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Comprehensive characterization of volatile and semi-volatile compounds in e-liquids for electronic cigarette using gas chromatography accurate mass spectrometry

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ABSTRACT

The consumption of electronic cigarettes is a habit with an increasing prevalence, particularly among youths. Knowing the composition of e-liquids used in these devices represents the first step to understand the potential impact of e-smoking in the health of consumers. Herein, a non-target screening methodology was applied to the identification of volatile and semi-volatile compounds in a set of e-liquids from different suppliers, with different flavors, and containing different kinds of additives, such as nicotine or cannabidiol. To this end, samples were characterized by gas chromatography accurate mass spectrometry, using a time-of-flight mass analyzer. Combination of deconvoluted electronic ionization mass spectra with linear retention index values, obtained for two columns with different selectivity, permitted the identification of more than 250 chemicals with different confidence levels. Among them, respiratory pro-inflammatory compounds, acetals of propylene glycol and glycerin with aldehydes, nicotine-related and non-related alkaloids, and psychoactive cannabinoids were confirmed as concerning compounds in e-liquid samples. Concentration ratios between propylene glycol acetals and parent aldehydes varied in the range from 2% (ethyl vanillin) to more than 80% (case of benzaldehyde). The ratios between the concentrations of delta-9-tetrahydrocannabinol and cannabidiol in e-liquids stayed in the range from 0.02% to 0.3%.

1. Introduction

Electronic cigarettes (e-cig) were marketed as a safe alternative to conventional cigarettes, avoiding, or at least limiting, human exposure to harmful compounds generated during combustion of tobacco, such as tar and polycyclic aromatic hydrocarbons [1]. The power supply unit in e-cig devices is activated by each puff, heating the stream of air which gets in contact with the e-liquid to produce an aerosol containing different flavours and aromatic compounds [2]. Given that temperatures in e-cig devices remain far below those reached during conventional smoking, the formation of toxic combustion by-products is avoided. Composition of liquid solutions vaporized during e-smoking is also different to that of tobacco. Major components are propylene glycol (PG) and vegetal glycerine (VG). In addition, e-liquids contain a large variety of flavouring agents [3,4], and some formulations incorporate other compounds, such as nicotine (NIC) [5] and/or cannabidiol (CBD) [6]. Even in these cases, exposure to NIC during e-smoking is reduced compared to smoking, CBD lacks psychotropic effects, and the employed flavours have been approved as food additives.

Despite above assumptions, e-smoking rises some concerns, particularly after associations between this habit and outbreaks of lung injury [7]. Risks derived from e-cig consumption are related to several factors. On one hand, some common flavors in e-liquids, such as maltol, cinnamaldehyde and coumarin are known to produce oxidative stress in cultures of pleural cells [8], through modulation of the formation of reactive oxygen species during their vaporization [3,9]. Thus, they might damage different tissues of the respiratory tract, including oral [10] and lung cells [11]. Furthermore, it was suggested that flavoring agents are transported from lungs to bloodstream, exerting cytotoxic effects in the cardiovascular and immune systems [12]. Another risk factor is the novo formation of concerning chemicals due to reactions among sub-

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stances mixed in e-liquids. In this vein, carbonyl species can react with alcohols (mainly with PG) to produce acetals, which are recognized as respiratory irritants. For very popular aldehyde flavors, such as benzaldehyde and vanillin, the rates of conversion to acetals have been estimated between 15% and 30% [13]. A third issue of concern is the generation of toxic species during the vaping process [14]. This latter group includes formaldehyde, acetaldehyde and glyoxal, which are produced from oxidation of base alcohols in e-liquids, as function of the voltage applied by the e-cig battery [15]. Finally, inclusion of addictive species in e-liquids, such as nicotine and cannabinoids, is regarded as an additional risk factor. In line with above concerns, the characterization of flavors existing in e-liquids, and those by-products formed during generation of the aerosol have become recurrent research topics [14]. Particularly, knowing the composition of e-liquids is the first step to identify concerning compounds attending to their toxicity, their addictive potential, and/or their role as precursors of toxic by-products, either generated directly in the e-liquid solutions, or produced during e-smoking.

Nuclear magnetic resonance (NMR) spectroscopy and liquid chromatography mass spectrometry (LC-MS) have been proposed for the quantification of major flavors [16], and the determination of specific families of compounds, such as volatile carbonyl species (after a derivatization reaction), and/or nicotine-related alkaloids in e-liquids [17,18]. However, gas chromatography (GC) MS is regarded as the gold standard for the analysis of e-liquids [2,19], either during quantitation of pre-selected compounds [20], or for the qualitative characterization of these mixtures [2,19,21].

So far, more than 140 volatile compounds have been reported in e-liquids [2]; however, considering the number of suppliers and the different available flavors, this number is likely below the figures of volatile and semi-volatile organic species included in these formulations. This statement is supported by several facts. First, most GC–MS studies rely on low-polarity, limited selectivity, siloxane-type columns, which fail to separate major components of e-liquids from minor flavors. Second, quadrupole-type MS instruments, employed in most of previous studies [2,11,21,22], offer a limited sensitivity when operated in the scan mode, so minor compounds might remain undetected, particularly if they co-elute with major e-liquid solvents. Finally, nominal resolution EI-MS spectra might lead to misidentification problems.

Despite the improved performance provided by accurate MS platforms, such as GC-TOF-MS and GC-Orbitrap-MS in non-target screening studies, as far as we could trace, they have not been used for the comprehensive characterization of e-liquids. Thus, the aim of the current study is to build a database of accurate EI-MS spectra for volatile and semi-volatile compounds often present in this matrix. To this end, a non-target data mining strategy was combined with the use of GC-TOF-MS, as main determination technique, under different chromatographic conditions. Particular attention was paid to (1) the identification of species related to well-known additives in e-liquids, such as minor alkaloids structurally related to NIC, and CBD-like compounds; and (2) the assessment of the presence of acetals in e-liquids and/or their potential formation as artefacts during GC–MS analysis. In addition to GC-TOF-MS, LC-MS was employed as complementary analytical technique to confirm those compounds prone to formation in the injector of the GC-TOF-MS instrument.

2. Material and methods

2.1. Samples and sample preparation

E-liquids (39 samples) were produced by nine different companies and purchased either from local retail markets, authorized for distribution of conventional cigarettes in Spain, or from on-line suppliers. Fourteen e-liquids contained nicotine (concentrations in the range from 3 to 12 mg mL^{-1}), and 6 samples declared the presence of cannabidiol (CBD). The range of flavors stated in e-liquids was relatively large, including tobacco, beverages, fruity and mint as main aroma descriptors. Table S1 summarizes the main features of the considered samples, including the ratio between PG and VG solvents. After acquisition, e-liquid samples were maintained at room temperature for a maximum of 1 month before opening. Thereafter, they were diluted with a suitable organic solvent (ethyl acetate and methanol for GC-TOF-MS and LC-MS analysis, respectively), and stored at −20 ºC until analysis. Unless otherwise stated, the dilution factor employed for GC-TOF-MS analysis was 1:100, whilst a 1:10 sample to solvent ratio was considered in LC-MS studies.

2.2. Solvents and standards

Ethyl acetate (trace analysis grade quality) was acquired from Merck (Darmstadt, Germany). Methanol (MeOH) and/or acetonitrile (ACN) for LC-MS, were provided by the same supplier. Ultrapure deionized water (18.2 MΩ cm^{-1}) was obtained from a Geni U system (Rephile, Shanghai, China). Standards of some tentatively identified flavors, and other volatile compounds detected in e-liquids were provided by Supelco (Bellefonte, PA, USA) and Sigma-Aldrich (St. Louis, Missouri USA). Mixtures of allergen fragrances were supplied by Restek (Bellefonte, PA, USA). Concentrated stock solutions of several cannabinoids, in MeOH, were also provided by Supelco. Individual stock standard solutions were prepared in MeOH, further dilutions and mixtures were made either in ethyl acetate, for GC-TOF-MS analysis, or in MeOH, when using LC-MS as determination technique. A mixture of n-alkanes (C_7 to C_{40}, 1000 µg mL^{-1} in dichloromethane) was provided by Supelco. Benzaldehyde-d_5 (deuterated in the aromatic ring) was purchased from Sigma-Aldrich.

2.3. GC-TOF-MS equipment

Identification of volatile compounds in e-liquids diluted solutions was carried out by GC–MS. The employed system was comprised of a 7200 quadrupole time-of-flight (QTOF) instrument (Agilent, Wilmington, DE), equipped with an EI source, and connected to a 7890 GC system from the same supplier. The ionization source and the quadrupole were maintained at 230 °C and 150 °C, respectively. The system was operated in the single MS mode (only the TOF analyzer was operative for separation of ions formed at the EI source), at 2.5 GHz, offering a typical mass resolution of 6000 (calculated as FWHM) at *m/z* 131. EI-TOF-MS spectra were recorded in the profile mode, within the range of masses comprised between 40 and 600 Da.

The e-liquids were analyzed using two capillary columns with different polarities. They were a semi-polar siloxane-type HP5-MS column (30 m x 0.25 mm, 0.25 µm), and a Carbowax, polyethylene glycol-type (DB-WAXetr), polar column with the same dimensions as the HP5-MS one, but a film thickness of 0.50 µm. Both were purchased from Agilent. They were operated using He as carrier gas, at a constant flow of 1 mL min^{-1}. The temperature of the injector was set at 280 ºC, and the transfer line with the MS instrument maintained at 270 ºC. For the HP5-MS column, a linear gradient at 5 ºC min^{-1}, from 65 ºC (1 min) to 260 ºC (8 min) was used. With the Carbowax one a first rate of 5 ºC min^{-1}, from 60 ºC (1 min) to 220 ºC, followed by a second one at 20 ºC min^{-1} to 240 ºC, were employed. In both cases, the final column temperature was held for different times to adjust the duration of chromatographic runs to 48 min.

2.4. Screening of volatile compounds in e-liquids from GC-TOF-MS data

GC-TOF-MS raw data were deconvoluted using the *Unknowns Analysis* (UA) tool, integrated in the Mass-Hunter software (version 10.0), which controlled all acquisition and data processing parameters of the GC-TOF-MS instrument. The workflow employed during data mining and compounds identification was similar to that described in previous articles [23,24]. In brief, chromatographic peaks with responses (peak heights) above a threshold of 10,000 counts were deconvoluted, and their accurate EI-MS spectra were compared to those compiled in NIST17 EI-MS library. Identifications were based on the following requirements: (1) spectral match above 75% between experimental and database spectra (spectral comparison was carried out using a mix of forward and reverse modes, with normalized contributions of 0.3 and 0.7, respectively); (2) differences between experimental and database linear retention index (LRI) values below 50 units for each chromatographic column; and (3) mass bias between deconvoluted spectra and calculated *m/z*, for known fragments in the NIST17 database, lower than 50 ppm, for a minimum of two intense ions. It is worth noting that, LRI values for Carbowax-type columns are relatively scarce compared to those existing for HP5 ones. In the first case, most LRI values were directly obtained from publications dealing with analysis of aroma and volatile compounds in vegetable origin foods [25] and beverages [26], or using the information accessible through the *Chemspider* database. In some cases, proposed identities were confirmed against standards.

Based on above statements, species in e-liquids were identified with different confidence levels. The highest one (level 1) was assigned to compounds fulfilling the three requirements (spectral, LRI and accurate mass match) and further confirmed against authentic standards with, at least, one of the columns. Level 2 corresponded to compounds not verified against standards, but matching spectral and retention time requirements in both columns. Finally, level 3 was assigned to compounds tentatively identified using just one of the columns. The latter situation mostly corresponds to, highly volatile species, poorly retained by the HP5-MS column; as well as to compounds detected in both columns, but without available reference LRI in one of them (usually the Carbowax one). The above confidence level identification scale was inspired in that proposed by Schymanski et al. [27], keeping in mind that, the latter has been proposed for MS and product ion scan accurate spectra obtained using soft ionization sources, such as ESI.

2.5. LC-MS confirmatory experiments

For certain compounds (identified by GC-TOF-MS at level 1), it was considered relevant to discriminate between their presence in the e-liquids, and their potential formation in the hot injector of the GC-TOF-MS system, through re-arrangements in the chemical structures of precursor species. In these cases, LC-MS was used as additional technique. Separations were carried out using a CORTECS Phenyl column (150 mm x 2.1 mm, 2.7 µm), acquired from Waters (Milford, MA, USA), and operated under reversed-phase conditions, with ultrapure water (A) and ACN (B), both 0.1% in FA, as mobile phases. The column was maintained at 40 ºC and the mobile phase flowrate was 0.3 mL min^{-1}. Different chromatographic gradients, and MS instruments, were considered depending on the investigated species: acetals of aldehydes, or cannabinoids. Further details on specific conditions for identification and/or determination of these compounds are given as supplementary information, Text S1 and S2. The complete data mining workflow, integrating data provided by GC-TOF-MS and LC-MS approaches, is provided as supplementary information, Fig. S1.

3. Results and discussion

3.1. Comprehensive overview of volatile organic compounds in e-liquids

Fig. 1A shows the total ion current (TIC) chromatogram for a diluted (1:100) e-liquid (sample code S3, Table S1) using the HP5-MS column. Several chromatographic items, of different intensities, are apparent. Moreover, the region below 11 min presents a broad chromatographic band (corresponding to VG) overlapping

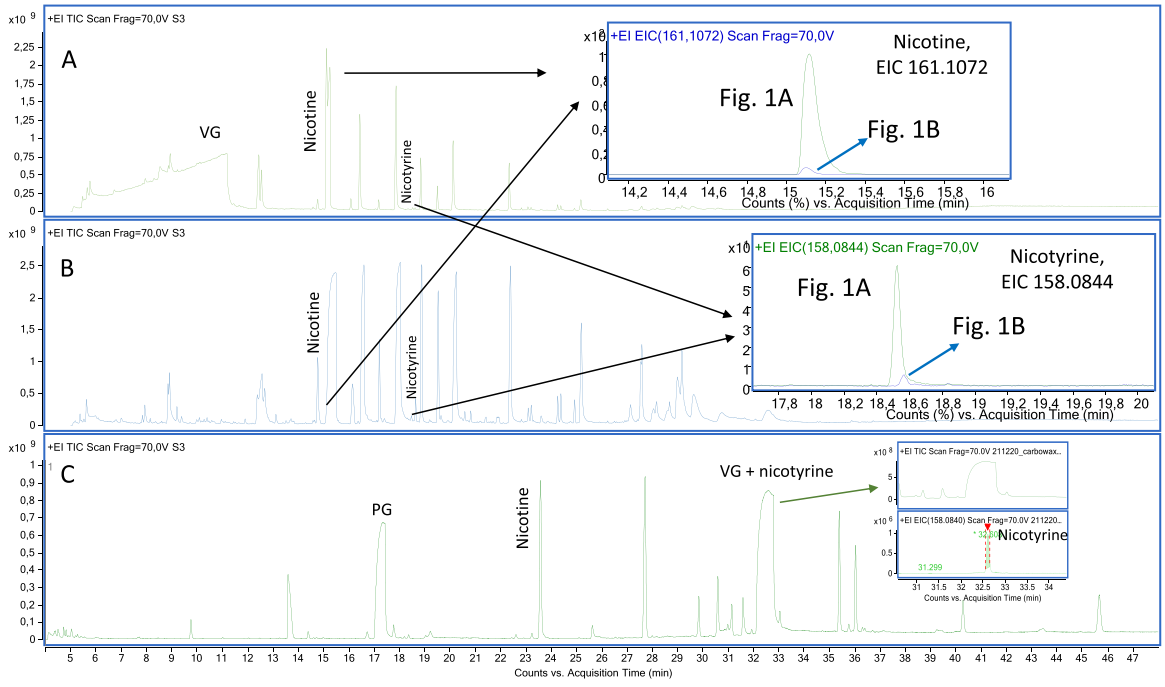

Fig. 1. GC-TOF-MS chromatograms for an e-liquid (sample code S3) under different conditions. A, Direct injection of a 100-times diluted sample using the HP5-MS column. B, Liquid-liquid extraction with ethyl acetate after water dilution (solvent to sample ratio 10:1) of same sample using the HP5-MS column. C, Direct injection of the diluted e-liquid (100-folds in ethyl acetate) using the Carbowax-type column.

the peaks of several compounds. Despite the data mining capabilities of the *Unknowns Analysis* deconvolution algorithm, this band might disturb the identification of minor species; moreover, it prevents the direct injection of e-liquids using lower dilution factors. Thus, different approaches were explored to allow a more comprehensive characterization of e-liquids. In first term, liquid-liquid extraction (LLE) of commercial samples with ethyl acetate (0.1 mL of e-liquids, diluted with 5 mL of ultrapure water and extracted with 1 mL of organic solvent) was assessed [2]. Fig. 1B shows the chromatogram obtained for same e-liquid as that in Fig. 1A after this process. LLE extraction removed the chromatographic band of VG and increased the number of noticeable peaks due to the use of a lower dilution factor; however, polar species present in some e-liquids, such as nicotine related alkaloids, remained mostly in the water phase, Fig. 1A and 1B. Table S2 summarizes the efficiency of the LLE process for a selection of compounds with different polarities. In addition to nicotine and nicotyrine, which were hardly recovered, extraction yields below 60% were observed for the acetals of vanillin with PG, several alcohols, such as maltol and benzyl alcohol, and the alkaloid acetyl pyrazine.

The second approach involved the testing of an alternative column for compound separation. Fig. 1C shows the chromatogram for same e-liquid (sample code S3, diluted 1:100 in ethyl acetate) with the Carbowax-type column. PG and VG increased their retention times and the latter rendered a narrower band than using the HP5-MS column. Moreover, chromatographic peaks for e-liquid components were distributed in a wider interval of retention times. Obviously, certain compounds could still be hindered by those of solvents, as illustrated for nicotyrine, Fig. 1C. In order to obtain a comprehensive characterization of e-liquids, retaining as much as possible of their original composition, LLE was not considered. Samples were just diluted 1:100 with ethyl acetate, injected by duplicate in both columns and the obtained chromatograms processed using the data mining workflow described in Material and Methods section.

Table 1 summarizes a list of 82 compounds observed in the chromatograms for the set of 39 e-liquid samples, using both columns, including their detection frequency ranges. These species were identified with a minimum confidence level of 2. Compounds are sorted attending to their increasing LRI in the HP5-MS column. In addition to CAS numbers and empirical formulae, the *m/z* ratios for the most intense peaks in their EI-MS spectra are provided. The largest number of species in Table 1 fit within the class of terpenes (including terpenes, sesquiterpenes and their hydroxylated terpenoids and sesquiterpenoids), followed by aromatic species and esters of carboxylic acids, Fig. 2A. Regarding their detection frequencies, vanillin and ethyl maltol were the compounds showing the highest prevalence in the set of processed e-liquids, Table 1.

Table S3 and S4 compile a selection of compounds mostly identified with a confidence level 3, and some that were confirmed with standards (confidence level 1). A total of 133 compounds fulfilled the criteria of mass accuracy, spectral match and agreement between experimental and database LRI values using the HP5-MS column, Table S3. In a few cases (i.e. quinolinamine), it was hard to discriminate between positional isomers, since the database LRI values for aminoquinoline analogues, substituted in different positions, differed in just 5–10 units. Most of these compounds were also apparent in the chromatograms corresponding to the Carbowax column; however, reference LRI values were not available for this stationary phase. On the other hand, limited volatility compounds, as it is the case of the cannabinoids and diterpenes, were not observed in chromatograms recorded with the Carbowax column. Likely, they were too strongly retained by this column, with thicker stationary phase and a lower maximum operational temperature than the HP5-MS one. As regards compounds identified only with the polar column, most of them are high volatility alcohols, aromatic compounds (including some solvents such as toluene and styrene), short chain carboxylic acids and some terpenes, Table S4. The latter ones likely co-eluted with more intense species, with several common ions in their spectra, when using the HP5-MS column, hampering their identification. It is worth noting that accuracy of EI-MS spectra was lost in case of saturated peaks; thus, the data mining strategy failed to identify some evident compounds, such as NIC and CBD, unless e-liquids were either injected in the split mode, or diluted up to 10,000 times.

The Venn diagram provided as supplementary information illustrates the advantage of combining the information provided by both columns for the comprehensive characterization of volatile compounds in e-liquids, Fig. S2. Globally, 253 compounds were identified in the processed e-liquids with confidence levels between 1 and 3. A recent review described the identification of 60 different compounds, including organic and inorganic species, in e-liquids [19]. Using a target GC–MS/MS method, 54 compounds, from a selection of 90 candidates, were confirmed in a set of 25 e-liquids from 5 different brands [20]. The pioneer study by Hutzler et al. [2] reported the identification of 140 organic substances in e-liquids. In summary, the number of compounds found using the non-target data-mining methodology reported in this research is larger than those so far compiled in the existing literature [2,19,20]. The accurate EI-MS spectra for compounds identified with confidence levels 1 and 2 have been made available through Zenodo repository (https://zendo.org; doi:10.5281/zenodo.7738079).

It is worth noting that, the processed e-liquids showed a high grade of heterogeneity, as regards their GC–MS profiles, see Fig. S3. This variability suggests that the number of species included in the formulation of e-liquids is likely even larger than those identified in this research. Within the set of tested samples, the detection frequency of a selection of aroma compounds suggested as respiratory pro-inflammatories, proved to display cytotoxic effects during in-vitro studies [12], and identified with a minimum confidence level of 2, are shown in Fig. 2B. Observed values varied from 13% for coumarin up to 68% for ethyl maltol.

3.2. Heterocyclic nitrogenated compounds

The main families of heterocyclic nitrogenated compounds identified in e-liquids were 3-pyrrol-pyridine compounds, 3-pyridine substituted species, and pyrazines. Occasionally, aminoquinolines, imidazoles, thiazoles and pyrimidine derivatives were also found. Fig. 3 shows their relative detection frequencies for the groups of nicotine (14 samples) and nicotine-free (25 samples) e-liquids. In addition to pyrrol-3-pyridine type compounds (cotinine, nicotine, myosmine, nicotyrine and nicotine-N-oxide) other heterocyclic species were mostly, or exclusively, found in nicotine-containing e-liquids, as it is the case of 3-pyridine carboxyaldehyde and 3-vinyl-pyridine, quinolinamine (the exact position of the amino group could not be identified), trimethylated-1,8-napthyridine (two isomers were detected) and pyrazino-pyrazine. Other alkaloids with a similar structure, such as anabasine and anatabine, previously reported in nicotine-containing e-liquids [17], were not found in this research. Minor nicotine related alkaloids might have either a natural origin, as it is the case of myosmine and cotinine [28], which are probably co-extracted together with nicotine from vegetable sources; or, they could be the result of the oxidation reactions occurring in e-liquid solutions, as reported for nicotyrine [22].

The rest of nitrogenated compounds included in Fig. 3 were less often detected, without a clear prevalence between nicotine-free and containing e-liquids. In the case of pyrazines, their presence was mostly associated to tobacco-flavored e-liquids, rather than to

Table 1
Summary of compounds identified using both columns. Compounds in bold were confirmed against authentic standards.

Compound	Chemical class	CAS number	Formula	[a]LRI, HP5-MS column		[a]LRI, Carbowax column		m/z ratios of relevant ions			[b]Detection Frequency
				Exp.	NIST17 database	Exp.	Database	Ion 1	Ion 2	Ion 3	
Camphene	Terpene	79-92-5	$C_{10}H_{16}$	960	952	1092	1092	93.0691	91.0532	121.0997	+
Benzaldehyde	Aldehyde	100-52-7	C_7H_6O	971	962	1551	1555	105.0329	77.0381	51.0224	+
Pyrazine, 2-methoxy-3-methyl-	Alkaloid	2847-30-5	$C_6H_8N_2O$	978	970	1394	1339	124.0618	106.048	95.0292	+
Bicyclo[3.1.0]hexane, 4-methylene-1-(1-methylethyl)- (	Terpene	3387-41-5	$C_{10}H_{16}$	984	974	1125	1120	93.0692	91.0533	77.0364	++
Hexanoic acid, ethyl ester	Ester	123-66-0	$C_8H_{16}O_2$	1001	1000	1247	1253	88.0497	73.027	99.0784	+
Thiazole, 4-methyl-2-(1-methylethyl)-	Alkaloid	15679-13-7	$C_7H_{11}NS$	1021	1022	1369	1339	126.0362	141.0599	70.9939	+
2-Acetylpyrazine	Alkaloid	22047-25-2	$C_6H_6N_2O$	1025	1023	1657	1646	94.0519	122.0476	80.0364	+
p-Cymene	Aromatic	99-87-6	$C_{10}H_{14}$	1027	1025	1291	1292	119.0845	134.1071	91.0538	+
D-Limonene	Terpene	5989-27-5	$C_{10}H_{16}$	1031	1018	1217	1219	67.0544	93.0693	121.1003	++
Eucalyptol	Terpenoid	470-82-6	$C_{10}H_{18}O$	1035	1032	1227	1228	93.0692	139.1113	154.1342	+
2-acetylpyridine	Alkaloid	1122-62-9	C_7H_7NO	1036	1035	1632	1603	79.0412	121.0516	93.0572	+
2-Cyclopenten-1-one, 2-hydroxy-3-methyl-	Ketone	80-71-7	$C_6H_8O_2$	1037	1034	1852	1839	112.052	84.0564	69.0335	++
Benzyl alcohol	Aromatic	100-51-6	C_7H_8O	1038	1036	1899	1917	79.0533	108.056	107.056	++
Butanoic acid, 3-methyl-, butyl ester	Ester	109-19-3	$C_9H_{18}O_2$	1047	1047	1261	1271	103.0748	57.0695	85.0642	+
Butanoic acid, 3-methylbutyl ester	Ester	106-27-4	$C_9H_{18}O_2$	1056	1056	1279	1256	70.0771	89.0587	115.074	+
Furaneol	Ketone	3658-77-3	$C_6H_8O_3$	1059	1070	2052	2050	128.0466	57.0331	85.0279	+
Gamma-Terpinene	Terpene	99-85-4	$C_{10}H_{16}$	1060	1060	1302	1263	93.0688	121.0998	136.1232	+
Pentanoic acid, 4-oxo-, ethyl ester	Ester	539-88-8	$C_7H_{12}O_3$	1063	1045	1636	1610	99.0434	129.0545	71.0481	+
Diethyl malonate	Ester	105-53-3	$C_7H_{12}O_4$	1072	1069	1597	1603	115.0381	133.0491	87.0069	+
Hexanoic acid, 2-propenyl ester	Ester	123-68-2	$C_9H_{16}O_2$	1082	1080	1387	1370	71.0849	99.0801	113.0597	+
Pyrazine, 2,3,5,6-tetramethyl-	Alkaloid	1124-11-4	$C_8H_{12}N_2$	1089	1089	1494	1466	136.0999	54.0466	94.0653	+
Terpinolene	Terpene	586-62-9	$C_{10}H_{16}$	1091	1088	1302	1293	93.0662	121.0986	136.1223	+
Butanoic acid, 2-methyl-, 3-methylbutyl ester	Ester	27625-35-0	$C_{10}H_{20}O_2$	1102	1101	1291	1276	103.0729	70.077	57.0695	+
Linalool	Terpenoid	78-70-6	$C_{10}H_{18}O$	1103	1099	1561	1565	93.0698	121.1002	71.0482	++
Butanoic acid, 3-methyl-, 3-methylbutyl ester	Ester	659-70-1	$C_{10}H_{20}O_2$	1107	1104	1308	1312	103.0736	85.0648	70.0772	+
(2R,4R)-4-Methyl-2-(2-methylprop-1-en-1-yl)tetrahydro-2H-pyran	Terpenoid	5258-11-7	$C_{10}H_{18}O$	1113	1127	1350	1371	139.1116	69.0326	83.0481	+
Maltol	ketone	118-71-8	$C_6H_6O_3$	1114	1110	1991	1991	126.0304	71.0117	97.0275	++
Phenyl ethyl alcohol	Aromatic	60-12-8	$C_8H_{10}O$	1120	1116	1935	1941	91.0541	92.0613	122.0731	+
Isophorone	Aldehyde	78-59-1	$C_9H_{14}O$	1125	1124	1623	1623	82.0413	54.0468	138.1045	+
Benzoic acid	Aromatic	65-85-0	$C_7H_6O_2$	1160	1170	2460	2475	105.0338	122.0371	77.0377	+
Benzene, 1,3-dimethoxy-	Aromatic	151-10-0	$C_8H_{10}O_2$	1170	1166	1775	1730	138.0677	109.0642	78.0453	+
endo-Borneol	Terpenoid	507-70-0	$C_{10}H_{18}O$	1171	1167	1723	1726	95.0851	67.054	110.1081	+
Benzenemethanol, .alpha.,.alpha.,4-trimethyl-	Aromatic	1197-01-9	$C_{10}H_{14}O$	1189	1183	1869	1851	135.0802	91.0534	115.0537	+
Butanoic acid, hexyl ester	Ester	2639-63-6	$C_{10}H_{20}O_2$	1193	1192	1430	1410	93.0691	121.1009	136.1245	+
Menthol	Terpenoid	89-78-1	$C_{10}H_{20}O$	1194	1174	1635	1626	81.0701	95.0859	123.1174	+
alpha.-Terpineol	Terpenoid	98-55-5	$C_{10}H_{18}O$	1195	1190	1718	1719	93.0672	121.1005	136.1247	++
Ethyl maltol	Ketone	4940-11-8	$C_7H_8O_3$	1200	1199	2041	2047	140.0463	139.0387	97.0282	+++
Gamma-Terpineol	Terpenoid	586-81-2	$C_{10}H_{18}O$	1202	1197	1690	1690	121.1006	93.0694	136.1244	+
2-Cyclohexen-1-ol, 2-methyl-5-(1-methylethenyl)-, cis-	Terpenoid	1197-06-4	$C_{10}H_{16}O$	1223	1229	1853	1845	109.0634	91.0525	84.0553	+
Citronellol	Terpenoid	106-22-9	$C_{10}H_{20}O$	1230	1228	1780	1776	67.0542	81.0699	123.116	+
Nerol	Terpenoid	106-25-2	$C_{10}H_{18}O$	1232	1228	1862	1818	69.0708	93.0705	121.1025	+
Pulegone	Terpenoid	89-82-7	$C_{10}H_{16}O$	1244	1237	1676	1665	81.0696	152.1199	137.0961	+
Benzeneacetic acid, ethyl ester	Aromatic	101-97-3	$C_{10}H_{12}O_2$	1248	1246	1783	1784	91.0536	164.0836	136.0538	+
Linalyl acetate	Ester	115-95-7	$C_{12}H_{20}O_2$	1257	1257	1561	1573	93.0703	121.102	80.0624	+
2-Cyclohexen-1-one, 3-methyl-6-(1-methylethyl)-	Terpenoid	89-81-6	$C_{10}H_{16}O$	1259	1253	1757	1841	110.0733	95.0495	137.097	+
Gamma-Octalactone	Lactone	104-50-7	$C_8H_{14}O_2$	1262	1261	1948	1946	85.0289	100.0526	57.0337	+
1,3-Dioxolane, 4-methyl-2-phenyl-	Acetal	2568-25-4	$C_{10}H_{12}O_2$	1271	1272	1840	1871	163.0752	105.0333	119.0464	++
Cinnamaldehyde, (E)-	Aldehyde	104-55-2	C_9H_8O	1274	1274	2043	2037	131.0507	103.0518	77.0381	+
5-Thiazoleethanol, 4-methyl	Alkaloid	137-00-8	C_6H_9NOS	1281	1288	2332	2311	112.0226	143.0417	85.0111	+
Anethole	Aromatic	4180-23-8	$C_{10}H_{12}O$	1289	1284	1854	1817	148.0897	147.0822	117.0708	+
Nonanoic acid, ethyl ester	Ester	123-29-5	$C_{11}H_{22}O_2$	1297	1296	1520	1526	88.0508	73.0272	61.0281	+
Thymol	Terpenoid	89-83-8	$C_{10}H_{14}O$	1303	1291	2234	2236	135.0798	150.1025	107.0836	+

(*continued on next page*)

Table 1 (*continued*)

Compound	Chemical class	CAS number	Formula	[a]LRI, HP5-MS column		[a]LRI, Carbowax column		m/z ratios of relevant ions			[b]Detection Frequency
				Exp.	NIST17 database	Exp.	Database	Ion 1	Ion 2	Ion 3	
Piperonal	Aldehyde	120-57-0	$C_8H_6O_3$	1337	1330	2268	2279	149.0224	150.0298	121.0274	+
Methyl anthranilate	Aromatic	134-20-3	$C_8H_9NO_2$	1345	1343	2271	2283	119.0371	151.0636	92.0268	+
Benzyl butyrate	Ester	103-37-7	$C_{11}H_{14}O_2$	1349	1345	1894	1866	108.0568	91.0538	178.087	+
4-Acetylanisole	Ketone	100-06-1	$C_9H_{10}O_2$	1356	1348	2173	2173	135.0441	150.0673	107.0489	+
Eugenol	Aromatic	97-53-0	$C_{10}H_{12}O_2$	1361	1357	2193	2207	164.0829	149.0582	131.0486	+
Nerol acetate	Ester	141-12-8	$C_{12}H_{20}O_2$	1385	1364	1774	1776	69.0698	93.0697	121.1008	+
Hydrocoumarin	Aromatic	119-84-6	$C_9H_8O_2$	1388	1387	2269	2269	148.0524	120.056	91.0537	+
2-Buten-1-one, 1-(2,6,6-trimethyl-1,3-cyclohexadien-1-yl)-, (E)-	Ketone	23726-93-4	$C_{13}H_{18}O$	1389	1386	1823	1847	121.1007	175.1108	105.069	+
beta.-Bourbonene	Sesquiterpene	5208-59-3	$C_{15}H_{24}$	1394	1384	1540	1539	81.0687	123.1158	161.1311	+
Vanillin	Aldehyde	121-33-5	$C_8H_8O_3$	1401	1404	2602	2623	151.0393	152.0467	123.044	+++
Diphenyl ether	Ether	101-84-8	$C_{12}H_{10}O$	1405	1404	2040	2017	170.0723	141.07	115.0541	+
2-Buten-1-one, 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-	Ketone	35044-68-9	$C_{13}H_{20}O$	1419	1417	1841	1836	177.1274	192.151	123.1158	+
Alpha-cedrene	Sesquiterpene	469-61-4	$C_{15}H_{24}$	1419	1411	1592	1599	119.0847	161.1306	204.1864	+
Myosmine	Alkaloid	532-12-7	$C_9H_{10}N_2$	1426	1427	2231	2236	145.0762	118.0536	146.0836	++
Cyclohexanepropanoic acid, 2-propenyl ester	Ester	2705-87-5	$C_{12}H_{20}O_2$	1426	1435	1820	1800	121.101	95.0851	113.0594	+
cis-Thujopsene	Sesquiterpene	470-40-6	$C_{15}H_{24}$	1438	1429	1627	1592	119.084	105.0685	91.0524	+
Coumarin	Aromatic	91-64-5	$C_9H_6O_2$	1441	1441	2501	2519	146.0354	118.0407	90.0456	+
Ethyl Vanillin	Aldehyde	121-32-4	$C_9H_{10}O_3$	1459	1453	2556	2570	137.0235	166.0626	109.028	+
Humulene	Sesquiterpene	6753-98-6	$C_{15}H_{24}$	1460	1454	1693	1682	93.0691	147.1155	121.0998	+
Gamma-decalactone	Lactone	706-14-9	$C_{10}H_{18}O_2$	1471	1470	2176	2179	85.029	57.0333	128.0824	++
(1ś, 2ś)-Nicotine-N$^{\prime}$oxide	Alkaloid	29419-55-4	$C_{10}H_{14}N_2O$	1479	**n.a.**	2203	n.a.	118.0652	119.0722	60.0439	++
trans-.beta.-Ionone	Ketone	79-77-6	$C_{13}H_{20}O$	1491	1486	1841	1863	177.1264	91.053	135.0787	+
Delta-decalactone	Lactone	705-86-2	$C_{10}H_{18}O_2$	1499	1496	2228	2201	71.0484	99.0441	43.0542	+
Isoeugenol methyl ether	Aromatic	93-16-3	$C_{11}H_{14}O_2$	1500	1492	2118	2176	178.0985	107.0536	163.0752	+
2H-1-Benzopyran-2-one, 6-methyl-	Aromatic	92-48-8	$C_{10}H_8O_2$	1563	1574	2551	2629	160.0524	132.0561	131.0489	+
Gamma-undecalactone	Lactone	104-67-6	$C_{11}H_{20}O_2$	1576	1576	2289	2259	85.028	95.0482	57.033	+
Hedione	Ester	24851-98-7	$C_{13}H_{22}O_3$	1658	1649	2307	2229	83.0488	153.1275	156.0782	+
Delta.-Dodecalactone	Lactone	713-95-1	$C_{12}H_{22}O_2$	1712	1719	2465	2467	71.0481	99.0433	55.0533	+
Benzyl Benzoate	Ester	120-51-4	$C_{14}H_{12}O_2$	1770	1762	2672	2693	105.0329	194.0721	167.0833	+
Phytol	Diterpenoid	150-86-7	$C_{20}H_{40}O$	2090	2114	2621	2633	123.115	95.0845	81.0689	+

[a] LRI, linear retention index.
[b] Frequency of detection: +(< 30% of samples), ++ (30%- 60% samples), +++ (> 60% samples).

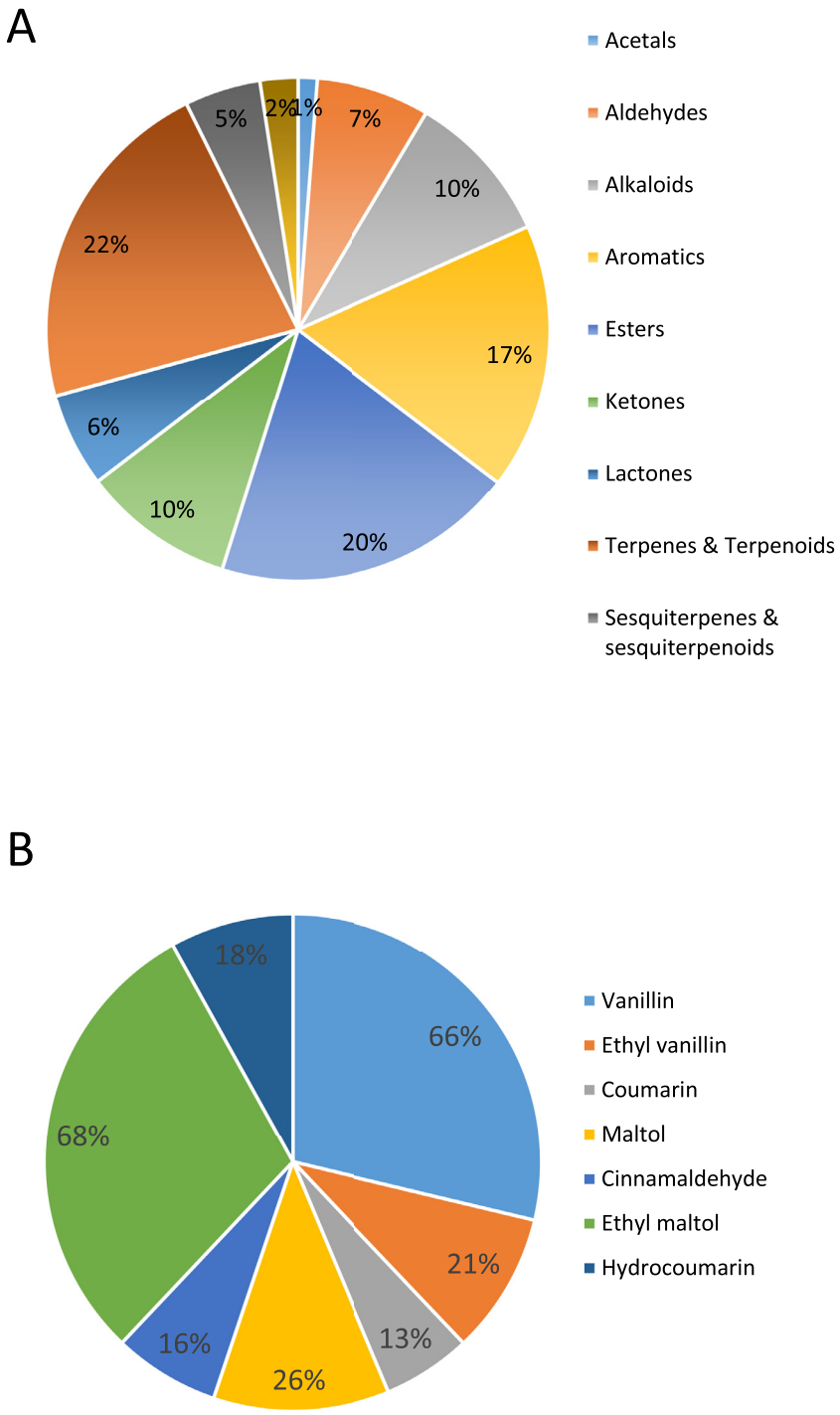

Fig. 2. A, Distribution of compounds identified with both column in chemical classes. B, Detection frequencies of respiratory pro-inflammatory compounds.

nicotine containing samples. Despite its similar chemical structure, methyl nicotinate appears to have a different origin than the rest of nicotine-like compounds, since it was identified in a limited number of both kinds of e-liquids. This compound has been correlated with dermatitis problems when included in topic use pharmaceutical preparations [29]; thus, it might behave also as an irritant of the respiratory system.

3.3. Acetals

Acetals are respiratory irritant compounds. Their presence in e-liquids is the result of reactions between aldehydes and alcohols. The data mining strategy described in the Material and Methods section, combined with manual inspection of GC-TOF-MS records, showed the frequent presence of two clusters of signals corresponding to the diastereomers of acetals formed between main aldehydes in e-liquids (i.e., vanillin and ethylvanillin) with PG (2 peaks) and VG (4 peaks). In the latter case, two different acetals corresponding to 5 and 6 member rings are possible. Fig. 4 plots the extracted ion chromatograms (obtained with the HP-5 MS column) and the accurate scan spectra for two representative species. Whatever their retention times, the congeners in both groups of vanillin acetals (with PG, or VG) showed identical spectra. They share the same fragment at *m/z* 151 (nominal mass) correspond-

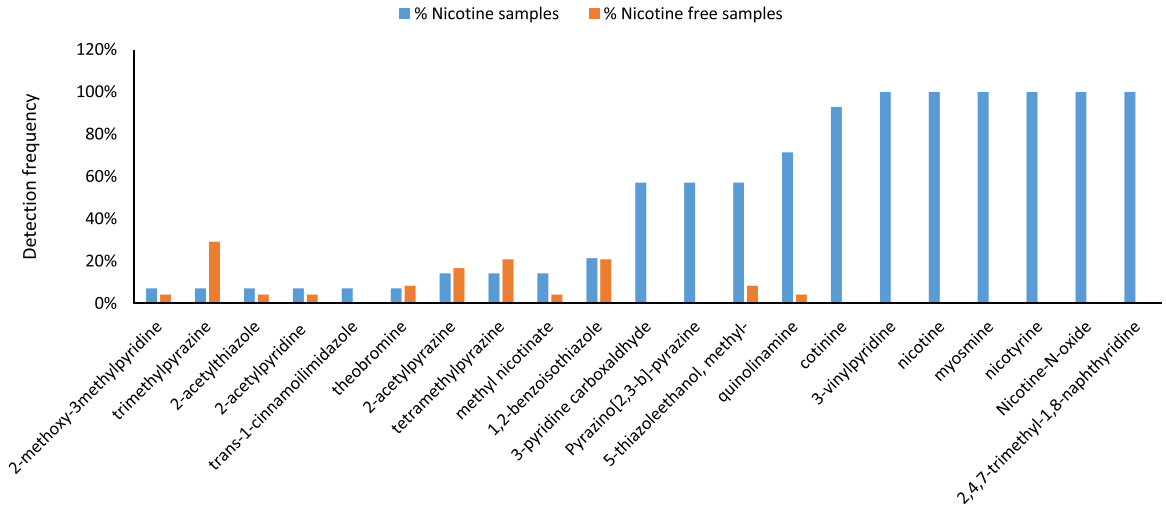

Fig. 3. Detection frequencies of heterocyclic nitrogenated compounds in nicotine and nicotine-free e-liquids.

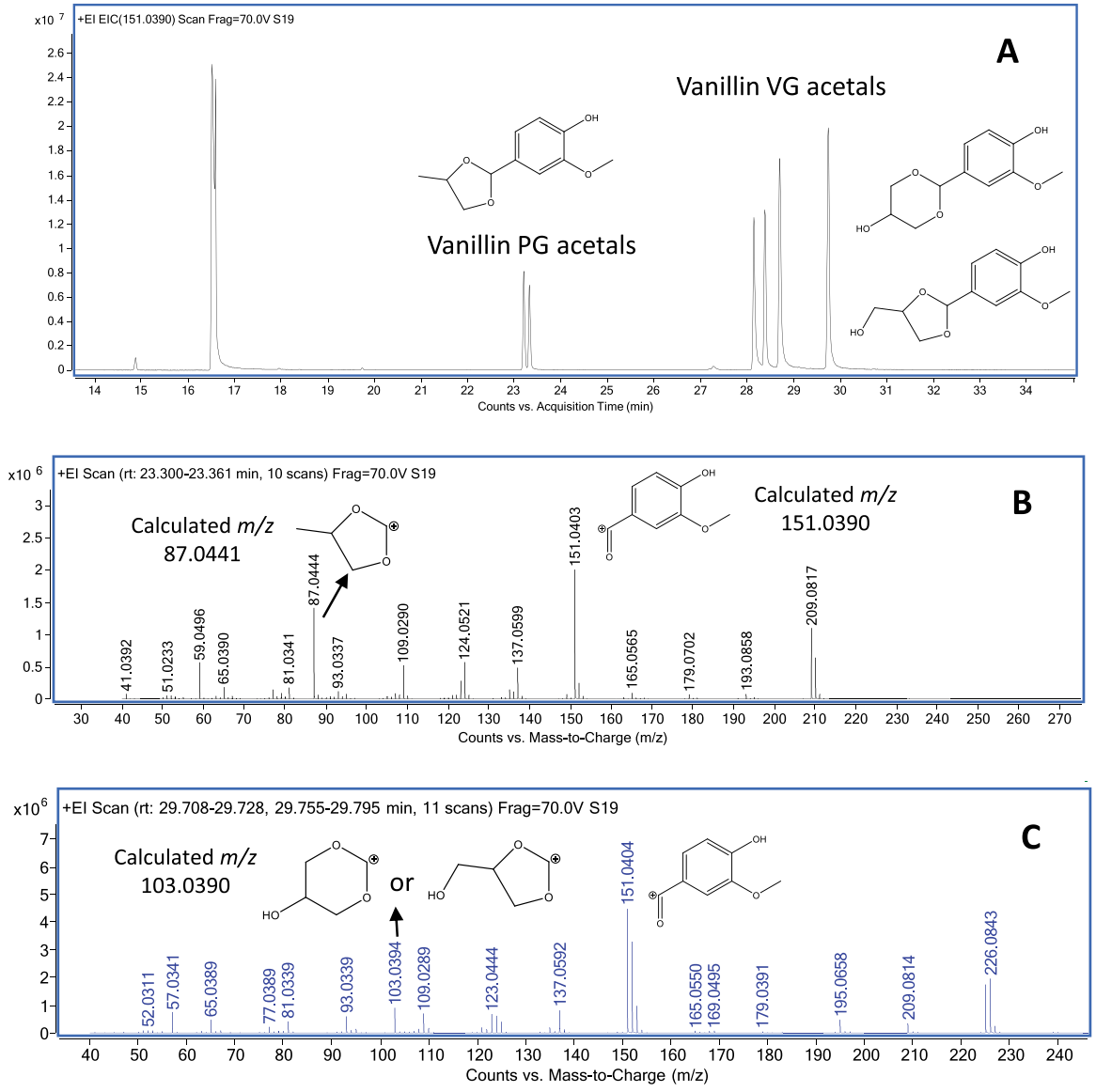

Fig. 4. A, EIC chromatogram at *m/z* 151.0390 (mass window 50 ppm) for sample S19. Accurate EI- MS spectra for the acetals of vanillin with PG (B) and VG (C).

Table 2
Concentrations of vanillin, ethyl vanillin, benzaldehyde and their acetals with PG in a selection of e-liquid samples. Average values for duplicate injections. Data in μg mL^{-1}.

Sample code	Brand	Vanillin	Ethyl Vanillin	Benzaldehyde	Vanillin Acetal	Ethyl Vanillin Acetal	Benzaldehyde acetal
1	A	754.3			33.4		
2	A	937.6			37.8		
3	A	1922.9	2447.0		77	121.1	
4	A	5365.0	1050.6		112.7	26.4	
5	B	467.8			15.6		
10	A	672.6		46.8	30.4		24.2
12	D	3752.9	625.5		217.1	29.6	
19	F	3923.0	485.4		225.1	23.4	
20	G	701.4			21.6		
21	G	4736.7	1051.1		283.8	58.2	
25	G	595.3			22.9		
30	G	487.8	289.5		13.5	9.6	
31	G	277.1		98.5	14.25		81.0
34	H	489.9			15.7		

ing to the deprotonated parent aldehyde ($[M\text{-}H]^+$ ion of vanillin); moreover, other ions, with calculated exact *m/z* values of 87.0441 and 103.0393, are compatible with the non-aromatic rings ($C_4H_7O_2$ and $C_4H_7O_3$ moieties) in the structures of vanillin-PG and vanillin-VG acetals. Same chromatographic and spectral behavior was observed for ethyl vanillin acetals. In case of benzaldehyde, a single peak corresponding to its acetal with PG was detected in the chromatograms for e-liquids, figure not shown.

The identities of the acetals of vanillin, ethyl vanillin and benzaldehyde with PG were confirmed with commercial standards. Verification of their presence in e-liquids, instead of formation at the injection of the GC–MS system, was achieved by LC-TOF-MS. Considering vanillin as potential precursor aldehyde, the acetals of this compound with PG and VG showed single peaks, at retention times slightly higher and lower than that of vanillin, respectively. The ESI (+) product ion (MS/MS) spectra of both acetals showed a product ion at *m/z* 153.0547, matching the $[M + H]^+$ ion of vanillin, Fig. S4. Further research to detect partial transformation of aldehydes to acetals, in the injector of the GC–MS instrument was carried out by adding benzaldehyde-d_5 (addition level 100 μg mL^{-1}) to ethyl acetate diluted e-liquids, just before GC–MS analysis. The obtained GC-TOF-MS chromatograms did not contain any extra peaks, neither at nominal *m/z* 168 not at *m/z* 184, corresponding to the acetals of benzaldehyde-d_5 with PG and VG, respectively. So, we concluded that acetals of the above aldehydes existed in e-liquids and that, they were not artifacts associated to thermally induced reactions in the injector of the GC-TOF-MS system.

Table 2 summarizes the concentrations of vanillin, ethyl vanillin and benzaldehyde together to those for their acetals with PG in the set of processed e-liquids. Concentrations were determined against solvent-based standards, considering split and splitless injection of diluted samples (1:100), for aldehydes and acetals respectively, and using benzaldehyde-d_5 as internal standard. Levels of vanillin and ethyl vanillin in positive samples varied between 0.3 mg mL^{-1} and 5.4 mg mL^{-1}, within the range of values reported in previous studies developed in Europe [20], and below maximum levels (33 mg mL^{-1} for vanillin) reported for samples purchased in USA [11]. The concentrations of their acetals with PG (as sum of diastereomers) represented between 2% and 6% of the content of parent aldehydes. These percentages are significantly lower than those reported in laboratory experiments, combining aldehydes with e-liquids containing different percentages of PG [13]. Benzaldehyde was found just in two out of 39 samples; however, the ratio between the concentration of its acetal with PG and the free aldehyde (values from 0.52 to 0.83) were higher than those observed for vanillin and ethyl vanillin.

3.4. Cannabinoids

Among commercially available e-liquids, those containing cannabidiol (CBD) are gaining popularity. This fact raises concerns in relation to consumers exposure to other cannabinoids, with potential psychotropic effects, either existing in cannabis extracts, or formed from transformation of CBD during consumption of e-cigarettes [30]. Fig. 5 shows the EI-MS spectra and the chemical structures assigned to cannabinoids identified in the GC-TOF-MS chromatograms for this type of e-liquids. Cannabinoids were detected only using the HP-5MS column due to their limited volatility. Fig. S5 shows the chromatographic profiles for the major congeners within this group of compounds. Two bicyclic species, with the same chemical structure of CBD, but shorter alkyl chains were identified as cannabidivarin (CBDV), and the homologue species with a butyl group bonded to carbon number 5 in the aromatic ring, Fig. 5A and 5B. Their structures were not confirmed with authentic standards; however little doubt exists on their identities considering differences between ions existing in their EI-MS spectra and that of CBD. To sum up, the radical cation $[(M^{\cdot+})]$ and the base peak in the spectra of these compounds are shifted in multiples of 14.0156 Da, versus those in the spectrum of CBD, Fig. 5A to 5C. The presence of cannabinol (CBN, $C_{21}H_{26}O_2$) was first identified, and then confirmed in e-liquids. Its spectrum is shown in Fig. 5D. A second group of cannabinoids, with the same empirical formula of CBD ($C_{21}H_{30}O_2$), were cannabichromene (CBC) Fig. 5E, with a similar spectrum but a most intense fragment at *m/z* 174, and a slightly higher retention time than CBD (Fig. S4), and delta-9-tetrahydrocannabinol (Δ9-THC) Fig. 5H. In addition, two relatively intense peaks, at longer retention times than that of CBD (Fig. S5), corresponding to three oxygenated species ($C_{21}H_{30}O_3$) with identical EI-MS spectra, were also detected, Fig. 5F and 5G. Identifications derived from NIST database search pointed out to cannabielsoin (CBE) as the most probable candidate for both peaks, whilst the retention time for a commercial CBE standard matched that obtained for the first species. CBE was already described by Tsujikawa et al. [31] in CBD-type e-liquids.

Taking into account reports describing the partial, and variable, decomposition of CBD in the injector of GC instruments (the percentage of CBD conversion to Δ9-THC varies depending on temperature and injection mode) [31], and the very low intensity of the peak assigned to Δ9-THC compared to that of CBD (Fig. S5), it was hard to determine whether the former compound (the only psychoactive cannabinol identified in this research) is present in e-liquids, or if it was an artifact generated in the injector of the GC-TOF-MS system. Thus, LC-MS/MS was used as complementary technique. Under conditions given in the supplementary informa-

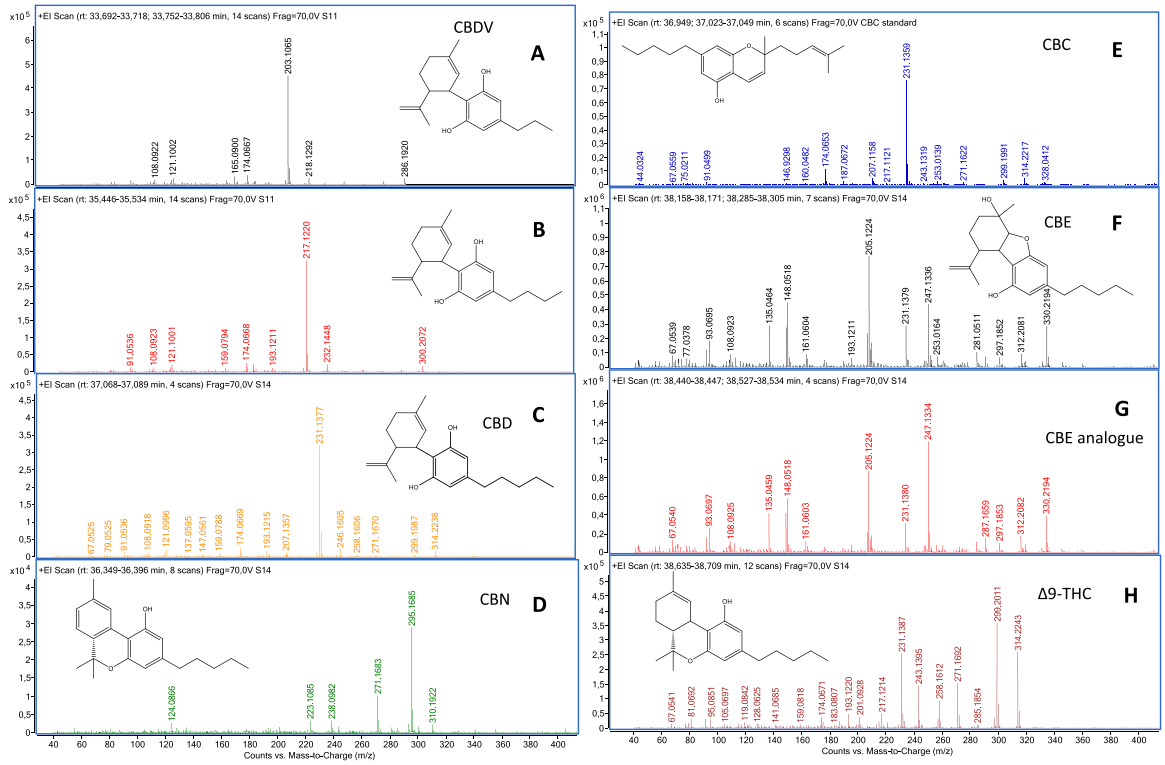

Fig. 5. Accurate EI-MS spectra and structures of cannabinoids identified in cannabidiol e-liquids. A, CBDV. B, homologue with a butyl bonded group bonded to carbon number 5 in the aromatic ring. C, CBD. D, CBN. E, CBC. F, CBE. G, CBE analogue. H, Δ9-THC.

Table 3
Concentrations (μg mL^{-1}) of delta-9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD) in e-liquids determined by LC-MS/MS, $n = 3$ replicates.

Sample code	Brand code	Δ9-THC	CBD	ratio
11	C	1.2	3202	0.04%
13	E	9.6	6814	0.14%
14	E	17.6	6163	0.29%
37	J	3.8	5984	0.06%
38	J	15.1	3718	0.41%
39	J	1.3	6183	0.02%

tion (Text S2), the retention times of CBD, Δ9-THC and CBC were 4.33, 6.34 and 7.34 min, respectively. The chromatograms for diluted e-liquids (1:10 dilution in methanol) confirmed the presence of CBC and Δ9-THC in e-liquids. Moreover, an extra species with same MRM transitions as Δ9-THC, and slightly higher retention time, was also evident, Fig. S6. The concentrations of CBD in e-liquids (obtained by LC-MS/MS) varied between 3.2 mg mL^{-1} and 6.2 mg mL^{-1}. The levels of Δ9-THC ranged from 1.2 μg mL^{-1} to 17.6 μg mL^{-1}, representing between 0.02% and 0.4% of those measured for CBD in the same e-liquids, Table 3. The therapeutic dose of Δ9-THC employed in commercial drugs, i.e. *marinol*, approved to treat side-effects of chemotherapy and in HIV infected patients, are in the range from 2.5 mg to 5 mg dose [32]. Considering a daily inhalation of 5 mL of e-liquids [11], direct exposure to Δ9-THC remains at least 20-times below the therapeutic value for oral administration. However, the potential conversion of CBD to Δ9-THC during e-smoking might increase the respiratory exposure to the latter species. Moreover, the bio-accessibility of the psychoactive compound probably differs depending on administration routes. So, possible therapeutic and/or addictive effects of Δ9-THC in consumers of CBD-containing e-liquids deserves further research.

4. Conclusions

E-liquids contain a large variety of volatile and semi-volatile compounds, at very different concentration levels, sometimes with same empirical formulae and/or with similar EI-MS spectra. Thus, the use of chromatographic retention index is mandatory to improve the confidence of tentative identifications derived from MS spectra. The enhanced sensitivity of the TOF mass analyzer, combined with accurate MS data, allowed the detection of a high number of volatile and semi-volatile features in e-liquids. Moreover, the employment of columns with different polarity improves the reliability of identifications derived from a non-target data mining strategy. Comprehensive characterization of e-liquids represents just the first step to understand possible risks associated to the e-smoking habit. Further studies should characterize the composition of their vaporized fraction, in order to determine the percentage of these compounds inhaled by consumers, and to identify potential transformation, and/or degradation processes, occurring during e-smoking. Spectral database created in this study are expected to be of usefulness in the further characterization of compounds present in vapors produced during e-smoking.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

M. Cobo Golpe: Investigation, Methodology, Writing – review & editing. **M. Ramil:** Supervision, Writing – review & editing. **I. Rodríguez:** Conceptualization, Supervision, Funding acquisition, Writing – original draft.

Data availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.chroma.2023.464114.

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