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Comprehensive comparative compositional study of the vapour phase of cigarette mainstream tobacco smoke and tobacco heating product aerosol☆

Benjamin Savareear[a], Juan Escobar-Arnanz[a], Michał Brokl[b], Malcolm J. Saxton[b], Chris Wright[b], Chuan Liu[b], Jean-François Focant[a,*]

[a] Centre for Analytical Research and Technologies (CART), University of Liege, Belgium
[b] Research and Development, British American Tobacco, Southampton, UK

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ABSTRACT

A simple direct sample collection/dilution and introduction method was developed using quartz wool and Tenax/sulficarb sorbents for thermal desorption and comprehensive two-dimensional gas chromatography (TD-GC × GC) analyses of volatile organic compounds from vapour phase (VP) fractions of aerosol produced by tobacco heating products (THP1.0) and 3R4F mainstream tobacco smoke (MTS). Analyses were carried out using flame ionisation detection (FID) for semi-quantification and both low and high resolution time-of-flight mass spectrometry (LR/HR-TOFMS) for qualitative comparison and peak assignment. Qualitative analysis was carried out by combining identification data based on linear retention indices (LRIs) with a match window of ±10 index units, mass spectral forward and reverse library searches (from LR and HRTOFMS spectra) with a match factor threshold of >700 (both forward and reverse), and accurate mass values of ± 3 ppm for increased confidence in peak identification. Using this comprehensive approach of data mining, a total of 79 out of 85 compounds and a total of 198 out of 202 compounds were identified in THP1.0 aerosol and in 3R4F MTS, respectively. Among the identified analytes, a set of 35 compounds was found in both VP sample types. Semi-quantitative analyses were carried out using a chemical class-based external calibration method. Acyclic, alicyclic, aromatic hydrocarbons and ketones appeared to be prominent in 3R4F MTS VP, whereas larger amounts of aldehydes, ketones, heterocyclic hydrocarbons and esters were present in THP1.0 aerosol VP. The results demontsrate the capability and versatility of the method for the characterization and comparison of complex aerosol samples and highlighted the relative chemical simplicity of THP1.0 aerosol in comparison to MTS.

1. Introduction

For the purpose of tobacco harm reduction, new generations of tobacco heating (heat-not-burn - HnB) products (THPs) were introduced in the market [1,2]. Such new electronically controlled heating devices significantly impact the global chemical composition of the aerosols, compared to conventional cigarettes. Despite the large amount of knowledge and standardised methods existing for the analysis of conventional cigarettes, very little information is currently available for THPs. In addition, some studies have reported the scientific assessment of THP based on target analyses of compounds typically found in combustible products [1,2] and only a few methods have been developed for the untargeted analysis of THP and combustible samples [3,4].

The mainstream tobacco smoke (MTS) that exits the filter of a cigarette is an extremely complex chemical mixture [5,6]. It consists of liquid/solid droplets called the particulate phase (PP), suspended in a mixture of gases and semi-volatiles called the vapour phase (VP). Apart from the bulk gases (nitrogen, oxygen, carbon oxides, nitrogen oxides, ammonia), VP also consists of VOCs and their importance on product cytotoxicity and carcinogenicity has been demonstrated in several cellular and animal systems [7]. Although it can be expected that THP aerosol is less complex than MTS, at present the chemical composition of the VP of THP aerosol has not been fully described [8]. Developing new qualitative and

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* Corresponding Author at: University of Liège, Chemistry Department – CART, Organic & Biological Analytical Chemistry, Allée du 6 Août B6c, B-4000, Liège, Belgium.
E-mail address: JF.Focant@uliege.be (J.-F. Focant).

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quantitative analytical methodologies capable of VP analyses for both THPs and MTS is therefore important to allow practical comparison.

MTS VP analyses require specific sampling strategies to ensure representative collection of the whole chemical profile across a very large dynamic range [5,9]. Various approaches, such as gas sampling bags [5], solid phase microextraction (SPME) [7], solvent-filled impinger trains [10], and cold traps [11] have been reported for this purpose. Direct sampling of VP on specific adsorbents has also been reported [12–14]. In the last few years, the use of adsorbents has increased in significance as thermal desorption (TD) capability has become more widely applicable and robust. Such a solvent-free technique offers several advantages over other solvent extraction methods that involve more manual steps and often suffer from reduced sensitivity due to multiple dilution steps before final measurement [15,16]. Amongst other applications [17,18] TD has recently been successfully used for the analysis of MTS VP of different cigarette types [5].

Comprehensive two-dimensional gas chromatography (GC × GC) coupled to time-of-flight mass spectrometry (TOFMS) is the established method of choice for detailed analysis of VOCs in medium-to-high complexity samples [17–19]. Advantages of the state-of-art GC × GC-TOFMS instrumentation have been described in several reports [17,20,21]. In the context of identification of unknowns, an important advantage of GC × GC is the spatial coordination of chemical classes in 2D chromatograms that provides a further identification point in addition to linear retention indices (LRIs), fragment ion and accurate mass MS data during the peak assignment process. In order to perform qualitative and semi-quantitative untargeted analyses, the simultaneous use of a flame ionisation detector (FID) and a TOFMS (dual detection) has been reported [21,22]. Despite the potential benefits of this approach in terms of speed and efficiency, relatively few reported applications involve such dual detection GC × GC instrumentation [23–28]. As GC × GC can now be more easily coupled to fast acquisition HRTOFMS, which offers mass accuracy at the sub-ppm level consistently on deconvoluted mass spectral signals, an extra dimension of elemental composition is made available for compound identification [29]. The utility of GC × GC-HRTOFMS is however constrained by the size of the acquired data files and associated data processing requirements [30,31]. Nevertheless, a GC × GC-HRTOFMS approach was successfully used for collecting accurate mass values (± 15 ppm) for increased confidence in peak identification of different hop essential oils [32].

In this study, we developed an original analytical method for the qualitative and semi-quantitative comparison of VOC constituents in the VP fraction of THP aerosol and combustible MTS. For this purpose, TD-GC × GC-TOFMS/FID and TD-GC × GC-HRTOFMS were used to maximize the identification confidence for the non-targeted screening approach.

2. Materials and methods

2.1. Analytical reagents and supplies

Saturated alkane standard solutions (C_5–C_{30}) were purchased from Sigma Aldrich (Diegem, Belgium). A custom standard mix made of benzene, toluene, 2-hexanone, p-xylene, styrene, bromobenzene and o-cresol, was prepared at concentrations of 0.25 and 0.5 μg/μL for the optimization of the split ratio between FID and TOFMS and the tuning of the recollection process. A custom standard mix (Supplementary Table S1) was prepared for building the calibration curves for semi-quantification purposes. All standards were purchased from Sigma-Aldrich (Diegem, Belgium), purity was >99.5%. All solutions were prepared volumetrically using methanol (Sigma-Aldrich) and stored at 4 °C. Quartz wool and Tenax/sulficarb stainless steel TD tubes were purchased from Markes (Pontyclun, UK).

2.2. Blank analysis procedure

Blank analysis were performed to ensure analytical systems were free from contaminations and that possible interferences were under control. All TD tubes were conditioned prior their use according to manufacturer's instructions. A blank test was always performed before use for each TD tube to check for possible carry-over. The smoking machines were located in separate rooms to avoid any interferences on the VOC profiles. Prior to sampling, air blank analyses were conducted on each smoking machine. For this a blank TD tube was placed in the smoking machine and the smoking procedure was run without tobacco consumables. For each recollection process, a blank run was always performed using blank TD tubes in the Unity-2 and recollection unit to check that the instrument was free of contamination. After this a chromatographic run sequence was made as follows: instrumental blank, smoking machine air blank, recollection procedure blank, and an instrumental blank prior analyses of unknown samples. This procedure was repeated for each sample and replicate analyses.

2.3. Sampling procedure

2.3.1. Samples and sample collection

The THP1.0 (glo™) device and consumables were provided by British American Tobacco (Southampton, UK). The description of THP1.0 device and sampling procedure details are illustrated in Fig. S1 (Supplementary Information). 3R4F research reference cigarettes were acquired from the University of Kentucky College of Agriculture (Kentucky Tobacco Research & Development Center, USA). THP consumables and reference cigarettes were conditioned in separate humidifier for at least 48 h at 60% relative air humidity and 22 °C [25]. For THP1.0 samples, VP aerosol samples were generated using a linear syringe drive system A14 (Borgwaldt KC GmbH, Germany). As no standard puffing regime has been defined for THP so far, all sample collections were conducted according to modified Health Canada Intense (HCI) puffing regime for cigarettes that consisted of bell-shaped puffs, each of 55 mL with puff duration of 2 s and with 30 s intervals between puffs [33] with air inlet zone not occluded. The number of puffs corresponds to the heating cycle available for THP1.0 used in the present study (8 puffs). One THP consumable was used for each analysis. For the 3R4F reference cigarette, MTS VP fraction was generated using a Borgwaldt RM20D smoking machine (Borgwaldt KC GmbH, Germany). Smoking was conducted according to the relevant ISO standards applying a 35 mL puff of 2 s duration taken every 60 s with no blocking of filter ventilation holes [34]. One reference cigarette was used for each analysis. Sampling procedure details are illustrated in supplementary Fig. S1. Routine airflow and puff volume measurements were performed prior to the smoke runs for each smoking machines. For TD sampling, two prepacked tubes (1st level) were connected in series, quartz wool TD tubes for trapping the total particulate phase (PP) fraction and Tenax/sulficarb TD tubes for trapping the VOC component of the vapour phase (VP) fraction. TD tubes were placed in between the consumable and the corresponding syringe pump of the smoking machines. The total volume of gas drawn through the sorbents for THP sampling was 440 mL for each analysis. The total volume of gas drawn through the sorbents for reference cigarette sampling was 280 mL for each analysis. TD tubes were capped with DiffLok® caps (Markes Ltd) directly after the sampling procedure was completed to preserve the integrity of samples.

2.3.2. VP fraction recollection/dilution process

The VP fraction of aerosol/smoke trapped on a TD tube was split across three 2nd level TD tubes filled with the same sorbent prior to the chromatographic injections to avoid overloading of chromatograms and contamination of the TD unit and GC column. For this purpose, a Recollect-10 device (SepSolve Analytical Ltd (Peterborough, UK) connected to Unity-2 TD unit through a heated transferline was used. This instrument is capable of recollecting gaseous samples across up to ten TD tubes at a time. The dilution procedure details are illustrated in supplementary Fig. S2. 1st level TD tubes were placed in the Unity-2 thermal desorber for two stages of desorption process. The pre-desorption stage consisted of 2 min of pre-purge of the sample tube at ambient temperature with a flow rate of 50 mL min^{-1}. During the tube desorption stage, the sample tube was desorbed at 320 °C for 10 min with a flow rate of 60 mL min^{-1} and the flow equally split across three tubes placed in the manifold. The manifold, transferline and flow path temperature were maintained at 200 °C. TD tubes were capped with DiffLok® caps (Markes Ltd) directly after the recollection procedure was completed and analysed immediately after using TD-GC × GC-TOFMS/FID and TD-GC × GC-HRTOFMS instruments.

2.4. Instrumental analysis

TD-GC × GC-TOFMS/FID analyses were performed using a LECO Pegasus 4D (LECO Corp., St. Joseph, MI, USA) GC × GC system equipped with a quad jet LN2 Cooled Thermal Modulator, a secondary GC oven, an Agilent Technologies (Santa Clara, CA, USA) capillary flow technology splitter, a thermal desorption unit (TD-100xr, Markes Ltd.), a LECO Pegasus time-of-flight mass spectrometer (TOFMS) and an Agilent Flame ionization detector (FID). TD-GC × GC-HRTOFMS analyses were performed using a LECO Pegasus GC-HRT 4D (LECO Corp.) system equipped with a quad jet LN2 Cooled Thermal Modulator, a secondary GC oven, a thermal desorption unit (TD-100xr, Markes Ltd.) and a LECO Pegasus high resolution time-of-flight mass spectrometer (TOFMS). A schematic overview of the TD-GC × GC-TOFMS/FID dual detection set-up and the TD-GC × GC-HRTOFMS set-up is given in supplementary information, Fig. S3.

2.4.1. Thermal desorption procedure

Sample TD tubes underwent three stages of desorption process. The pre-desorption stage consisted of 0.1 min of pre-purge of the sample tube at ambient temperature with a flow rate of 50 mL min^{-1}. During the tube desorption stage, the sample tube was desorbed at 300 °C for 8 min with a flow rate of 50 mL min^{-1}. Samples were recollected on a cold trap containing proprietary sorbent from Markes ('sulphur/labile' carbon number C_3-C_{30}) at a temperature of 25 °C. The cold trap plus sample was purged for 2 min at a flow rate of 50 mL min^{-1} to remove possible traces of undesirable water by diverting them to the vent port prior to sample desorption into the GC × GC instrument. The cold trap was desorbed at the maximum heating rate of 24 °C sec^{-1} from 25 °C to 315 °C, at which it was held subsequently for another 6 min A transfer line of 1.5 m deactivated fused silica column was connected between the TD-100xr and the GC column inlet and maintained at 200 °C. The split ratio for GC × GC-TOFMS/FID analysis was set to 1:50 and for GC × GC-HRTOFMS analysis was set to 1:100.

2.4.2. GC × GC-TOFMS/FID analyses

For all analyses a non-polar, 5% diphenyl 95% dimethyl polysiloxane phase (60 m × 0.25 mm i.d. × 0.5 μm df) (Rtx-5SilMS, Restek Corp., Bellefonte, PA, USA) was used as the first dimension (^{1}D) column. Two 30 m columns were connected to make a 60 m column. The second dimension (^{2}D) was a midpolar Crossbond® silarylene phase column exhibiting similar selectivity to 50% phenyl/50% dimethyl polysiloxane (1 m × 0.25 mm i.d. × 0.25 μm df) (Rxi®-17SilMS, Restek Corp.). All column connections, including the transfer line of TD to the ^{1}D column and two 30 m ^{1}D columns and ^{2}D column were made using SilTite™ μ-Unions (SGE International, Victoria, Australia). The effluent of the ^{2}D column was directed to an Agilent three-way capillary flow splitter and the effluent was split via restrictors R1 and R2 to the TOFMS and FID. A constant split pressure of 3.8 PSI was used for calculating the 1:1 split between the TOFMS/FID setup, corresponding restrictors (deactivated fused silica) were R_1: 2.78 m × 0.15 mm i.d. and R_2:0.53 m × 0.15 mm i.d. The carrier gas was helium at a corrected constant flow rate of 1.2 mL min^{-1}. The main oven temperature program started with an isothermal period at 40 °C for 5 min, then a ramp of 5 °C min^{-1} up to 300 °C, a final isothermal period at 300 °C for 3 min. The secondary oven was programmed with a 5 °C offset above the primary oven temperature. The modulation parameters consisted of a 3 s modulation period (P_M) (0.7 s hot pulse and 0.8 s cold pulse time) and a temperature offset of 15 °C above the secondary oven temperature. The FID temperature was 350 °C, using an air flow of 400 mL min^{-1}, hydrogen flow of 40 mL min^{-1} and a N_2 make up gas flow of 30 mL min^{-1}. The TOFMS was operated in electron impact mode using 70 eV, detector voltage was at 1800 V, ion source temperature was set at 230 °C, transfer line temperature was set at 250 °C and mass scan range *m/z* 35–500 at the acquisition rate of 100 spectra s^{-1}. Daily mass calibration and auto tuning were performed using perfluorotributylamine (PFTBA). Samples were acquired using ChromaTOF® (LECO Corp.) software version 4.50.8.

2.4.3. GC × GC-HRTOFMS analyses

^{1}D and ^{2}D columns were similar to TD-GC × GC-TOFMS/FID setup except the ^{2}D column was 1.5 m long in the TD-GC × GC-HRTOFMS setup. Since there was no splitter configuration in this instrument, the ^{2}D column effluent was directed to the mass spectrometer. The main oven temperature program started with an isothermal period at 40 °C for 5 min, then a ramp of 2.2 °C min^{-1} up to 130 °C, followed by a ramp of 2.8 °C min^{-1} to 300 °C and a final isothermal period at 300 °C for 3 min. Mass spectra were acquired in the range *m/z* 35–500 at the acquisition rate of 100 spectra s^{-1}, in a high resolution mode with a resolving power >25,000 FWHM for *m/z* 218.9851. Samples were acquired using LECO ChromaTOF®-HRT (LECO Corp.) software version 1.91. All other parameters were the same as for GC × GC-TOFMS/FID analyses.

2.5. Data processing

The scheme of data production and processing is illustrated in supplementary information, Fig. S4. TOFMS/FID data were exported as. peg and. csv files for both TOFMS and FID, respectively. These data were separately processed and summarised (retention times, peak areas, library comparison etc.) using the pixel-based GC Image™ (ZOEX Corp., Houston, TX, USA) software package version R2.5. For the analysis of VP and the comparison of samples, chromatograms were aligned following a procedure based on the creation of a template chromatogram that records peak patterns and carrying out resampling of the data to match retention times using GC Project™, part of the GC Image™ software package (Supplementary Fig. S5). The following blob detection criteria were used: area 22, volume 300,000 and SN > 200 were applied on each individual chromatogram for TOFMS and FID, based on a compromise between the number of detected signals and the quality of the recorded signals, the later depending strongly on peak shapes over the large dynamic range. For HRTOFMS data, peaks were matched using mass spectral and GC × GC structured chromatogram pattern (^1t_R and ^2t_R) information (Supplementary Information, Fig. S6).

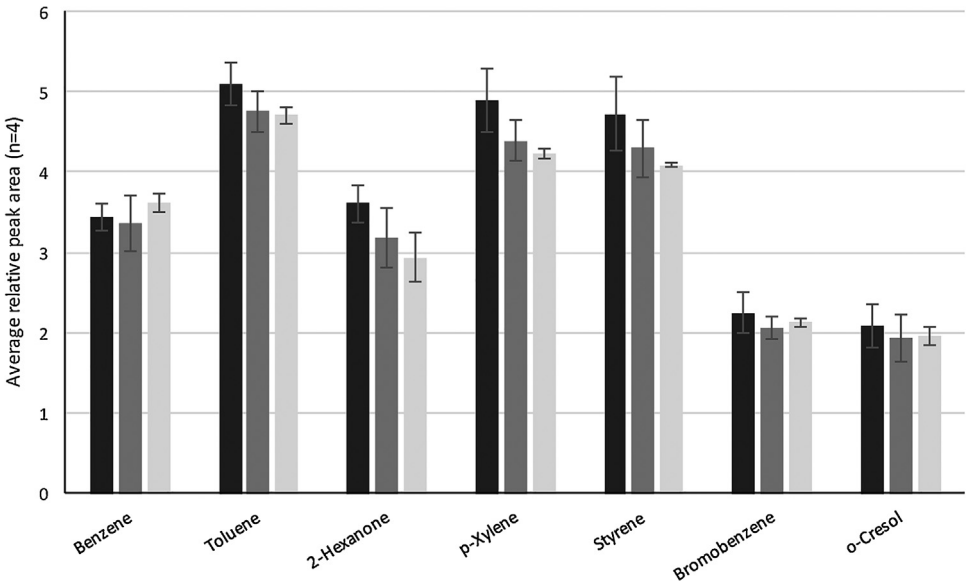

Fig. 1. Repeatability of the recollection process based on average peak area obtained from direct TD injection (Black), recollection over one TD tube (Grey), and three tubes (White) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Qualitative analysis was carried out using linear retention indices C_5-C_{25} (LRI window ±10) and mass spectral similarity/reverse match (similarity/reverse > 700 MS spectra match) against library spectra from LRTOFMS and HRTOFMS instruments. In addition, an accurate mass value of < ± 3 ppm was applied to give increased confidence for tentatively identified peaks as such mass accuracy values allowed to univocally attribute a molecular formula to most compounds of molecular weights below 200 Da [35]. Library searches of blobs/compounds (both TOFMS and HRTOFMS) were performed using NIST/EPA/NIH Mass Spectral Library (NIST 14) and Wiley Registry of Mass Spectral Data (9th edition) with a match factor threshold of >700. Further analyses of GC × GC–TOFMS/FID results using interactive LRI filters (±10 range) were performed using NIST/EPA/NIH Mass Spectral Library (NIST 14) database. If not available in the NIST14 database, WEB based RI collections (PubChem) information was used [36].

3. Results and discussion

3.1. Method development

3.1.1. Thermal desorption sampling

Based on a previous study [5] thermal desorption (TD) was used as a unique approach to accommodate the chemical complexity and the large dynamic range covered by components of MTS and THP samples. Despite the fact that sample production from THP and combustible products requires different apparatus, whole smoke/aerosol TD sampling was carried out by placing a set of TD tubes in the output stream (Supplementary Fig. S1). At first, a single TD tube (Tenax/sulficarb) was used but breakthrough was observed (data not shown), even on a single puff basis. Based on recent research [5], we included glass fiber filter pads (Cambridge filter pads, CFP) which resolved the breakthrough issue (Supplementary Information, Fig. S7). To simplify the process the CFP was replaced by a TD tube containing quartz wool, creating a sample train that comprised a first level tube (Tube 1) containing quartz wool for particulate phase (PP) trapping and another first level tube (Tube 2) containing Tenax/sulficarb for VP trapping. The impact on back pressure and airflow of two TD tubes between the product and the puffing machine was minimized (<10 mL/min) by limiting the quantity of packed quartz wool to 700 mg/tube. The efficiency of sampling was evaluated by monitoring potential breakthrough of compounds using a third tube placed after the Tube 2. Under the above set up there was no breakthorugh for both THP1.0 V P and 3R4F MTS VP samples, which is a significant factor to consider for comparison of the samples (Supplementary Information, Fig.S8).

The emissions from a whole consumable were collected in order to manage known variations between individual puffs. This resulted in highly concentrated samples that required dilution before TD-GC × GC-TOFMS/FID analysis to prevent overloading of instruments and carry-over between samples. The recollection/dilution procedure (Supplementary Information, Fig. S2) was also optimized to prevent breakthrough on the recollection tubes and to allow quantitative dilution of the samples. As illustrated in Fig. 1 for a set of representative compounds, acceptable losses were observed when a TD tube containing a sample was recollected onto one or three TD tubes. The average loss based on peak areas was 9% and ranged between 4% (Benzene) and 19% (2-Hexanone), with RSDs ranging between 4% (Toluene) and 13% (o-Cresol).

The potential impact on sample integrity of the storage of TD tubes prior to analysis was evaluated by monitoring peak areas of a set of selected analytes (2-Methylbutane, 2-Butanone, Benzene, Dimethylfurane, 2-Hexanone, Pyridine, Ethylbenzene, Styrene, Limonene) over time. Peak areas did not significantly vary (<20%) over a period of five days. Nevertheless, samples were always analysed within 48 h of collection on TD tubes. Tube desorption conditions were optimized to ensure the complete transfer of all analytes from the TD tube to the ^{1}D GC column. This was systematically controlled by monitoring blank levels of TD tubes and of the thermal desorber cold trap.

3.1.2. Chromatography

The TD-GC × GC-TOFMS/FID instrumental set-up (Supplementary information, Fig. S3) was optimized by using a constant split pressure approach. The desired split ratio (1:1) was maintained during the whole temperature program by calculating column flows of both restrictors. The split ratio was validated by replicate (n = 6) sequential analysis of a test mixture by single (FID) and dual detection (FID and TOFMS). Ratio of average peak areas of the single and dual detection analysis demonstrated the efficient 1:1 split ratio (Supplementary information, Fig. S9) with excellent repro-

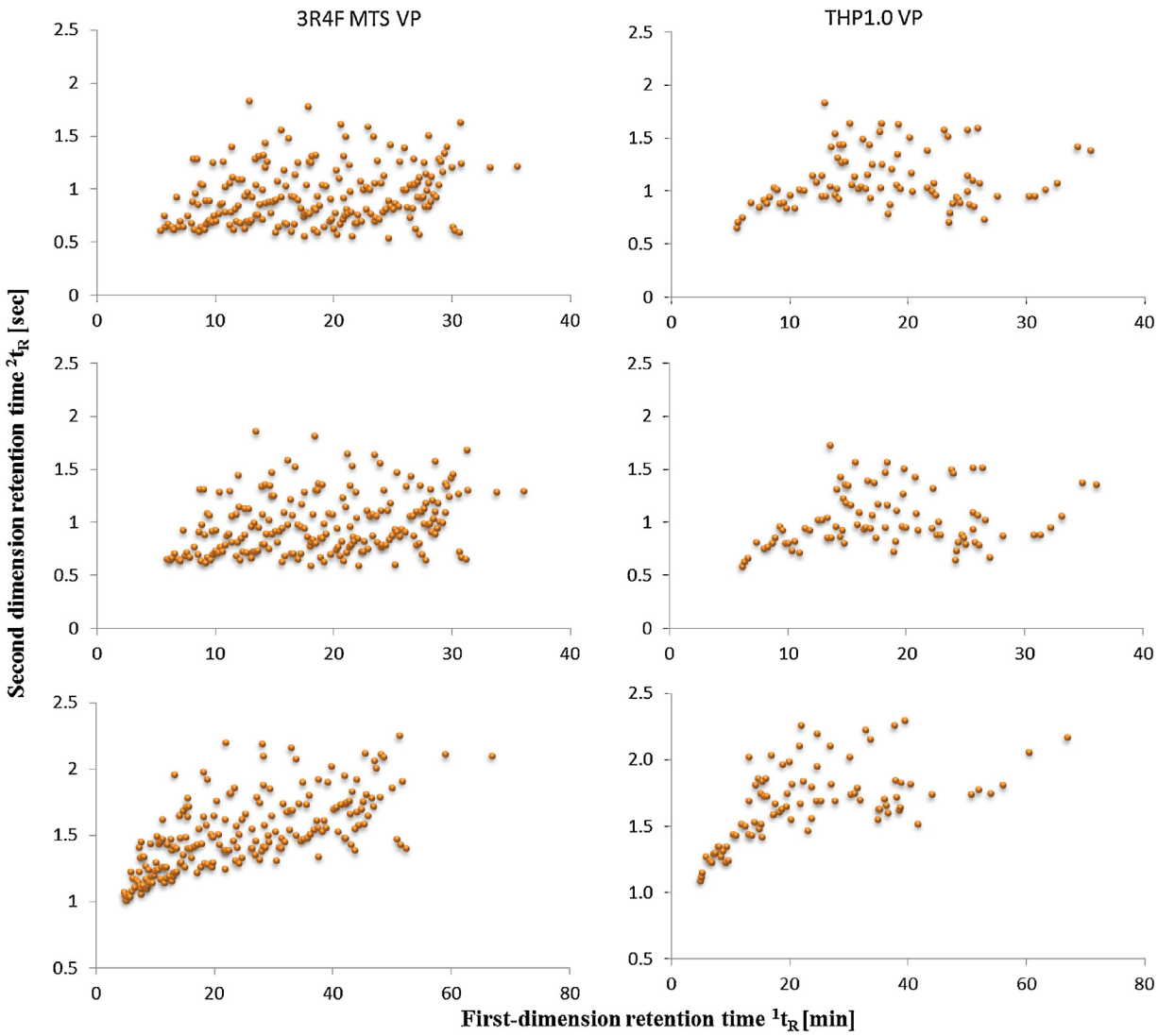

Fig. 2. Apex plot of vapour phase sample from 3R4F MTS and THP1.0 aerosol obtained from FID (top), LRTOFMS (middle) and HRTOFMS (bottom).

duciblity (average ratio of 0,496 ± 0,03; RSD values from 4,1% to 8,7%).

The chromatograms (three individual chromatograms from three second level TD tubes) were processed for both FID and LRTOFMS separately (Supplementary Information, Fig. S5). After manually cleaning the images from column bleed, artifact peaks and mutliple hits due to peak tailing effects for highly abundant compounds, they were manually matched on a compound-by-compound basis using first and second dimension retention time (^1t_R and ^2t_R) matching. Under this approach, the total numbers of peaks found to be present in the VP fraction of THP1.0 and MTS were 88 and 207, respectively. Fig. 2 shows the reconstructed chromatograms (apex plots) obtained for TD-GC × GC-TOFMS/FID and used for data processing.

In order to also combine high accuracy MS data to compound identification, the TD- GC × GC-TOFMS/FID method was transposed to TD-GC × GC-HRTOFMS. Although it might be considered a trivial step, the transposition of chromatographic methods between vacuum outlet instruments from one that includes splitting of the flow to another that uses a significantly longer transfer line (Supplementary Information, Fig. S3) was not straightforward. Despite all efforts (variations of flows, column dimensions and coating, and other GC × GC operational conditions) it appeared to be impossible to obtain chromatograms that align retention times between LRTOFMS and HRTOFMS.

The TD-GC × GC-HRTOFMS apex plots shown in Fig. 2 for THP1.0 and 3R4F MTS represent the best compromise that could be obtained in terms of run time and chromatographic resolution. Each of the HRTOFMS signals was matched with the corresponding FID/LRTOFMS signal. This required significant manual intervention to locate the corresponding peak based on first dimension linear retention index, position of the peak in the second dimension retention plane and mass spectral data for each compound. Despite the technical challenges explained above, the FID, LRTOFMS and HRTOFMS signals of 88 and 207 compounds were matched for THP1.0 and 3R4F MTS, respectively.

The developed analytical method was capable of analysing molecules in the range of C_4-C_{25}. However, a limited number of unresolved (Supplementary Information, Fig. S10) compounds eluting before the C_5 region were not considered further because of the lack of linear retention index information and a lack of fragment ions below *m/z* 35 giving inaccurate peak assignment against library match. A dedicated analytical methodology coupled to the use of standards would be required to consider analytes below the C_5 region but was out of the scope of the present study. When considering the region above C_5, 85 and 202 compounds were selected for

Table 1
Qualitative and semi-quantitative results of vapour phase fraction of THP1.0 aerosol.

Peak No.	Compound name	Chemical formula	FID			LRTOFMS		HRTOFMS			
			LRI	$LRI_{lib.}$	Amount (μg/stick) [a]Mean ± SD	MS forward match	MS reverse match	MS forward match	MS reverse match	Mass accuracy (ppm)	Chemical class
1	2-Propanone*/	C_3H_6O	519	509	13.3 ± 0.15	964	964	886	899	1.4	8
2	Acetic acid, methyl ester	$C_3H_6O_2$	545	536	3.9 ± 0.28	952	960	963	963	−1.1	9
3	Carbon disulfide	CS_2	555	549	0.3 ± 0.04	899	944	960	989	−1.5	11
4	Propanal, 2-methyl-*	C_4H_8O	565	561	8.4 ± 0.13	967	967	933	933	−1.0	7
5	2-Propenal, 2-methyl-*	C_4H_6O	573	567	5.4 ± 0.24	962	962	940	940	−0.4	7
6	2,3-Butanedione*	$C_4H_6O_2$	588	595	15.7 ± 0.21	885	891	963	974	−1.4	8
7	2-Butanone*/$	C_4H_8O	595	598	1.2 ± 0.08	966	966	832	929	−1.0	8
8	Furan, 2-methyl-*	C_5H_6O	600	606	3.1 ± 0.09	929	934	960	960	−1.0	3
9	Furan, 3-methyl-*	C_5H_6O	609	614	0.7 ± 0.02	762	785	799	884	−0.7	3
10	Unknown	–	618	–	0.1 ± 0.00	–	–	–	–	–	13
11	Propanoic acid, methyl ester	$C_4H_8O_2$	626	627	0.3 ± 0.03	856	856	849	897	−0.3	9
12	1,3-Pentadiene, 3-methyl-, (E)-*	C_6H_{10}	638	643	0.6 ± 0.05	865	878	744	864	−0.3	1
13	Butanal, 3-methyl-*	$C_5H_{10}O$	652	652	7.4 ± 0.02	952	952	942	942	−0.4	7
14	Butanal, 2-methyl-	$C_5H_{10}O$	662	662	5.9 ± 0.24	953	953	944	947	−0.6	7
15	1-Penten-3-one	C_5H_8O	685	681	0.3 ± 0.03	899	899	720	764	0.0	8
16	2,3-Pentanedione*	$C_5H_8O_2$	694	698	5.2 ± 0.09	945	948	953	958	−0.5	8
17	Furan, 2,5-dimethyl-*	C_6H_8O	706	707	trace	941	962	959	959	−0.4	3
18	2-Butanone, 3-hydroxy-	$C_4H_8O_2$	706	706	1.2 ± 0.14	885	892	973	980	−0.2	8
19	Thiocyanic acid, methyl ester*	C_2H_3NS	713	711	1.6 ± 0.25	907	907	959	967	−0.7	9
20	2,4-Dimethylfuran*	C_6H_8O	715	711	0.2 ± 0.01	838	856	952	952	−0.8	3
21	2-Vinylfuran*	C_6H_6O	725	725	0.3 ± 0.01	886	893	928	930	−0.1	3
22	Propanoic acid, 2-oxo-, methyl ester	$C_4H_6O_3$	727	722	0.6 ± 0.06	927	959	958	958	−0.1	9
23	1-Butanol, 3-methyl-	$C_5H_{12}O$	734	736	0.1 ± 0.01	826	879	903	911	1.5^	6
24	pyrazine	$C_4H_4N_2$	735	736	0.2 ± 0.01	958	958	967	967	−0.3	3
25	2-Pentanone, 4-methyl-*	$C_6H_{12}O$	739	735	0.1 ± 0.00	726	766	–	–	1.2	8
26	1H-Pyrrole, 1-methyl-*	C_5H_7N	741	743	1.0 ± 0.01	948	948	936	940	0.3	3
27	Unknown	–	743	–	trace	–	–	–	–	–	13
28	Pyridine*/$	C_5H_5N	746	746	1.8 ± 0.25	959	963	969	969	−0.8	3
29	Disulfide, dimethyl*	$C_2H_6S_2$	748	746	2.1 ± 0.04	960	961	967	967	−2.5	11
30	1H-Pyrrole	C_4H_5N	752	755	2.3 ± 0.31	926	949	948	954	−1.4	3
31	2-Pentenal, (E)-	C_5H_8O	757	754	1.8 ± 0.06	900	900	875	875	−0.6	7
32	1,4-Dioxin, 2,3-dihydro-	$C_4H_6O_2$	767	680#	0.2 ± 0.01	748	757	806	815	−0.6	12
33	Toluene*/$	C_7H_8	771	770	0.4 ± 0.02	917	927	949	958	−0.2	4
34	Thiophene, 3-methyl-*	C_5H_6S	776	776	0.2 ± 0.01	708	814	801	818	−0.4	3
35	3-Hexanone	$C_6H_{12}O$	785	784	0.3 ± 0.02	935	935	950	952	−0.2	8
36	2-Hexanone*$	$C_6H_{12}O$	790	790	0.1 ± 0.01	783	805	903	903	1.0	8
37	Cyclopentanone*	C_5H_8O	794	791	0.1 ± 0.01	971	971	935	945	0.2	8
38	Hexanal	$C_6H_{12}O$	800	800	0.9 ± 0.14	905	905	810	837	2.4^	7
39	2,4-Pentanedione	$C_6H_{12}O$	804	795	0.1 ± 0.00	880	915	757	768	−0.3	8
40	3(2 H)-Furanone, dihydro-2-methyl-	$C_5H_8O_2$	808	809	1.5 ± 0.17	947	947	954	954	−0.4	9
41	Furan, 2-ethyl-5-methyl-*	$C_7H_{10}O$	810	802	0.2 ± 0.01	773	783	777	789	−0.8	3
42	1H-Pyrrole, 1-ethyl-*	C_6H_9N	816	821	0.2 ± 0.01	892	892	906	906	−0.1	3
43	2,5-Furandione	$C_5H_6O_2$	831	830	0.6 ± 0.09	726	906	737	879	1.2^	9
44	2-Vinyl-5-methylfuran*	C_7H_8O	832	826	0.5 ± 0.06	909	959	883	924	−0.5	3
45	2-Furancarboxaldehyde	$C_5H_4O_2$	835	833	15.7 ± 0.23	957	957	950	950	−1.8	7

46	Vinyl crotonate	$C_6H_8O_2$	836	783#	0.3 ± 0.04	755	815	765	850	0.1	9
47	1,3-Cyclopentadiene, 5-(1,1dimethylethyl)-	C_9H_{14}	849	839	1.0 ± 0.01	777	845	863	864	−0.5	2
48	2,5-Diethylfuran	$C_8H_{12}O$	855	888#	0.1 ± 0.01	854	854	777	856	−0.0	3
49	2-Hexenal, (E)-	$C_6H_{10}O$	857	854	trace	864	969	918	923	0.2	7
50	p-Xylene*$	C_8H_{10}	869	865	trace	758	889	880	880	0.3	4
51	1H-Pyrrole, 2,5-dimethyl-	C_6H_9N	870	867	0.2 ± 0.02	772	828	864	867	−0.0	3
52	2(3 H)-Furanone, 5-methyl-	$C_5H_6O_2$	873	873	0.6 ± 0.04	907	933	931	935	−0.1	9
53	o-Xylene*	C_8H_{10}	877	881	0.3 ± 0.00	936	947	953	953	−0.4	4
54	Bicyclo[3.1.0]hexan-2-one	C_6H_8O	897	793#	0.1 ± 0.01	763	778	831	835	0.1	8
55	Styrene*″$	C_8H_8	900	893	0.1 ± 0.01	797	911	889	919	−0.4	4
56	Heptanal	$C_7H_{14}O$	904	901	0.1 ± 0.01	730	782	892	911	−0.5^	7
57	2-Methyl-5-isopropenylfuran	$C_8H_{10}O$	938	933	0.2 ± 0.00	854	854	847	921	−0.8	3
58	6,8-Dioxabicyclo[3.2.1]octane	$C_6H_{10}O_2$	939	839#	0.2 ± 0.02	834	850	796	796	−0.2	12
59	Oxepine, 2,7-dimethyl-	$C_8H_{10}O$	949	944	0.2 ± 0.00	786	786	782	782	−0.6	3
60	1H-Pyrrole, 1-butyl-	$C_8H_{13}N$	953	975#	0.1 ± 0.00	855	867	812	849	−0.7	3
61	2-Heptanone, 6-methyl-	$C_8H_{16}O$	957	953	0.1 ± 0.00	753	832	931	933	1.1^	8
62	Benzaldehyde*	C_7H_6O	978	971	0.1 ± 0.10	936	936	898	919	−0.3	7
63	Dimethyl trisulfide*	$C_2H_6S_3$	986	984	0.4 ± 0.03	941	941	919	924	−0.2	11
64	beta-Myrcene	$C_{10}H_{16}$	989	991	0.4 ± 0.01	929	965	873	877	0.7^	1
65	Furan, 2-pentyl-	$C_9H_{14}O$	992	993	0.2 ± 0.01	924	924	909	912	−0.4	3
66	Unknown	–	997	–	trace	–	–	–	–	–	13
67	Octanal	$C_8H_{16}O$	1008	1003	trace	831	851	894	905	0.8^	7
68	Unknown	–	1012	–	trace	–	–	–	–	–	13
69	delta-3-Carene*	$C_{10}H_{16}$	1017	1011	0.9 ± 0.05	850	891	847	851	−0.5	2
70	o-Cymene*	$C_{10}H_{14}$	1035	1026	trace	874	952	950	950	0.0	4
71	Benzene, 1,2,3-trimethyl-	C_9H_{12}	1035	1033	0.1 ± 0.00	776	871	923	923	−0.0	4
72	Benzylamine	C_7H_9N	1036	1035	trace	753	829	855	855	−0.5	4
73	Limonene*	$C_{10}H_{16}$	1039	1030	1.0 ± 0.01	860	885	880	880	−0.2	2
74	Cyclohexanone, 2,2,6-trimethyl-	$C_9H_{16}O$	1048	1047	0.1 ± 0.01	759	848	815	905	0.1	8
75	trans-beta-Ocimene*	$C_{10}H_{16}$	1052	1049	0.4 ± 0.06	812	891	–	–	2.6	1
76	Benzeneacetaldehyde	C_8H_8O	1061	1060	1.6 ± 0.29	808	929	952	956	−0.7	7
77	4-tert-Butyltoluene	$C_{11}H_{16}$	1067	1066	0.1 ± 0.01	802	816	–	–	0.9	4
78	Unknown	–	1079	–	trace	–	–	–	–	–	13
79	Nonanal	$C_9H_{18}O$	1113	1109	0.1 ± 0.01	766	779	888	888	1.4^	7
80	1-Methoxyadamantane	$C_{11}H_{18}O$	1198	1179#	0.1 ± 0.00	786	796	766	786	1.3	12
81	Decanal	$C_{10}H_{20}O$	1216	1214	0.1 ± 0.00	–	–	844	875	0.4^	7
82	Unknown	–	1247	–	trace	–	–	–	–	–	13
83	Trimethyl-tetrahydronaphthalene	$C_{13}H_{18}$	1279	1250#	0.9 ± 0.02	906	940	832	845	1.0	5
84	Triacetin	$C_9H_{14}O_6$	1343	1344	0.1 ± 0.00	785	902	915	915	−1.0^	9
85	Naphthalene, 1,3-dimethyl-*	$C_{12}H_{12}$	1385	1385	0.7 ± 0.01	–	–	899	899	−1.0	5

[a]sample mean (n = 4) along with standard deviation of the measurements, * compounds found in reference cigarette smoke VP sample, ″ compounds found in Hoffmann list, $ compounds were positively identified using their respective standard, - information not available, trace- concentration below 0.1 μg/stick, # estimated non-polar retention index from NIST database, but semi-standard column retention index information not available from searched libraries database, ^base peak or characteristics peak mass accuracy values due to the absence or weak molecular ion, chemical classes labelled herein numerical defined in Tables 2 or S1.

qualitative and quantitative investigation in THP1.0 V P and 3R4F MTS VP, respectively.

3.2. Comparisons of VP aerosol fraction from THP1.0 and 3R4F MTS

3.2.1. Qualitative aspects using low and high resolution TOFMS

Qualitative analysis of the VP fraction of THP1.0 aerosol and MTS was carried out using several identification criteria such as retention times (^1t_R and ^2t_R) of available authentic reference standards, ^1t_R linear retention index matches (±10 window), and mass spectral forward and reverse similarity matches (>700) against spectral libraries for both TOFMS and HRTOFMS data. In addition, accurate mass information within ± 3 ppm window based on either parent ions or abundant fragments (limited cases) was employed to improve the confidence of identification of compounds. As seen in Tables 1 and S2, in some limited cases, either LRI data were not available or the MS match factor was not obtained from either the low or high resolution mass analyser because of interfering ions, but peak assignment was always backed up by at least good MS match (>700) on the other MS analyser and good mass accuracy (< ± 3 ppm) values. In addition, the spatial coordination of homologous series of compounds in GC × GC chromatograms aided further confirmation of identities.

As expected, reverse library matches (ranged 757–971 and 764–989 for LRTOFMS and HRTOFMS, respectively) were slightly better than forward matches (ranged 708–971 and 720–973 for LRTOFMS and HRTOFMS, respectively) and HRTOFMS matches were globally better than LRTOFMS matches, even though MS libraries are made of LRMS data sets. This can be explained partly by the higher mass resolution of the HRTOFMS instrument, which provides narrower mass windows and reduces the impact of interfering ions from co-eluting species and background noise [37].

Because of the operation of the HRTOFMS in electron impact mode (70 eV) to provide the desired fragmentation for MS library search purpose, for some compounds the abundance of the molecular ion was very low. This was particularly the case for alkanes, aldehydes, alcohols and nitriles, for which the most abundant fragment ion was used to estimate mass accuracy, as reported earlier [32]. The use of a softer ionisation technique such as UV-based photo-ionisation (PI) is currently under investigation in other projects and may improve MS data quality for fragment ions and molecular ions [38]. In practice, 82% and 94% of the identified analytes presented a usable molecular ion for identification for THP1.0 and 3R4F MTS, respectively. Among these, 70% of the assigned peaks exhibited a mass accuracy of ± 1 ppm, for both sample types while 15% and 25% of assigned peaks exhibited a mass accuracy between ±1 and ± 3 ppm for THP1.0 and 3R4F MTS, respectively. Despite the high added value of accurate mass to MS library comparisons for identification of compounds [39], the unequivocal identification of compounds present in different isomeric forms still requires the use of LRIs and ideally the analysis of pure standard compounds, which is difficult to implement in non-targeted studies. By applying the comprehensive data mining strategies described previously 79 (out of the 85) (Table 1) and 198 (out of the 202) compounds were identified in the THP1.0 aerosol VP and 3R4F MTS VP (Supplementary Table S2), respectively. The remaining few compounds could not be identified at this stage. Nevertheless, for both THP1.0 V P and 3R4F MTS VP samples, it constitutes the first comprehensive list of VOCs composing their chemical profile. Previously, a TD-GC × GC-TOFMS approach was able to tentatively identify 127 compounds [5]. When compared to our current approach that was able to identify 181 compounds in the carbon number range C_6-C_{14}, a set of 56 compounds were found to be common to both studies (Table S2).

When we consider the identified compounds of THP1.0 V P and 3R4F MTS VP samples, 35 compounds were common to both THP1.0 aerosol VP and 3R4F MTS VP samples and are highlighted in Table 1 and in Supplementary information, Table S2. The identified compounds were further grouped in chemical classes (Table 2) to highlight major chemical differences between the two types of aerosol VP. It appeared that the higher chemical complexity of 3R4F MTS samples (202 compounds versus 85 compounds for THP1.0 aerosol VP) was mainly due to the large number of acyclic, alicyclic and monocyclic aromatic hydrocarbons. In 3R4F MTS VP, these three chemical families accounted for 71% of the 202 compounds found. For THP1.0 V P, these three chemical families accounted for 16% of the 85 compounds found, while heterocyclics, aldehydes and ketones accounted for 53%. These data illustrate the chemical difference between the VP produced by combustion and pyrolysis of tobacco and the VP of an aerosol produced by lower temperature heating of tobacco [4]. Interestingly, it also appeared that, among the so-called 'Hoffmann list' of 44 compounds of prime interest in terms of toxicity, seven and six analytes were present in VP samples generated in 3R4F MTS (Supplementary Information, Table S2) and THP1.0 aerosol (Table 1), respectively. Among them, there were 5 common compounds (2-propanone, 2-butanone, pyridine, toluene and styrene).

3.2.2. Semi-quantitative analysis using FID

FID/TOFMS dual detection was intended to facilitate semi-quantitative analysis of the samples. Tobacco-related samples contain hundreds of compounds over several orders of magnitude of concentration [5,40]. This presents a challenge for mass analysers that have linear dynamic ranges limited to 3 or 4 decades. After robust assignment of compound identities based on (HR)TOFMS, FID signals were used for semi-quantification [21,22]. Because of the non-targeted nature of analysis, a generic, external calibration was constructed using representative compounds from thirteen chemical classes (Supplementary Information, Table S1). The selection of standard compounds was based on the assigned VOC chemical classes in VP fractions of THP1.0 aerosol and 3R4F MTS samples. The calibration range was based on detectability of both FID and TOFMS detectors (data not shown). The lowest point was set at 0.1 μg/μL, lower concentrations were reported as traces. The highest point (50 μg/μL) was set after measuring THP1.0 V P samples. Three compounds in 3R4F MTS VP (Table S2) were out of that range, thus these compounds concentrations were estimated from an extention of the calibration plot. Compounds were semi-quantified using the response factor obtained for the representative substance of the same class in the calibration solution after normalisation between samples and calibration using another external standard to address potential instrumental drift. If no representative compound was included in calibration, non-classified compounds (organosulfur, miscellaneous and unknowns) were semi-quantified using the factors obtained for bromobenzene, acetonitrile and p-xylene, respectively.

The results of the external 9-point calibration (n = 4) at the μg/μL level demonstrated acceptable reproducibility (RSD% < 6%, range 3–6%) for all compounds (Supplementary Information, Table S1). Semi-quantitative results for chemical classes identified in the vapour phase fractions of THP1.0 aerosol and 3R4F MTS are presented in Table 2.

Fig. 3 illustrates the differences in chemical composition and abundance between THP1.0 V P and 3R4F MTS VP samples. THP1.0 V P generally contained lower abundances of the less volatile components of chemical classes, which would be expected when considering the temperatures at which the aerosols were formed. The major THP1.0 V P classes were aldehydes, ketones, esters and heterocyclic compounds. In 3R4F MTS VP, hydrocarbons, ketones, and heterocyclic compounds were more abundant and spanned a wider range of volatility.

Table 2
Summary of qualitative and semi-quantitative information for VP samples of THP1.0 aerosol and 3R4F cigarette smoke with their respective relative percentage.

		THP1.0 V P				3R4F MTS VP			
Chemical class	Chemical class name	No. of analytes	Relative % of analyte	Amount (μg/stick)	Relative % of amount	No. of analytes	Relative % of analyte	Amount (μg/stick)	Relative % of amount
1	Acyclic hydrocarbons	3	4	1.4	1	70	35	496.8	40
2	Alicyclic hydrocarbons	3	4	2.8	2	41	20	173.1	14
3	Heterocyclic compounds	18	21	11.9	10	17	8	69.4	6
4	Monocyclic aromatic	9	11	1.1	1	33	16	119.0	10
5	hydrocarbons	2	2	1.6	1	3	1	2.4	0
6	Polycyclic aromatic	1	1	0.1	0	ND	ND	0.0	0
7	hydrocarbons	14	16	48.3	41	7	3	57.6	5
8	Alcohols	14	16	37.9	32	14	7	264.4	22
9	Aldehydes	9	11	9.5	8	1	0	2.5	0
10	Ketones	ND	ND	0.0	0	8	4	36.8	3
11	Esters	3	4	2.8	2	2	1	4.7	0
12	Nitriles	3	4	0.2	0	2	1	1.2	0
13	Organosulfur compounds	6	7	0.1	0	4	2	1.0	0
	Miscellaneous compounds								
	Unknowns								

ND-not detected.

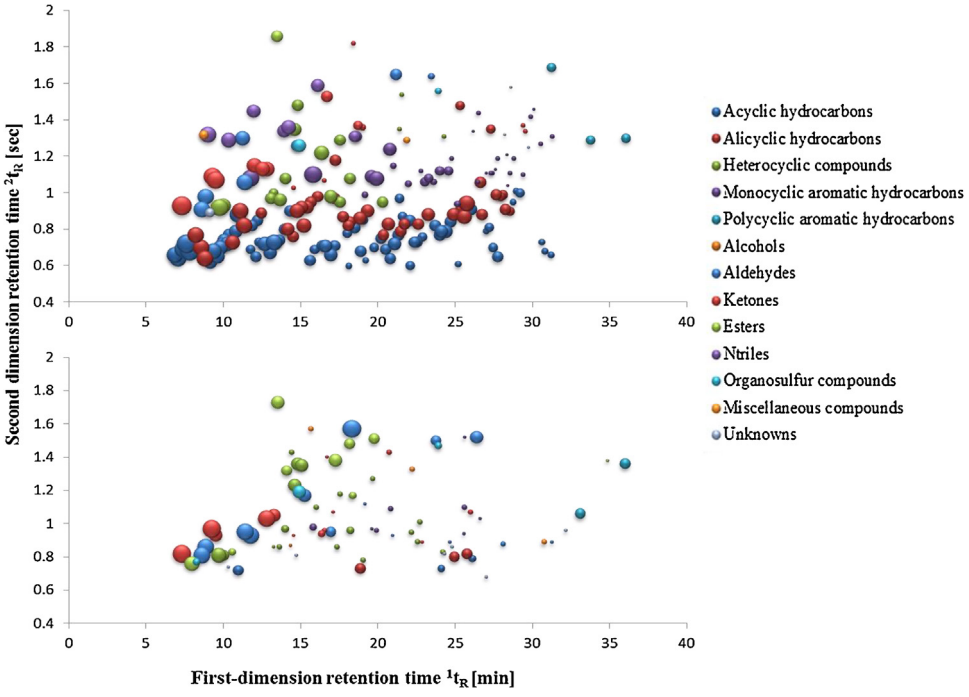

Fig. 3. TD-GC × GC-LRTOFMS two-dimensional apex bubble plot illustrating the difference in relative chemical complexity between 3R4F MTS (top) and THP1.0 aerosol (bottom). Bubble sizes are related to levels of analytes. For data visualisation purpose, bubble sizes were rescaled based on concentration intervals: <0.1 μg = 1; 0.1-0.25 μg = 2.5; 0.25-0.5 μg = 5; 0.5–1 μg = 10; 1–2.5 μg = 15; 2.5–5 μg = 20; 5–10 μg = 25; 10–25 μg = 30; 25–50 μg = 35; 50–100 μg = 40; >100 μg = 60 (see Tables 1 and S2 for detailed values).

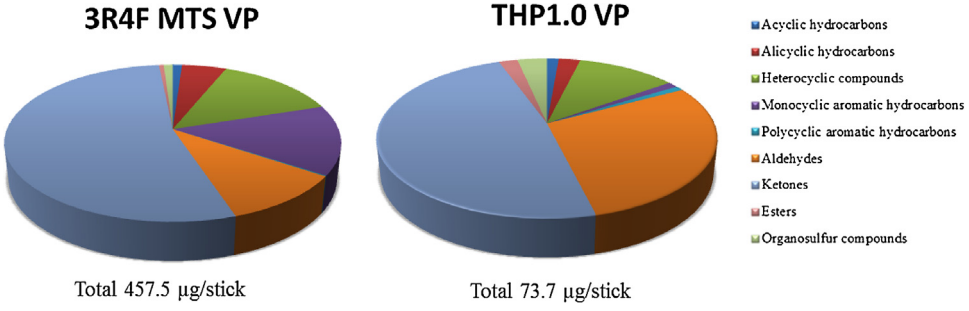

Fig. 4. Illustrating the distribution of chemical concentration based on their chemical classes for compounds found in both THP1.0 V P and 3R4F MTS VP samples.

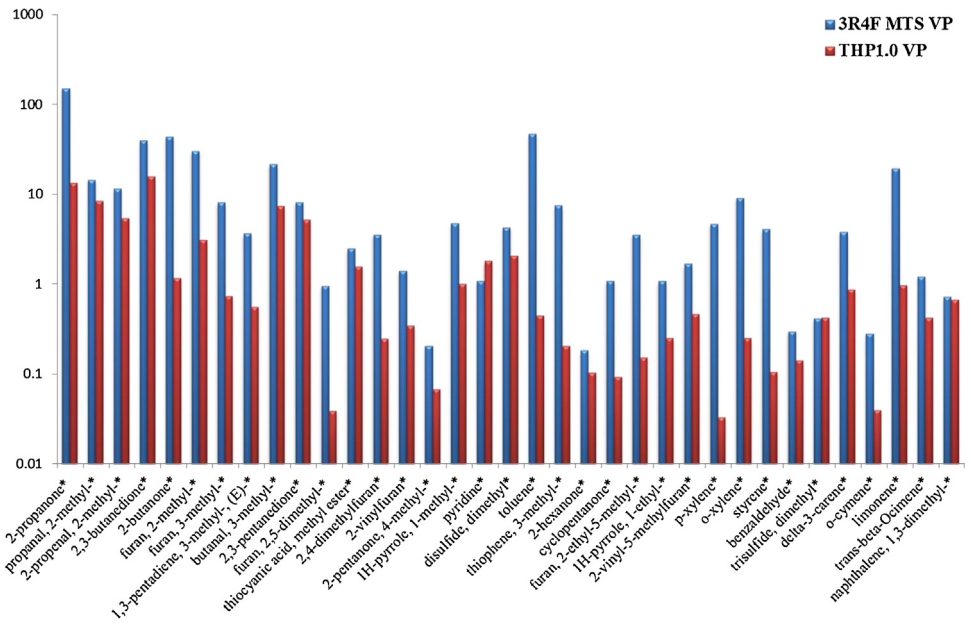

Fig. 5. Differences of chemical concentration of 35 overlapping compounds found in both 3R4F MTS VP and THP1.0 V P samples. Y-axis inserted as logarithmic scale for data visualisation purpose (actual values are provided in Tables 1 and S2).

The total abundance of compounds present in the VP fraction of 3R4F MTS was estimated to be ten times greater than in THP1.0 aerosol VP. In 3R4F MTS VP, acyclic, alicyclic and monocyclic aromatic hydrocarbons accounted for 64% in terms of the total estimated concentration. For THP1.0 V P, these three chemical families represented less than 4% of the total estimated concentration. Aldehydes, ketones, and heterocyclics accounted for 41%, 32% and 10% respectively of the total estimated concentration of analytes in THP1.0 V P. Table 1 (and Supplementary information, Table S2) provides individual semi-quantitative values in μg per consumable (stick) for each assigned compound. Fig. 4 illustrates the chemical distribution of the 35 compounds present in both sample types. The summed concentration of these 35 compounds was six times higher in 3R4F MTS VP (457.5 μg/stick) than in THP1.0 V P (73.7 μg/stick). When considering relative amounts, of the 35 common compounds found in THP1.0 and 3R4F MTS products, higher concentrations were systematically measured in MTS, on a whole product basis, except for pyridine and dimethyl trisulfide (Fig. 5). In these two cases, the levels in THP1.0 appeared to be marginally higher but confirmation of any difference would require quantitative analysis. Finally, in terms of semi-quantification, 2-propanone (one of the 'Hoffmann list' toxicants) was present at significantly lower concentrations in THP1.0 V P samples (13.3 μg/stick) than in 3R4F MTS VP (152 μg/stick). Similarly, the concentrations of other Hoffmann list compounds (e.g. toluene, 2-butanone and styrene) were significantly reduced in THP1.0 V P compared to 3R4F MTS VP (see Tables 1 and Table S2 for detailed values). Results were also compared to Li et al. data [3], despite the fact that they used a target approach using different THP 2.2 product to compare to MTS VP. They studied the percentage reduction of analytes concentration between THP2.2 and MTS samples. The percentage reduction rate of toluene and 2-propanone were 97% and 87%, respectively. Almost similar results were found in the present work for toluene (99%) and 2-propanone (91%). The reduction rate of 2-butnaone was found to be 41% in their study [3] although a 97% reduction rate was observed for THP1.0 V P sample. The present work was based on a preliminary semi-quantitative approach that requires further validtion using specific calibration solutions, ideally using stable isotope dilution.

4. Conclusions

A novel characterization approach based on the use of independent and complementary TD-GC × GC-TOFMS/FID and TD-GC × GC-HRTOFMS methods have been developed for the analysis of the VP aerosol fraction of THP1.0 and 3R4F MTS. Compounds were identified using LRIs, MS matches against spectral libraries using both LRTOFMS and HRTOFMS data, and accurate mass values. This comprehensive data mining approach permitted the assignment of chemical identity for more than 90% of the detected constituents for both sample types. The chemical composition of the VP of THP1.0 aerosol was observed to be much less complex than 3R4F MTS VP. The GC × GC-FID semi-quantitative data indicated that the total abundance of analytes in the THP1.0 V P was ten times lower than in the 3R4F MTS VP. In conclusion, the present study provides data that contribute to a more extensive chemical characterisation of the aerosols generated by tobacco heating products.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.chroma.2018.10.035.

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