyl ester
31	24.52	Disulfide, dimethyl
32	25.22	Toluene
33	25.70	Propanoic acid, 2-methyl-, ethyl ester
34	26.11	1-Butanol, 3-methyl-
35	26.10	1-Butanol, 2-methyl-
36	26.56	S - ethyl enthanethioate
37	26.85	Butanoic acid, 2-methyl, methyl ester
38	26.96	Acetoin
39	28.00	Butanoic acid, ethyl ester
40	28.53	Propanoic acid, propyl ester
41	29.49	Methyl ethyl disulfide
42	30.33	Butanoic acid, 2-methyl-, ethyl ester
43	30.50	Butanoic acid, 3-methyl-, ethyl ester
44	30.65	Propanoic acid, 2-methyl-, propyl ester
45	30.70	2-Butenoic acid, ethyl ester, (E)-
46	31.00	s-Ethyl thiopropionate
47	32.20	1-Hexanol
48	32.52	Butanoic acid, propyl ester
49	33.26	Diethyl disulfide
50	33.57	Disulfide, methyl propyl
51	33.92	Butanoic acid, 2-methyl - propylester
52	34.80	Ethane, 1,1-bis(ethylthio)-
53	35.00	Hexanoic acid, ethyl ester
54	35.42	Disulfide, ethyl 1-methylethyl
55	37.33	Trisulfide, diethyl
56*	37.39	1,2,4-Trithiolane, 3,5-dimethyl-
57*	37.47	1,2,4-Trithiolane, 3,5-dimethyl-
58	37.70	Octanoic acid, ethyl ester

*Likely to be isomers and cannot be differentiated from mass spectra.

More PAL Turnkey Headspace Methods for Your Laboratory

BTEX and VOC Compounds according to EPA Method 502.2

See: Meggiolaro N., „BTEX and VOC Compounds according to EPA Method 502.2 are analysed using ITEX sample preparation technique", in: ITEX Dynamic Headspace Application Notes, CTC Analytics AG (2016).
https://www.palsystem.com/fileadmin/public/docs/Downloads/Application_notes/ITEX_Apps_Feb2016.pdf

VOCs from Groundwater

See: Jochmann M.A., Yuan X., et al. „In-tube Extraction (ITEX) for Extraction of Volatile Organic Hydrocarbons from Groundwater", in: ITEX Dynamic Headspace Application Notes, (2016). Anal. Chem. 2010, 82, 7641–7648.
http://www.ncbi.nlm.nih.gov/pubmed/20722393

VOCs in Water by HS-SPME and GC-MS

See: Kremser A., Jochmann M.A., Schmidt T.C. (2015) „PAL SPME Arrow—evaluation of a novel solid-phase microextraction device for freely dissolved PAHs in water". Anal Bioanal Chem 408 (3):943-952
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See: Devos C., David F., "Analysis of Suspected Flavor and Fragrance Allergens in Lotion Samples. A comparison between Static Headspace, SPME, HSSE and ITEX Headspace Sampling," in: ITEX Dynamic Headspace Application Notes, CTC Analytics AG (2016).
https://www.palsystem.com/fileadmin/public/docs/Downloads/Application_notes/ITEX_Apps_Feb2016.pdf

Arson Detection

See: Devos C., David F., „Arson Detection using ITEX Headspace Sampling", in: ITEX Dynamic Headspace Application Notes, CTC Analytics AG (2016).
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VOCs in Beer

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See: Rudy, H., Mosel, D. L. R. and Curvers, J. A. J. (2014) "Keeping Beer Tasting Fresh — Batch-to-Batch GC Quality Analysis and Quality Control", The Column, 10(1), pp. 20–23.

Metabolomic Signature of Brain Cancer

See: Pandey R., Caflisch L., et al. "Metabolomic signature of brain cancer", Mol. Carcinog. 2017, 56(11):2355-2371. DOI: 10.1002/mc.22694

eCigarette Juice Analysis

Chong C.M., Huebschmann H.-J. and Zhang N., "Fully Automated Analysis of E-Cigarette Juice", Poster at the ISCC 2020, Riva del Garda. https://www.palsystem.com/fileadmin/public/docs/Downloads/Application_notes/Fully_Automated_Analysis_of_E-Cigarette_Juice.pdf

Volatiles in Sea Buckthorn

Socaci, S. A. et al. (2013) "In-tube Extraction and GC–MS Analysis of Volatile Components from Wild and Cultivated Sea Buckthorn (Hippophae rhamnoides L. ssp. Carpatica) Berry Varieties and Juice", Phytochemical Analysis, 15. Jan. DOI: 10.1002/pca.2413.

Differentiation of Tomato Cultivars

Socaci S.A. , Socaciu C., et al., "Chemometric Discrimination of Different Tomato Cultivars Based on Their Volatile Fingerprint in Relation to Lycopene and Total Phenolics Content", Phytochemical Anal. (2014) 25(2), 161-169. https://doi.org/10.1002/pca.2483

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Zapata, J., Lopez, R. and Ferreira, V. (2012) "Multiple automated headspace in-tube extraction for the accurate analysis of relevant wine aroma compounds and for the estimation of their relative liquid–gas transfer rates". J. Chrom. A (1266) 1-9. https://doi.org/10.1016/j.chroma.2012.10.015

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Kaziur-Cegla, W., L Wykowski, et al. (2021) "In-tube dynamic extraction a green solventless alternative for a sensitive headspace analysis of volatile organic compounds in olive oils", Advances in Sample Preparation, 1(December), p. 100002. DOI: 10.1016/j.sampre.2021.100002.y

VOCs from Food Packaging

Pelagatti S., Gemme S., et al. "Unattended Quantitative Determination of VOCs in Food Packaging Samples Using a Robotic Sampler for Standard Addition and Analysis", PittCon 2012, Poster. https://tools.thermofisher.com/content/sfs/brochures/Unattended-Auto-Standard-Addition-and-Headspace-Analysis-for-the-Quant-of-VOCs-in-Food-Packaging.pdf

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