Atmospheric pressure gas chromatography coupled to quadrupole-time of flight mass spectrometry as a powerful tool for identification of non intentionally added substances in acrylic adhesives used in food packaging materials☆

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A B S T R A C T

Acrylic adhesives are used to manufacture multilayer laminates that are used in food packaging to form the geometric shape of the package as well as to stick labels on the packages. Once applied on the packaging adhesives can supply potential migrants that could endanger the packaged food. Adhesives are complex matrices where intentionally and non intentionally added substances are present, but the identification of the migrants is required by law. In this study atmospheric pressure gas chromatography coupled to a quadrupole hyphenated to a time of flight mass spectrometer (APGC–MS/Q-TOF) has been explored for identification of unknowns coming from three different acrylic adhesives. The results are compared to those obtained by conventional GC–MS-Q (quadrupole). Sixteen compounds were identified by GC–MS/Q and five of them were confirmed by APGC–MS/Q-TOF as their molecular ions were found. Moreover, additional three new compounds were identified and their structure was elucidated working with the spectra obtained by APGC–MS/Q-TOF. This finding was very relevant as these compounds were biocides suspected to be allergenic and cytotoxic in humans. Migration studies were carried out using Tenax as solid food simulant and the results showed that the three acrylic adhesives tested in this work were safe for being used in food packaging materials since the migration of compounds previously identified was below the limit established in the current legislation.

1. Introduction

Gas chromatography coupled to mass spectrometry (GC–MS) is a well established and powerful technique for the analysis of volatile and semi-volatile compounds. Most of the commercial GC–MS systems use ionization under vacuum conditions: electron impact ionization (EI) and chemical ionization (CI) [1]. EI is considered as a hard ionization technique, meaning that the energy of the electrons is high enough to produce highly reproducible fragmentation patterns of small molecules. On the contrary, CI where ions are formed because of the reaction with a reagent gas is a softer ionization technique and fewer fragments are formed. Moreover, since the fragmentation pattern depends on the properties of the reagent gas, different structural information can be obtained from different reagent gases.

The use of GC–MS with a recently developed atmospheric pressure chemical ionization (APCI) source is an alternative technology for the analysis of this type of compounds. This technique, named atmospheric pressure gas chromatography (APGC) was introduced in early seventies by Horning et al. [2] but for technical reasons it has remained an unusual application. In recent years several groups have been hybridizing available technologies for better coverage of increasingly diverse target compounds by LC–MS [3–6]. In 2005, a simple modification of the atmospheric pressure ion sources used in LC/MS instrumentation converts the source into a more universal ion source able to perform APGC in addition to APCI or electrospray ionization (ESI). The combination ion source can be readily adapted to most LC/MS instruments without reduction of LC/MS sensitivity. Both positive and negative ion APGC spectra can be obtained with high sensitivity.

Since this technique is based on APCI, it is a relatively soft ionization process compared with EI. Moreover, APGC operates at atmospheric pressure which removes the restriction imposed by pumps, allowing a much wider range of flow rates for fully GC separations. In addition, all the capabilities common with LC/MS instruments such as high-resolution and accurate mass measurement, cone voltage fragmentation, MS^n,

and multiple reaction monitoring can be also applied to APGC [7,8].

The aim of this paper is to carry out an analytical evaluation of APGC–MS/Q-TOF platform to show the benefits of soft ionization source for GC in combination with a quadrupole time of flight mass analyzer for confirming a previous identification of non-targeted compounds by GC–MS and for identifying compounds that are not ionized by GC–MS. The matrix studied will be acrylic adhesives used in food packaging materials to form the geometrical shape of the package or to stick labels on it. Adhesives are complex matrixes that can include a high variety of compounds [9]. Most of these compounds are unknowns because companies' suppliers of raw materials have confidential agreements. In the adhesives formula, often non intentionally added substances could appear as consequence of impurities from the raw materials used [10–12] decomposition of the initial ones or because of the chemical interaction between several components. These compounds could migrate from the package to the food and affect the food safety. Therefore, it is very important to identify them in order to study their possible migration.

2. Materials and methods

2.1. Reagents and solutions

Three acrylic adhesives were selected for this study (adhesives A, B and C). They were representative of commonly used adhesives in commercial food packaging but their origin and main characteristics are confidential.

100 μm PDMS SPME fibres were supplied by Supelco (Bellefonte, PA, USA). Methanol, acetonitrile and ultrapurified water were from J. T. Baker (Deventer, the Netherlands).

Chromafil Xtra PET-45/25 & Co filters were supplied by Macherey-Nayer GmbH (Düren).

2.2. Instrumental

2.2.1. GC–MS/Q

The equipment used was a CTC Analytics CombiPal autosampler coupled to an Agilent 6890N gas chromatograph with a mass spectrometer MS 5975B detector. All of them from Agilent Technologies (Madrid, Spain).

The capillary column used was a HP-5MS (30 m × 0.25 μm × 250 μm) from Agilent Technologies (Madrid, Spain). The oven program was as follows: 40 °C for 2 min, with rate of 10 °C/min up to 300 °C, maintained for 2 min. The injection type was splitless and the helium flow was 1 mL/min. The mass detector was set at SCAN mode (in the range m/z 45–350) for the identification of the compounds and SIM mode for the quantification of the compounds in the migration extracts.

2.2.2. APGC–MS/Q-TOF

The equipment used for the chromatography was a CTC Analytics CombiPal autosampler coupled to an Agilent 6890N de Agilent. The capillary column used was a HP-5MS (30 m × 0.25 μm × 250 μm) from Agilent Technologies (Madrid, Spain). The oven program was as follows: 40 °C for 2 min, with rate of 10 °C/min up to 300 °C, maintained for 2 min. The injection type was splitless and the helium flow was 1 mL/min.

The detector was an APGC (atmospheric pressure gas chromatography) source coupled to mass spectrometer consisting of an hexapole, a quadrupole, a collision cell and a time of flight analyzer (Q-TOF) Xevo G2 from Waters (Milford, MA, USA).

API positive polarity and sensitivity analyzer mode were selected. The mass range considered was m/z 45–350. The corona voltage was 2.1 kV, the sampling cone voltage was 30 V and the source temperature was 150 °C.

MS^E mode was selected for the acquisition; collision ramp energy from 20 to 40 V was used.

3. Identification

3.1. Sample preparation for the identification

Samples were extracted by HS-SPME extraction and by liquid extraction.

HS-SPME extraction conditions were: T_{ext} 80 °C, t_{ext} 30 min and T_{des} 1 min. The fiber selected for the study was PDMS 100 μm. The extraction was done with the CombiPal autosampler.

Liquid extraction was performed adding 10 mL of acetonitrile to 1 mL of adhesive. The polymer contained in the adhesive precipitated and the supernatant solution containing the additives (small molecules) was filtered and diluted 1:100 with methanol. 1 μL was injected in both GC–MS/Q and APGC–MS/Q-TOF systems.

3.2. Identification

Identification was performed using the software ChromaLynx XS (SCN 714) in both targeted mode and non targeted modes. For the targeted mode, a library database that contained the 19 target previously identified by GC–MS was built and use for this purpose. The theoretical accurate masses of the compounds (M^+), protonated compounds ($M+H^+$) and unprotonated ($M-H^-$) compounds were taken into account for the creation of the data base (57 masses). The criteria of mass tolerance and retention time were set to ±15 mDa and ±0.2 min, respectively. The raw data were processed with ChromaLynx XS and if the criteria were met a positive hit was generated. Chemspider and Scifinder [13,14] databases were used to find the molecular structure with the exact mass and the mass fragments obtained in each case.

4. Migration studies

Eight three-layer laminates or three layer glued samples forming the structure [substrate 1–adhesive–substrate 2] have been studied in this work:

- Laminate 1: paper (70 μm)–adhesive A (11 g/m^2)–matt PP (15 μm)
- Laminate 2: paper (70 μm)–adhesive A–shine PP (25 μm)
- Laminate 3: paper (70 μm)–adhesive A–cellulose acetate (15 μm)
- Laminate 4: paper (70 μm)–adhesive A–PET (12 μm)
- Laminate 5: paper (70 μm)–adhesive C–matt PP (15 μm)
- Laminate 6: paper (70 μm)–adhesive C–shine PP (25 μm)
- Laminate 7: paper (70 μm)–adhesive C–cellulose acetate (15 μm)
- Laminate 8: paper (70 μm)–adhesive C–PET (12 μm)

The migration experiments were designed to be performed with Tenax® as food simulant. Tenax® is composed of small granules of modified polyphenylene oxide. The density of this material is about 0.25 g cm^{-3} which roughly means that about 75% of the Tenax® is air. One of the main properties of Tenax® is its high adsorption potential. Tenax® was extracted following the procedure optimized by Vera et al. [11]. Two consecutive extractions with 3.4 mL of acetone were applied to Tenax, the obtained extracts were put together and 10 μL of internal standard solution A were added. Finally, the total solution was concentrated under a N_2 stream to 200 μL.

For the migration experiments, cut-outs of the laminates with a 100% of its surface containing adhesive were selected. The plastic surface of these laminates was fully covered with Tenax® which

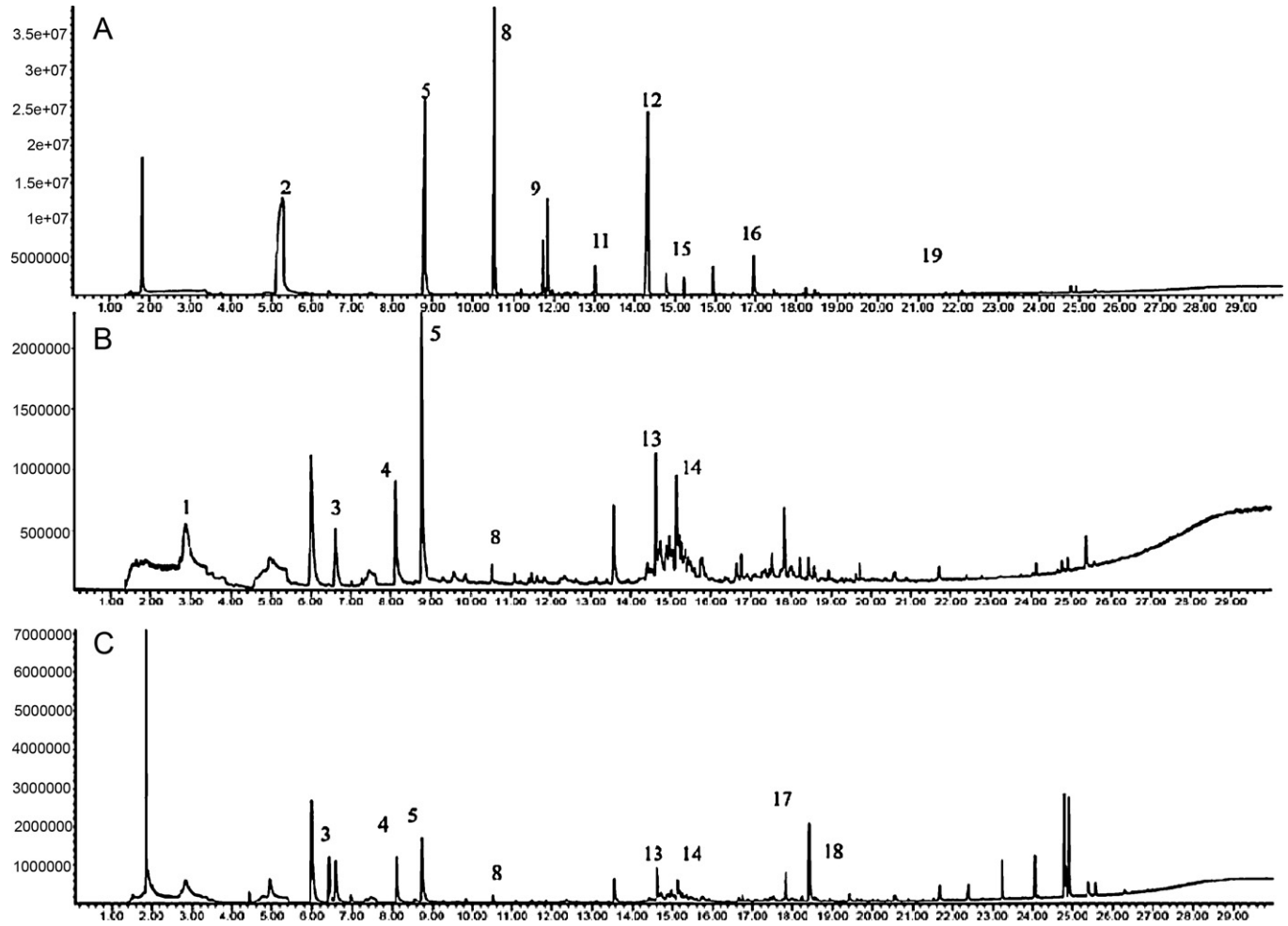

Fig. 1. Chromatograms of the liquid extracts of the samples A, B and C obtained by GC–MS/Q.

had been previously purified by Soxhlet extraction with acetone during 6 h. For migration tests 1 cm × 8.5 cm cut-outs of laminates were covered with 0.34 g of Tenax® forming a uniform layer (4 g_{Tenax} per dm^2 laminate according to UNE-EN 14338) [15]. This system was placed inside a Petri dish and kept in the oven at 40 °C for 10 days. After this period, Tenax® was extracted following the previous methodology and analyzed by GC–MS. The Tenax® was extracted following the previous methodology and analyzed by GC–MS/Q and APGC–MS/Q-TOF.

For building the calibration curves, standard solutions of the compounds at different concentration levels were prepared in acetone and analyzed by GC–MS. Three replicates of each concentration level were analyzed to determine the reproducibility.

5. Results

5.1. GC–MS/Q

In the first place, the identification of the compounds was carried out by GC–MS/Q. Samples were extracted by HS-SPME extraction and by liquid extraction, following the procedures optimized and proposed in previous works related with adhesives [12]. The compounds were identified by comparing their mass spectra with the NIST electronic Mass Spectral Database, available in the equipment. As can be seen in Fig. 1 and Table 1, a series of compounds could be tentatively identified as alcohols, esters, alkanes and carboxylic acids. Acetic acid 2-ethylhexyl ester and 1-hexanol-2-ethyl were found in the three samples studied as this ester is a common monomer used for the polymerization of acrylic adhesives and the alcohol is used for its manufacture. Propanoic acid butyl ester, butanoic acid butyl ester and 2-propenoic acid 2-ethylhexyl ester are also residual monomers coming from the polymerization. Moreover, propylene glycol, 2,4,7,9-tetramethyl,5-decyn-4,7-diol and 2,4,7,9-tetramethyl-5-decyne-4,7-diol ethoxylate ($n = 1$) are commonly used as surfactants in adhesives.

5.2. APGC–MS/Q-TOF

Atmospheric pressure gas chromatography (APGC) is a new analytical tool that allows coupling GC to a LC–MS detector. APGC ionization is an atmospheric pressure chemical ionization process, with a plasma generated by the corona pin supplying reagent ions to ionize the target molecules. The ionization processes are driven by a plasma formed by the interaction between Nitrogen molecules and electrons. The ionization has two possible processes, charge transfer or protonation therefore mass spectra can be dominated by M^+, $M+H^+$ o $M-H^-$ [16,17].

In the first place, this technique was used in order to try to confirm some of the compounds identified by GC–MS/Q as the APGC spectra were dominated by molecular ion. For this purpose an automated identification ChromaLynx XS software in targeted mode was performed. Since both M^+, $M+H^+$ o $M-H^-$ were possible, the theoretical accurate masses of the compounds (M^+), protonated compounds ($M+H^+$) and unprotonated ($M-H^-$) compounds were

Table 1
Compounds identified by GC–MS/Q and APGC–MS/Q-TOF and number of the compounds on the chromatograms shown in Figs. 1 and 2.

Compound name	No.	Sample A		Sample B		Sample C	
		GC–MS/Q	APGC–MS/Q-TOF	GC–MS/Q MS	APGC–MS/Q-TOF	GC–MS/Q	APGC–MS/Q-TOF
1-Butanol	1			+			
Propylene glycol	2	+					
Propanoic acid butyl ester	3			+	+	+	+
Butanoic acid butyl ester	4			+		+	
1-Hexanol-2-ethyl	5	+	+	+	+	+	+
2-Methyl-1,2-thiazol-3(2H)-one	6				+		+
5-Chloro-2-methyl-1,2-thiazol-3(2H)-one	7				+		+
Acetic acid 2-ethylhexyl ester	8	+	+	+		+	
2-Propenoic acid 2-ethylhexyl ester	9	+					
1,2-Benzothiazol-3(2H)-one	10				+		+
n-Butyric acid 2-ethylhexyl ester	11	+					
2,4,7,9-Tetramethyl, 5-decyn-4,7-diol	12	+	+				
Dodecene	13			+		+	
Cyclodecane	14			+		+	
Decane,5,6-dipropyl	15	+					
2,4,7,9-Tetramethyl-5-decyne-4,7-diol ethoxylate ($n = 1$)	16	+					
Phenol 2(1-phenylethyl)	17					+	
Isopropyl myristirate	18					+	
Bis (2-ethylhexyl) maleate	19	+	+				

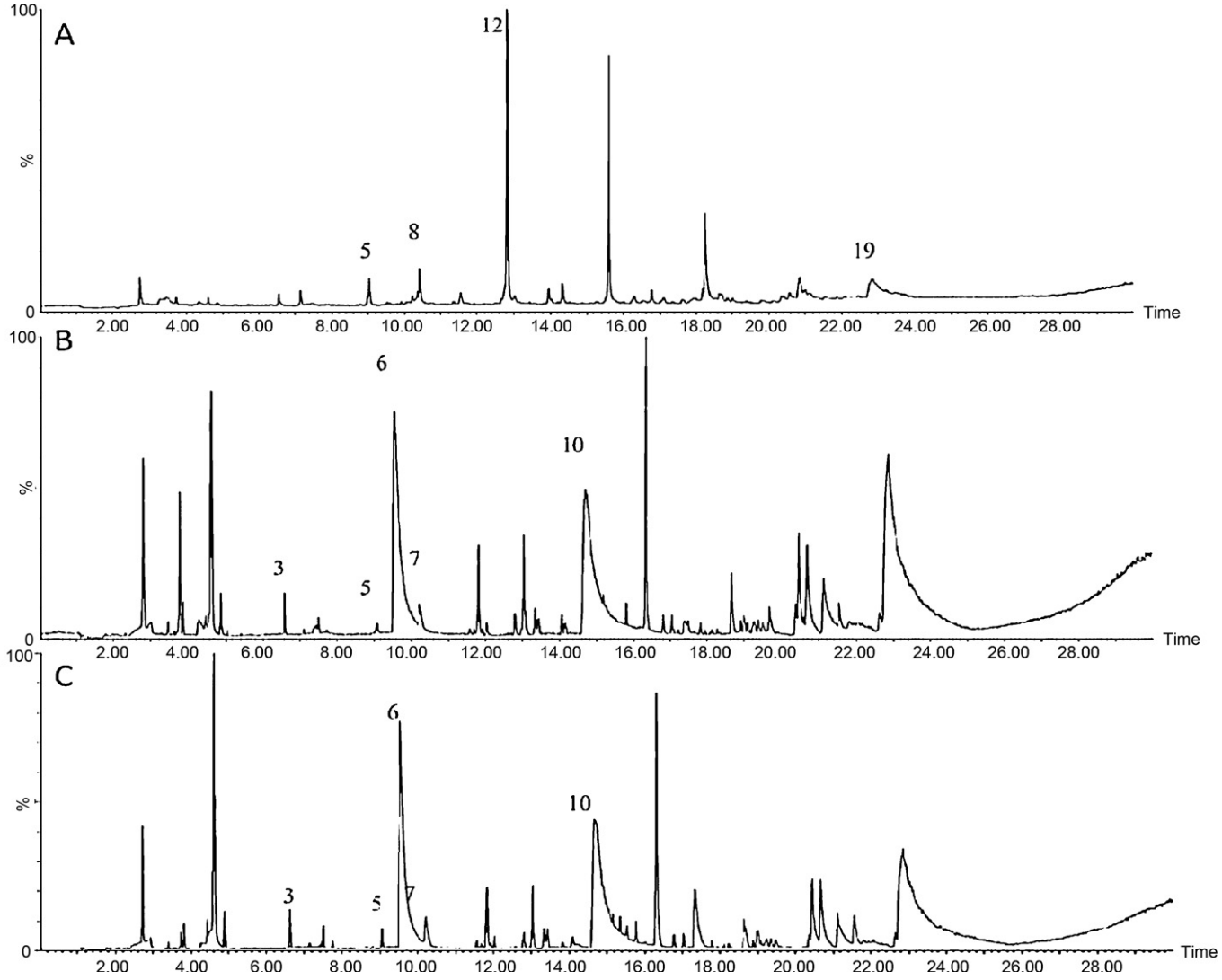

Fig. 2. Chromatograms of the liquid extracts of the samples A, B and C obtained by APGC–MS/Q-TOF.

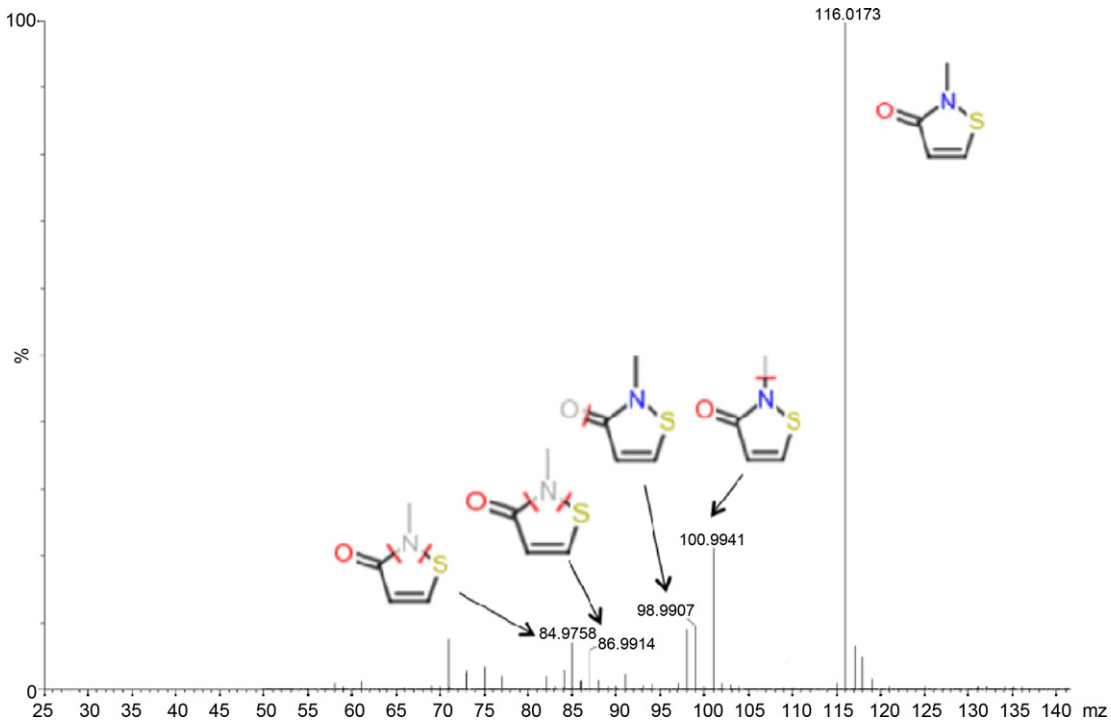

Fig. 3. High energy spectrum of the compound 2-methyl-1,2-thiazol-3(2H)-one.

taken into account for the creation of the database used for the study.

Table 1 shows that automated identification with the ChromaLynx XS software gave 5 positive hits (1-hexanol-2-ethyl, acetic acid 2-ethylhexyl ester, propanoic acid butyl ester, 2,4,7,9-tetramethyl, 5-decyn-4,7-diol and bis (2-ethylhexyl) maleate). The mass accuracy was less than ±6.6 mDa, and the median mass accuracy was 4.1 mDa.ChromaLynx XS proved to be a fast and accurate identification software for this study, when using only an accurate mass window of ±15 mDa and a retention time window of ±0.20 min as automated identification parameters.

It is very remarkable that some compounds were detected working with this technique but they were not detected by GC–MS/Q (Fig. 2).

The chromatogram was acquired in MS^E in order to try to elucidate new molecules. MS^E is a method of data acquisition that records exact mass precursor and fragment ion information in the same run. This method alternates between two functions: function

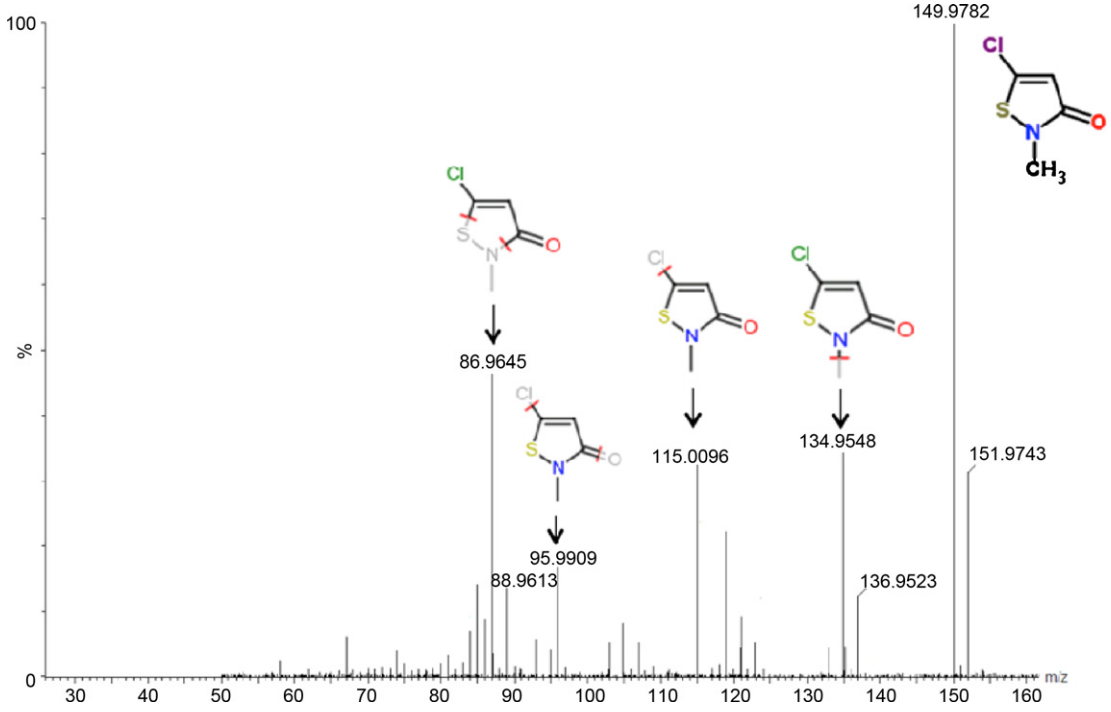

Fig. 4. High energy spectrum of the compound 5-chloro-2-methyl-1,2-thiazol-3(2H)-one.

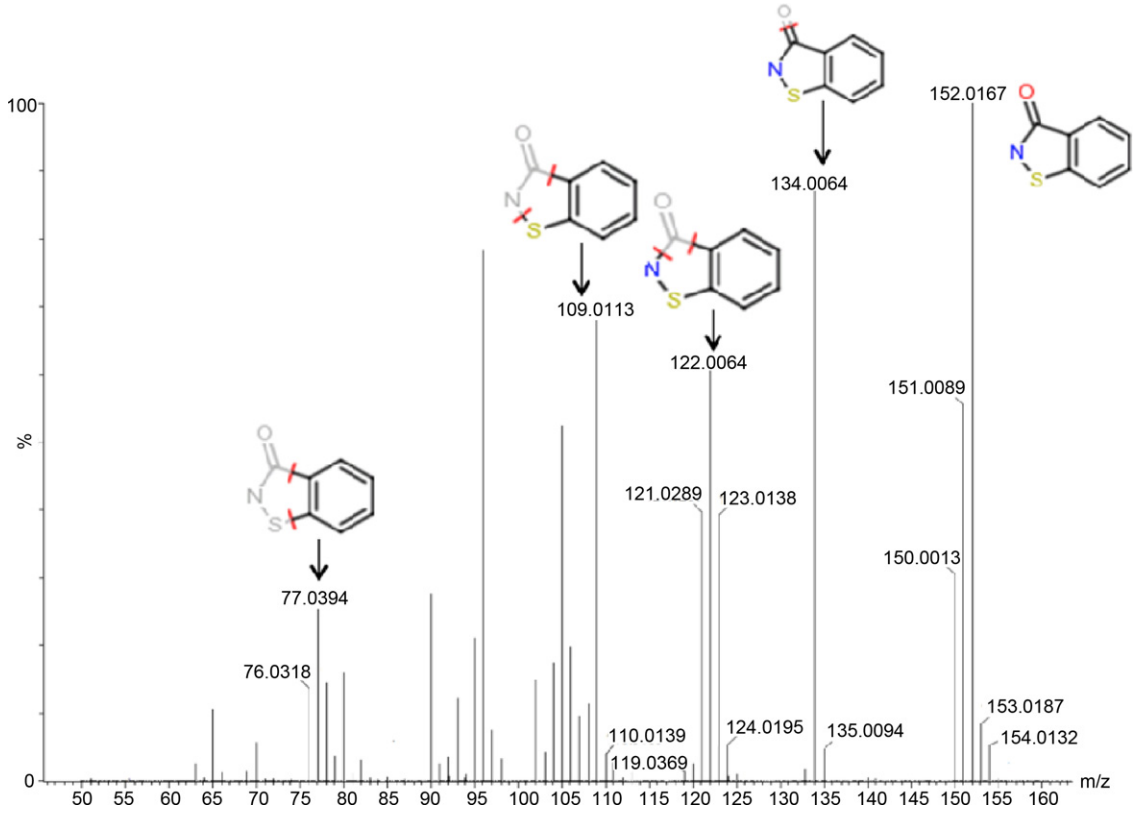

Fig. 5. High energy spectrum of the compound 1,2-benzothiazol-3(2H)-one.

1, when acquiring low-energy exact mass precursor ion spectra and function 2 when acquiring elevated-energy exact mass fragment ions.

For the purpose of identifying these compounds, ChromaLynx XS software in non targeted mode was performed. This software deconvolved the spectra (using function 1) and provided a list with the retention times, accurate mass and abundance of each mass detected by the equipment. Then the comparison of the data to the blank in each case provided the list of masses that were only present in the adhesives. Once the list of accurate masses of each adhesive were known, different possibilities for elemental composition were established considering that the molecules were formed with the most common element (C, H, O, N, Cl, S, Br).

Once different options for elemental composition of each accurate mass were known, it was necessary to use a database of chemical compounds and to know the typical composition of an acrylic adhesive in order to elucidate the possible compounds that could be present. For this work the database [13] was used in order to obtain a list of candidates for the identification.

Then, using the high energy function (function 2) the fragmentation spectra were obtained. These data were used to know if the accurate masses of the fragments would come from the candidates and then confirm their identification.

Following this methodology three compounds were identified: 2-methyl-1,2-thiazol-3(2H)-one, 5-chloro-2-methyl-1,2-thiazol-3(2H)-one and 1,2-benzothiazol-3(2H)-one.

Firstly, the elemental composition of these compounds was obtained using the spectra of the function 1: C_4H_5NOS, C_4H_4ClNOS and C_7H_5NOS respectively.

These elemental compositions were introduced in the chemical database. As a result, 65 hits were obtained for C_4H_5NOS, 19 hits for C_4H_4ClNOS and 79 hits for C_7H_5NOS. A bibliographic search about adhesives composition was done and it was found out that these molecular formulas corresponded to common biocides used in acrylic adhesive formulations. These biocides were taken as candidates. Then, using the high energy function (function 2) the fragmentation spectra were used to know if the accurate masses of the fragments would come from the biocides proposed as candidates and finally confirm their identification.

Figs. 3–5 show the high energy spectrum (function 2) of the compounds 2-methyl-1,2-thiazol-3(2H)-one, 5-chloro-2-methyl-1,2-thiazol-3(2H)-one and 1,2-benzothiazol-3(2H)-one. As can be seen there, the main fragments obtained in the spectra were the ones that only imply one rupture in the molecule. The accurate masses of the fragments allowed to confirm the identification of the candidates proposed initially.

This finding is very relevant, as these compounds are suspected to cause contact allergy in humans [18,19] and to be cytotoxic [20,21].

Therefore it is crucial to study their migration from the adhesive used to make the food packaging to the food, because in case these compounds migrate it would contaminate the food.

Finally the identification of all the compounds proposed was confirmed by injecting the pure standards by GC–MS/Q and APGC–MS/Q-TOF.

5.3. Migration results

Tenax® was selected as food simulant since most of the laminates contained paper or cardboard in their structure. Thus the use of liquid food simulants was not possible because they would have damaged the substrates and/or structures of these laminates. The extracts coming from the migration were analyzed by GC–MS/Q and APGC–MS/Q-TOF. Migration results are shown in Table 2. As can be seen there, only 5 compounds migrated above their limits of detection. Limits of detection for all the compounds analyzed by GC–MS/Q and APGC–MS/Q-TOF were below 10 μg of compound/kg

Table 2
Migration results from laminates to tenax expressed as mg compound/kg simulant and EDI (estimated daily intake) mg/person/day.

Compounds	LOD	RSD	L1		L2		L3		L4		L5		L6		L7		L8	
	μg/kg simulant	%	mg/kg	EDI	mg/kg	EDI	mg/kg	EDI	mg/kg	EDI	mg/kg	EDI	mg/kg	EDI	mg/kg	EDI	mg/kg	EDI
1-Hexanol-2-ethyl	2.2	4.2	0.22	0.09	0.14	0.06	0.19	0.08	0.18	0.03	0.07	0.03	0.14	0.06	0.04	0.02	0.05	0.02
Acetic acid 2-ethylhexyl ester	3.1	3.5	0.11	0.05	0.11	0.05	0.12	0.05	0.11	0.04	0.09	0.04	0.10	0.04	0.12	0.05	0.10	0.04
n-Butyric acid 2-ethylhexyl ester	4.3	4.5	0.04	0.01	0.03	0.01	0.05	0.02	0.07	0.02	0.04	0.02	0.05	0.02	0.07	0.03	0.06	0.02
2,4,7,9-Tetramethyl.5-decyn-4,7-diol	1.2	2.2	0.65	0.27	0.85	0.36	0.22	0.09	0.28	0.09	0.22	0.09	0.26	0.11	0.06	0.03	0.14	0.06
2,4,7,9-Tetramethyl.5-decyn-4,7-diol ethoxylate ($n=1$)	4.0	2.3	0.16	0.07	1.02	0.43	0.15	0.06	0.10	0.04	0.10	0.04	0.10	0.04	0.11	0.05	0.11	0.05

simulant. Moreover, reproducibility was satisfactory as the % RSD was below 5% for all the compounds studied.

Adhesives are not included in the current European regulation for food contact materials. Nevertheless, the compound 1-hexanol-2-ethyl is present in the positive list of the Plastics Directive UE N° 10/2011 [22] with a specific migration limit of 30 mg/kg simulant, a value much higher than that obtained in the migration studies.

For the rest of the compounds, the estimated daily intake (EDI) values were calculated from the migration values as was described in Aznar et al. [10]. The EDI values obtained were compared with their LOAEL (lowest-observed-adverse-effect-level) in order to know if the migration values could cause some toxic effect. Acetic acid 2-ethylhexyl ester and n-butyric acid 2-ethylhexyl ester had a LOAEL of 108 mg/kg/day and 2,4,7,9-tetramethyl,5-decyn-4,7-diol and 2,4,7,9-tetramethyl,5-decyn-4,7-diol ethoxylate had a LOAEL of 1200 mg/kg/day. In Table 2 it can be seen that the EDI values were too low compared to the LOAEL values. Therefore, it can be concluded that the migration of these compounds did not implied toxic effects for the human health.

6. Conclusions

This work demonstrates that APGC–MS/Q-TOF is a powerful technique for the identification of volatile and semivolatile compounds and it can be considered as a complementary tool to the conventional GC–MS. It has been shown to be very satisfactory for the confirmation of compounds previously identified by GC–MS/Q due to the possibility of obtaining accurate molecular ion information with no fragmentation. Moreover it has been demonstrated to be a very useful technique for the elucidation of non intentionally added substances (NIAS) based on both accurate molecular ions with exact mass and their fragments due to the use of the collision cell and the TOF analyzer. As expected, the results obtained by GC–MS and by APGC–MS/Q-TOF were not identical, as the ionization steps plays a critical role in the MS process. Additionally, when unknowns appear in EI-GC–MS/Q it is very difficult to elucidate the chemical structure. However, using the exact mass and the additional fragmentation together with the deconvolution of peak fragments and the chemical database, the candidates for chemical structure can be obtained. Of course the expert eye from the chemical point of view is essential to decide which one of the candidates matches with the data. The biocides identified in this work are of common use in adhesive recipes but they are very difficult to analyze, because of the lack of sensitivity by the current analytical techniques, such as GC–MS or HPLC-UV. APGC–MS/Q-TOF demonstrated that the sensitivity is also very high, even better than expected for this type of compounds. This behavior emphasizes even more the importance of this study and supplies the analytical method for testing these biocides in many different samples.

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