

The migration of NIAS from ethylene-vinyl acetate corks and their identification using gas chromatography mass spectrometry and liquid chromatography ion mobility quadrupole time-of-flight mass spectrometry

Paula Vera^a, Elena Canellas^a, Cristina Nerín^{a,*}, Nicola Dreolin^b, Jeff Goshawk^b

^a Analytical Chemistry Department, GUIA Group, I3A, EINA, University of Zaragoza, M^o de Luna 3, 50018 Zaragoza, Spain

^b Waters Corporation, Altrincham Road, SK9 4AX, Wilmslow, United Kingdom

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ABSTRACT

An exhaustive migration study of eight corks, made of ethylene–vinyl acetate, was carried out to identify any non-volatile and volatile compounds using an untargeted approach. The challenge associated with the structural elucidation of unknowns was undertaken using both ultra-high-performance liquid chromatography coupled to an ion-mobility separation quadrupole-time of flight mass spectrometer and gas chromatography mass spectrometry. A total of fifty compounds were observed to migrate from the corks, and among these additives such as antioxidants (Butyl 4-hydroxybenzoate, Irganox 1010, Irganox 1075, Irgafos 168 and BHT) or lubricants (EBO and octadecanamide, N,N'-1,2-ethanediybis-) were identified. A high proportion (84%) of the detected compounds was non-intentionally added substances (NIAS), and included several cyclic oligomers with different chain sequences. NIAS, such as 2,6-bis(1,1-dimethylethyl)-4-ethyl and 7,9-ditert-butyl-1-oxaspiro[4.5]deca-6,9-diene-2,8-dione, break-down products, including hexa-, hepta- and nonadecanamide, N,N'-1,2-ethanediybis-, and oxidation products were also identified. One cork was found to be unsuitable for use as a food contact material.

1. Introduction

Plastics are indispensable materials for the food industry that are used to protect packaged products, to preserve the nutritional quality, and sensorial and health characteristics of the products, and to minimize any effects of any external factors. Food packaging materials can contain intentionally added (IAS) and non-intentionally added substances (NIAS), the latter resulting from degradation processes and/or impurities present in the raw materials, which can migrate to food and affect the quality and safety of the food.

The most common plastics used for food contact materials are polyolefins such as polypropylene and polyethylene, followed by copolymers of ethylene, substituted olefins, polyesters, polyamides and polycarbonate. Ethylene-vinyl acetate (EVA) is a copolymer of ethylene and vinyl acetate. It is a highly elastic and tough thermoplastic with excellent clarity. Additionally, it adheres well to many substrates and it is heat sealable. However, EVA does not provide a good barrier to gases and moisture and it is usually combined with other types of plastic. EVA can also be applied as sealant for meat and dairy packaging. In general,

the mechanical properties of EVA will depend on the amount of vinyl acetate it contains with a higher content resulting in better clarity but providing a lower barrier to gas and moisture (Robertson, 2005). The main uses of EVA as a food contact material (FCM) are as a seal for carbonated beverage caps, also for wine, cider or champagne bottles, as a heat sealing layer in the extrusion coating of PET (polyethylene terephthalate) and BOPP (biaxially oriented polypropylene) films, and as an interlayer to bond dissimilar materials such as PET and LDPE (low density polyethylene).

Literature in which the chemical migration from EVA is assessed is not extensive. Several targeted analyses have been performed to study the migration of known additives such as metals (Mattiazzi, Bohrer, Viana, do Nascimento, Veiga, & De Carvalho, 2019), ionic surfactants (Waldo-Mendoza, Quinones-Jurado, Perez-Medina, Yanez-Soto, & Ramirez-Gonzalez, 2017), Irganox 1076 (Coltro & Machado, 2011), isobutyl-4-Hydroxybenzoate (Cottaz, Bouarab, De Clercq, Oulahl, Degraeve, & Joly, 2019) and phthalates in EVA bags. Additionally, studies have been performed to assess parabens and sorbic acid in gel-filled baby teethers (Potouridis, Knauz, Berger, & Puttmann, 2019),

* Corresponding author.

E-mail address: cnerin@unizar.es (C. Nerín).

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kits for intravenous administration (Veiga, Bohrer, Nascimento, Ramirez, Carvalho, & Binotto, 2012) and chimassorb 81 in films for agricultural soil covers (Nerin, Salafranca, & Cacho, 1996). Nanoparticle migration has been assessed from manufactured EVA materials (Aghjeh, Asadi, Mehdijabbar, Khonakdar, & Jafari, 2016; Bott & Franz, 2018; Elias, Fenouillot, Majeste, Martin, & Cassagnau, 2008). Only three studies consider the untargeted screening for volatile compounds from PE/EVA films (Felix, Domeno, & Nerin, 2013), liners of EVA/PP (Song, Al-Taher, & Sadler, 2003) and adhesives based on EVA (Vera, Aznar, Mercea, & Nerin, 2011).

In general, there are two types of studies that can be undertaken to aid the risk assessment of a material which is intended to be in contact with food. Targeted analysis is usually applied to understand the migration of known additives in the material, while non-targeted analysis is used to identify chemical compounds present in a food or simulant after it has been in contact with the material for a certain period of time.

The analysis of NIAS represents a major analytical challenge. Ultra-high performance liquid chromatography (UHPLC) coupled to quadrupole time of flight mass spectrometry (QTOF-MS) is probably one of the most powerful techniques for the analysis of non-volatile NIAS compounds. This technique involves the simultaneous acquisition of full scan mass spectra which contain accurate mass measurements of both the precursor ion, in a low energy function, and fragment ions in a high energy function, without compromising acquisition speed. The incorporation of travelling wave ion mobility separation (TWIMS) together with a high resolution mass spectrometry analyzer has recently been applied to the analysis of contaminants and substances migrating from various materials (Canellas, Vera, & Nerin, 2019; Canellas, Vera, Nerin, Dreolin, & Goshawk, 2020; Canellas, Vera, Song, Nerin, Goshawk, & Dreolin, 2021; Vera, Canellas, Barknowitz, Goshawk, & Nerin, 2019). TWIMS can separate ions with different mobility by measuring of the residence time in the ion-mobility drift region. An ion-mobility calibration can then be used to derive the collision cross-section (CCS) of an ion, a quantity related to the rotationally averaged size and shape of the ion, together with the total charge of the ion and the charge distribution. The CCS can be used in addition to accurate mass, retention time, the isotopic distribution and the fragmentation pattern to confirm the identity of a molecular species.

The principles of such devices have been extensively described elsewhere (Giles, Pringle, Worthington, Little, Wildgoose, & Bateman, 2004; Richardson, Langridge, & Giles, 2018). Briefly, ions are directed through a stationary buffer gas in an electric field that is generated by a sequence of symmetric potential waves (traveling waves) continually propagating through the drift region. Wave height and wave velocity can be optimized to control the separation of ions. As a result, three-dimensional spectra are obtained (mass-to-charge ratio, ion intensity, and drift time). An alignment of precursors and fragment ions in both retention time and drift time dimensions provide higher peak capacity and cleaner spectra are obtained. This is extremely advantageous when analyzing complex matrices since potential interfering compounds of the same mass, at the same retention time, but with different mobility, will be filtered out.

For the screening of volatile compounds, the most common technique used is gas chromatography-electron impact ionization mass spectrometry (GC-MS) (Canellas, Vera, & Nerin, 2016; Nerin et al., 2013; Su et al., 2019; Wrona, Vera, Pezo, & Nerin, 2017) which is supported by commercially available spectral libraries, such as NIST and Wiley, containing the spectra of several hundreds of thousands of compounds. The employment of both liquid and gas chromatography provides a comprehensive view of the chemical profile of a sample, allowing meaningful information in an untargeted study to be obtained.

The aim of this work was to identify and quantify the volatile and non-volatile NIAS migrating from several EVA corks, as well as to expand the knowledge of new by-products and their origins. A risk assessment was also applied to the tested materials.

2. Materials and methods

2.1. Reagents

The standards methacrylic acid, diester with triethylene glycol (CAS: 109-16-0), butyl 4-hydroxybenzoate (CAS: 94-26-8), Irganox 1010 (CAS: 6683-19-8), Irganox 1076 (CAS: 2082-79-3), octadecanamide, N, N'-1,2-ethanediybis- (CAS: 110-30-5), Irgafos 168 (CAS: 31570-04-4), EBO (CAS: 110-31-6), 7,9-ditert-butyl-1-oxaspiro[4.5]deca-6,9-diene-2,8-dione (CAS: 82304-66-3), dodecane (CAS: 112-40-3) phenol, 2,6-bis(1,1-dimethylethyl)-4-ethyl (CAS: 4130-42-1), BHT (CAS:128-37-0), formic acid and acetic acid were purchased from Sigma-Aldrich Química S.A (Madrid, Spain). All standards were of analytical quality. Ethanol, water and methanol of HPLC grade were supplied by Scharlau Chemie S.A (Sentmenat, Spain).

2.2. Commercial samples

Eight different plastic corks, made of ethylene-vinyl acetate (EVA), used to seal wine bottles were studied. The dimensions of the corks were 2.2 cm in diameter and 4.3 cm in length. The intended use of the corks is to seal bottles of capacity 125, 750 or 1000 mL. The samples were supplied by different European companies and information regarding the material composition of the corks was not disclosed by the manufacturers.

2.3. Migration assays

Migration assays were carried out according to Regulation <https://doi.org/10/2011/EU> and its amendments (“COMMISSION REGULATION (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food,”). The simulants selected were 3% acetic acid (simulant B) and 20% ethanol (simulant C) for non-alcoholic beverages or alcoholic beverages of an alcoholic strength lower than or equal to 6 % volume. This latest simulant was also used for alcoholic beverages of an alcoholic content between 6 % and 20 % volume. As the corks studied were intended to seal bottles of wine whose alcoholic content is lower than 20 %, both simulants were tested.

For the migration tests, each sample was separately immersed in both simulant B and simulant C. To model the worst-case scenario, that for the smaller 125 mL bottles, half of each cork was in contact with the simulant. The samples were stored for 10 days at 60 °C, to simulate contact times over 30 days at room temperature or below. Three replicates of each sample and simulant combination were prepared.

Following the exposure, the simulant samples were analyzed using UHPLC-IMS-QTOF and GC-MS to determine whether compounds had migrated from the corks. Blank samples of the simulants were also analyzed in triplicate.

2.4. UHPLC-IMS-QTOF analysis

The analyses were carried out using an ACQUITY UHPLC system (binary solvent manager and flow-through needle injector) coupled to a Vion IMS QTOF mass spectrometer with an electrospray interface (ESI), (Waters, Manchester, UK). A UHPLC BEH C18 column (1.7 µm particle size, 2.1 mm × 100 mm) was used with a flow rate of 0.3 mL/min. The mobile phases were water (phase A) and methanol (phase B), both with 0.1 % formic acid (v/v). The gradient used was from 5% phase B to 100% phase B over 13 min, followed by washing and re-equilibration steps of 3 and 2 min respectively. The injection volume was 5 µL, while the column temperature was 40 °C.

Raw data were acquired in positive and negative ionization modes. The capillary and sampling cone voltages were set to 1 kV and 30 V, respectively. The source and desolvation temperatures were set to 150 and 450 °C, respectively, and the desolvation gas flow was 600 L/h. The

cone gas flow rate was 50 L/h and spectra were acquired over the range from 50 to 1000 m/z .

The acquisition mode was high definition MS^E (HDMS^E), with a collision energy of 6 eV for the low energy data and a collision energy ramp of 20–40 eV for the high energy data. Data were processed using UNIFI v1.8 software (Waters Corp.).

2.5. GC-MS analysis

The instrumentation used was a CTC Analytics CombiPal autosampler coupled to an Agilent 6890 N gas chromatograph with a MS 5975B mass spectrometer detector from Agilent Technologies (Madrid, Spain). An electron ionization source operating at 70 eV was interfaced to the mass spectrometer.

Chromatographic separations were carried out on a HP-5MS capillary column (30 m × 0.25 μm × 250 μm) from Agilent Technologies (Madrid, Spain). The oven program was set as follows: 50 °C for 5 min, a temperature ramp of 10 °C/min up to 300 °C over 5 mins. Splitless injection mode and a helium flow of 1 mL/min were used. The acquisition was carried out in SCAN mode over the range 50–450 m/z .

Solid phase micro-extraction (SPME) was used in immersion mode. The SPME syringe was dipped in 20 mL vials containing the food simulant. The fibre coating was polydimethylsiloxane (PDMS) with thickness of 100 μm. The fibre coating and thickness were selected to ensure a high extraction capacity for non-polar compounds, as has already been demonstrated in previous work for this type of material (Vera, Aznar, Mercea, & Nerin, 2011). An extraction temperature of 50 °C over a 15 min extraction window was used together with a 2.5 min desorption phase at 250 °C.

2.6. Identification of migrant compounds from EVA corks

2.6.1. Identification of non-volatile compounds using a UHPLC-IMS-QTOF

Prior to identification, the migration data acquired for both simulants, for each of the samples, were peak detected in the UNIFI Scientific Information System to yield a list of detected components, each of which is uniquely defined by combination of an accurate m/z , retention time and drift time. The components were collated into markers across different injections using the following threshold criteria: $m/z \pm 10$ ppm, retention time ± 0.05 min and drift time ± 0.5 ms. The markers

were transferred directly from UNIFI into the multivariate analysis (MVA) package EZInfo (Umetrics, Umea).

MVA allows the comparison of replicates of different sample classes. In a migration study, a binary comparison between two classes, *Blank* (class A) against *Sample* (class B), is usually performed to detect the features responsible for any class separation. Particular attention is paid to the markers present in the *Sample* and absent from the *Blank*. Such markers are likely to represent migration markers, and it is the identity of these markers that is sought through a structural elucidation procedure.

An exploratory orthogonal partial least-squares discriminant analysis (OPLS-DA) was performed which yields an S-plot, from which the components responsible for separation of the classes can be determined. The S-plot is constructed by plotting the covariance of the markers, the magnitude of change (x-axis), against the correlation of the markers, the consistency of the change (y-axis). The upper right quadrant highlights markers that are elevated in the migration sample (Class B), while the lower left quadrant shows markers elevated in the blank (Class A). The farther along the x-axis a marker is located, the greater its contribution to the variance between the groups, while markers farther along the y-axis represent a higher reliability of the analytical result. Therefore, the markers of interest are those in the upper right quadrant of the S-plot that lie further away from both the x and y axes (Fig. 1).

Following the selection of the markers for each sample and simulant, structural elucidation was carried out using the UNIFI Discovery Tool. The selected marker were submitted for an automated process in which elemental compositions are calculated, the Chemspider database is searched, and fragments of the returned structures are compared to the measured high collision energy data. In most cases, several compounds are suggested for each marker and the final assignment was made using the author's expertise in the interpretation of mass spectra. Candidate compounds were identified according to the greater number of fragment matches, as well as, the better matched isotopic pattern for the measured low energy data (i-FIT score). The number and type of scientific citations available for each candidate compound, as provided by the UNIFI literature search, was also considered.

For an unequivocal identification, commercially available analytical standards of the suggested compounds were analyzed using the same experimental conditions, and the retention time, product ions and CCS values for the main adducts of the precursor ion were compared to the

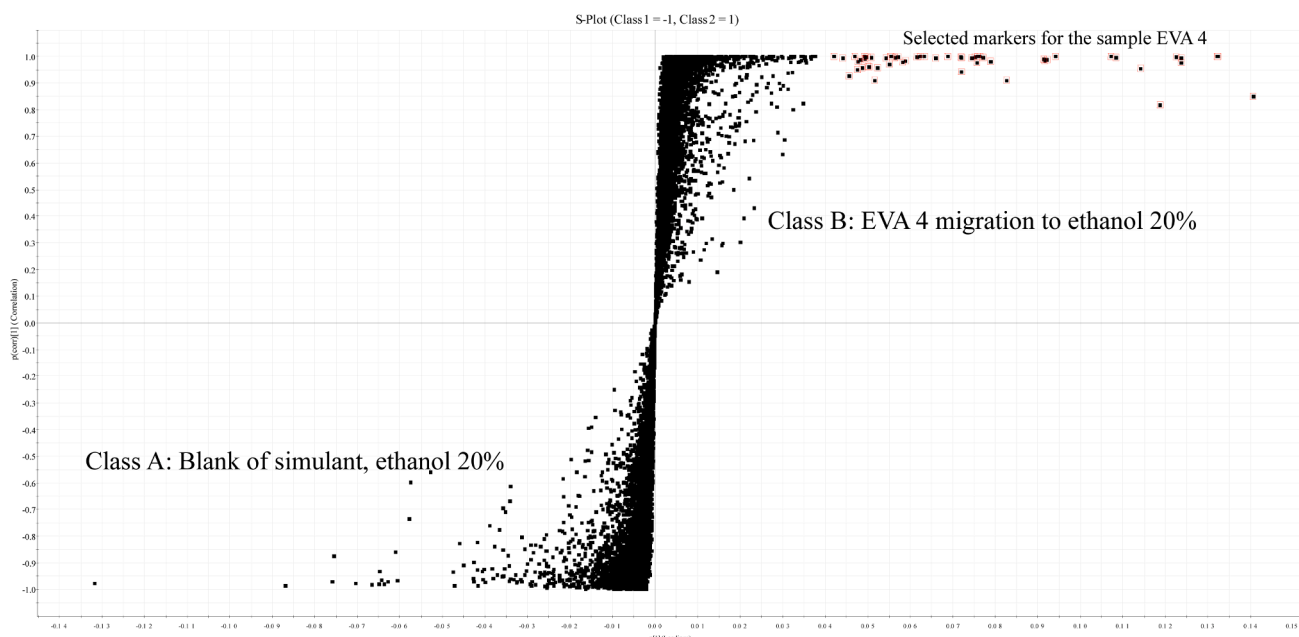


Fig. 1. S-plot for the Class B on the right (markers migrating from EVA 4 to 20% ethanol) and Class A (blank simulant 20% ethanol) on the left.

relevant data from the samples and simulants. The acceptance criteria for CCS agreement was 2%.

2.6.2. Identification of volatile compounds by GC-MS

To detect the compounds migrating from each sample, a manual comparison was performed by overlapping the chromatograms for each migration sample and its respective blank.

The identification of each migrant was carried out by comparing the spectra of any chromatographic peaks unique to the sample to the NIST and WILEY mass spectra libraries. To confirm an identification, where possible, standards of the candidate compounds were injected under the same chromatographic and MS conditions as the original samples and the retention times and mass spectra from the standards and samples were compared.

2.7. Quantification of migrants and risk assessment.

Standard solutions in ethanol were prepared and analyzed by UHPLC-IMS-QTOF in order to produce calibration curves to quantify the non-volatile compounds detected. For the volatile compounds, 18 mL of standard solutions were placed into 20 mL vials and extracted by automatic SPME in immersion mode-GC-MS, as described in section 2.5.

If a commercial standard was not available, the migrant was semi-quantified using an analogue with similar molecular structure.

The migration concentrations were expressed as mg of compound per kg of simulant.

To perform the risk assessment, a search of the positive list of Regulation <https://doi.org/10/2011/EU> for each compound was performed and, if found, the specific migration limit (SML) from the regulation was applied. For those compounds not in the EU positive list, the toxicity was determined using Cramer's classification in conjunction with the software Toxtree®. Depending upon the molecular structure of each compound it was classified in one of three toxicity classes. Subsequently, the estimated daily intake (EDI) value for each compound already established by Cramer as 1.80, 0.54 and 0.09 mg/Kg for Class I, II and III, respectively was used ("Threshold of toxicological concern (TTC). ILSI Europe concise monograph series (2005)").

3. Results and discussion

Eight different corks made of EVA and used to cap bottles of wine were subjected to migration assays and analyzed by GC-MS and UHPLC-IMS-QTOF in a non-targeted analysis to identify all volatile and non-volatile migrants (IAS and NIAS). A risk assessment was subsequently carried out to evaluate whether the level of migration of these materials complies with current legislation.

3.1. Identification of migrants found in EVA corks.

3.1.1. Identification of non-volatile compounds

Potential migrants from each sample and in each simulant were determined from an S-plot produced by an OPLS-DA analysis, as described in section 2.6.1. An example of the marker selection is provided in Fig. 1 which shows the S-plot for the 20% ethanol blank vs the 20% ethanol exposed to EVA 4 sample. The markers highlighted in red are elevated in the sample of 20% ethanol exposed to the EVA sample and are likely to represent compounds that have migrated from the sample into the simulant. In this instance, forty one markers have been selected.

Table 1 lists a total of 43 migrants detected in all EVA samples. The compounds are sorted by retention time, grouped by their chemical family, and the m/z , adducts, matched fragments and CCS values are given for each compound. Compounds 1 to 7 are additives, several of which were determined to be the antioxidants butyl 4-hydroxybenzoate, Irganox 1010, Irgafos 168 and Irganox 1076. Additionally, the methacrylic acid, diester with triethylene glycol as a cross-linking agent was

also detected, as well as the compounds N,N'-Ethylene bis oleamide (EBO) and octadecanamide, N,N'-1,2-ethanediybis-, which are commonly used as lubricants (Ash, 2004). These compounds were confirmed by comparing their retention times, spectra and CCS values (tolerance within $\pm 2\%$) to those of commercial standards acquired under the same conditions.

The remaining compounds, from 8 to 43 were Non-Intentionally Added Substances (NIAS), among which, 7,9-ditert-butyl-1-oxaspiro [4.5]deca-6,9-diene-2,8-dione was detected as a degradation product of Irganox 1010 (Su et al., 2019).

Many of the NIAS (family 1, compounds from 9 to 38) were found to originate from the copolymerization of the monomer of ethylene (C_2H_4)_n with the monomer of vinyl acetate ($C_4H_6O_2$)_m to produce the copolymer EVA (Fig. 2). The number of ethylene and vinyl acetate monomer units in the resulting co-oligomers are given by n and m respectively.

According to the literature (Alison J. Scott, 2017), monomer sequences of copolymers manufactured from monomers A and B, can be classified as: *random copolymer* (which has irregular alternating A and B units, for example, A-B-A-A-B-B-B-A-B-A-A...), or *alternating copolymer* (which has regular alternating A and B units, and it is often described by: -A-B-A-B-A-B-A-B-A-B-, or -(A-B)-n-), or *block copolymer* (which has variable sequence length of A chain followed by B chain, for example, A-A-A-A-B-B-B-B-A-A-A-A...), or finally, *graft copolymer*, which has a main chain of monomer A while monomer B is only found on side branches.

Several groups of sequences were detected in the EVA 4 and 5 samples. The first one was m = 2 combined with n = 1 to n = 13 (corresponding to the compounds 9–21). The second sequence corresponded to m = 3 with n = 1 to n = 13 (compounds 22–34) and the last one to m = 4 with n = 1 and 4 (compounds 35 and 39). All of these compounds were detected by the UHPLC-IM-QTOF analysis as a sequence of peaks separated by approximately 0.30 min from each other, where the difference in m/z for each consecutive peak of the same group was 28.0312 m/z (corresponding to the C_2H_4) and the difference between groups was 86.0366 m/z (corresponding to $C_4H_6O_2$).

The identification of these compounds was not straightforward due to the fact that none of them appear in any chemical database. Therefore, using the elemental composition of each compound proposed by the UNIFI discovery tool, an exhaustive study was carried out to determine the relationship between sequences, which was facilitated by SciFinder software (Albrecht, Brull, Macko, Malz, & Pasch, 2009; "Sci-finder.cas.org").

The molecules were drawn, using Office ChemDraw software, combining co-oligomer sequences of the vinyl acetate (A) and ethylene (B) monomers for the different molecular bond possibilities (random, alternating, block or graft geometry). Subsequently, the different possible co-oligomers constructed were subjected to an *in-silico* fragmentation by Fragment Match tool in UNIFI, which mimics a Collision Induced Dissociation-type fragmentation (CID). The theoretical fragments and their relative intensity were compared to the product ions acquired in the high-energy spectra.

It is worth noting that the detected molecules were not linear co-oligomers, but rather cyclic co-oligomers, due to the lack of two hydrogen atoms in the elemental composition. Following an extensive analysis of the mass spectra, it was concluded that the co-oligomers detected correspond to different fragments of a *graft copolymer* in which sequences of chain A, the vinyl acetate monomer, followed by chain B, the ethylene monomer, are combined in different lengths. Therefore, the detected groups 1, 2 and 3 shown in Table 1, correspond to chain A, formed from two, three and four molecules of vinyl acetate, respectively, followed by chain B formed from 1 to 13 molecules of ethylene.

Fig. 3a shows the high energy spectra of two cyclic co-oligomers and highlights the most representative product ions. Compound 12 (Fig. 3a) is formed by two vinyl acetate monomers, m = 2, combined in graft

Table 1

Non-volatile compounds found in migration solutions from EVA corks, retention time (RT), mass-to-charge ratio (m/z) of the most abundant adduct, molecular formula, candidate name with its CAS number, fragment matches, CCS and relevant remarks, and sample group.

N	RT and m/z	Ion	Molecular formula	Candidate name	Fragment matches	CCS	Remarks	Samples
Additives								
1	5.43_309.1317	[MNa] ⁺	C14H22O6	Methacrylic acid, diester with triethylene glycol, CAS: 109-16-0	229.0707	166.8 ± 0.8	Cross-linking agent	EVA 4
2	7.40_194.0943	[MH] ⁺	C11H14O3	Butyl 4-hydroxybenzoate, CAS: 94-26-8	121.0284	148.0 ± 0.5	Antioxidant	EVA 4,5
3	8.63_1199.7827	[MNa] ⁺	C73H108O12	Irganox 1010, CAS:6683-19-8	731.4154/899.6032	372.3 ± 5.5	Antioxidant	EVA 1,2,3,4
4	9.92_589.5676	[MH] ⁺	C38H72N2O2	EBO, CAS 110-31-6	308.2954/325.3219/ 280.2643/573.5354	272.9 ± 3.9	Lubricant	EVA 1,3
5	10.22_553.4596	[MNa] ⁺	C35H62O3	Irganox 1076, CAS: 2082-79-3	107.0491/149.0597/ 163.1117/311.2945/ 283.2632	248.6 ± 3.7	Antioxidant	EVA 5,7
6	11.72_593.5993	[MH] ⁺	C38H76N2O2	Octadecanamide, N,N'-1,2-ethanedylbis-CAS: 110-30-5	3https://doi.org/10.3095/327.3360/282.2779	280.5 ± 4.1	Lubricant	EVA 4
7	11.56_647.4586	[MH] ⁺	C42H63O3P	Irgafos 168, CAS: 31570-04-4	441.2917/591.3963/ 385.2291/329.1665/ 535.3336	283.4 ± 4.5	Antioxidant	EVA 1,2,3,4
NIAS								
8	6.53_277.1794	[MH] ⁺	C17H24O3	7,9-ditert-butyl-1-oxaspiro[4.5]deca-6,9-diene-2,8-dione, CAS: 82304-66-3	235.1693/179.1067/ 249.1849/233.1536/ 219.1382	174.1 ± 1.8	Degradation products Irganox 1010 Confirmed with standard	EVA 1,2,3,4
Family 1: Co-oligomers								
Group 1, m = 2								
9	5.92_223.0938	[MNa] ⁺	C10H16O4	Cyclic (C2H4) _n (C4H6O2) _m , n = 1, m = 2	*	152.8 ± 3.1		EVA 4,5
10	6.13_251.1259	[MNa] ⁺	C12H20O4	Cyclic (C2H4) _n (C4H6O2) _m , n = 2, m = 2	*	161.2 ± 2.9		EVA 4,5
11	6.78_279.1566	[MNa] ⁺	C14H24O4	Cyclic (C2H4) _n (C4H6O2) _m , n = 3, m = 2	*	170.8 ± 3.5		EVA 4,5
12	7.27_307.1876	[MNa] ⁺	C16H28O4	Cyclic (C2H4) _n (C4H6O2) _m , n = 4, m = 2	*	179.7 ± 3.3		EVA 4,5
13	7.65_335.2193	[MNa] ⁺	C18H32O4	Cyclic (C2H4) _n (C4H6O2) _m , n = 5, m = 2	*	188.5 ± 3.7		EVA 4,5
14	8.13_363.2504	[MNa] ⁺	C20H36O4	Cyclic (C2H4) _n (C4H6O2) _m , n = 6, m = 2	*	194.3 ± 2.7		EVA 4,5
15	8.33_391.2819	[MNa] ⁺	C22H40O4	Cyclic (C2H4) _n (C4H6O2) _m , n = 7, m = 2	*	204.7 ± 3.1		EVA 4,5
16	8.67_419.3177	[MNa] ⁺	C24H44O4	Cyclic (C2H4) _n (C4H6O2) _m , n = 8, m = 2	*	212.5 ± 2.9		EVA 4,5
17	8.99_447.3428	[MNa] ⁺	C26H48O4	Cyclic (C2H4) _n (C4H6O2) _m , n = 9, m = 2	*	220.2 ± 3.4		EVA 4,5
18	9.42_475.3763	[MNa] ⁺	C28H52O4	Cyclic (C2H4) _n (C4H6O2) _m , n = 10, m = 2	*	229.3 ± 4.3		EVA 4,5
19	10.10_503.4081	[MNa] ⁺	C30H56O4	Cyclic (C2H4) _n (C4H6O2) _m , n = 11, m = 2	*	236.4 ± 3.5		EVA 4,5
20	11.02_531.4394	[MNa] ⁺	C32H60O4	Cyclic (C2H4) _n (C4H6O2) _m , n = 12, m = 2	*	244.4 ± 4.5		EVA 4,5
21	11.90_559.4710	[MNa] ⁺	C34H64O4	Cyclic (C2H4) _n (C4H6O2) _m , n = 13, m = 2	*	252.5 ± 4.2		EVA 4,5
Group 2, m = 3								
22	5.65_309.1314	[MNa] ⁺	C14H22O6	Cyclic (C2H4) _n (C4H6O2) _m , n = 1, m = 3	*	167.0 ± 2.3		EVA 4,5
23	6.19_337.1619	[MNa] ⁺	C16H26O6	Cyclic (C2H4) _n (C4H6O2) _m , n = 2, m = 3	*	174.6 ± 2.3		EVA 4,5
24	6.77_365.1933	[MNa] ⁺	C18H30O6	Cyclic (C2H4) _n (C4H6O2) _m , n = 3, m = 3	*	184.9 ± 2.5		EVA 4,5
25	7.10_393.2244	[MNa] ⁺	C20H34O6	Cyclic (C2H4) _n (C4H6O2) _m , n = 4, m = 3	*	193.8 ± 3.8		EVA 4,5
26	7.45_421.2560	[MNa] ⁺	C22H38O6	Cyclic (C2H4) _n (C4H6O2) _m , n = 5, m = 3	*	202.4 ± 3.5		EVA 4,5
27	7.73_449.2875	[MNa] ⁺	C24H42O6	Cyclic (C2H4) _n (C4H6O2) _m , n = 6, m = 3	*	211.7 ± 4.2		EVA 4,5
28	7.99_477.3190	[MNa] ⁺	C26H46O6	Cyclic (C2H4) _n (C4H6O2) _m , n = 7, m = 3	*	220.7 ± 5.1		EVA 4,5
29	8.21_505.3504	[MNa] ⁺	C28H50O6	Cyclic (C2H4) _n (C4H6O2) _m , n = 8, m = 3	*	229.3 ± 4.2		EVA 4,5
30	8.70_533.3816	[MNa] ⁺	C30H54O6	Cyclic (C2H4) _n (C4H6O2) _m , n = 9, m = 3	*	237.2 ± 3.9		EVA 4,5
31	8.75_561.4152	[MNa] ⁺	C32H58O6	Cyclic (C2H4) _n (C4H6O2) _m , n = 10, m = 3	*	244.6 ± 5.5		EVA 4,5
32	9.26_589.4443	[MNa] ⁺	C34H62O6		*			EVA 4,5

(continued on next page)

Table 1 (continued)

N	RT and m/z	Ion	Molecular formula	Candidate name	Fragment matches	CCS	Remarks	Samples
33	9.67_617.4760	[MNa] ⁺	C36H66O6	Cyclic (C2H4) _n (C4H6O2) _m , n = 11, m = 3	*	255.1 ± 5.1		EVA 4,5
34	10.64_645.5079	[MNa] ⁺	C38H70O6	Cyclic (C2H4) _n (C4H6O2) _m , n = 12, m = 3	*	260.9 ± 4.9		EVA 4,5
Group 3, m = 4								
35	9.06_703.5132	[MNa] ⁺	C40H72O8	Cyclic (C2H4) _n (C4H6O2) _m , n = 1, m = 4	*	272.6 ± 3.8		EVA 4,5
36	9.52_731.5448	[MNa] ⁺	C42H76O8	Cyclic (C2H4) _n (C4H6O2) _m , n = 2, m = 4	*	273.8 ± 5.2		EVA 4,5
37	10.12_759.5761	[MNa] ⁺	C44H80O8	Cyclic (C2H4) _n (C4H6O2) _m , n = 3, m = 4	*	283.2 ± 4.8		EVA 4,5
38	10.98_787.6062	[MNa] ⁺	C46H84O8	Cyclic (C2H4) _n (C4H6O2) _m , n = 4, m = 4	*	291.4 ± 4.9		EVA 4,5
Family 2: two amides bonded by ethylene								
39	10.91_531.4865	[MNa] ⁺	C32H64N2O2	Pentadecanamide, N,N'-1,2-ethanediylbis- CAS:175031-37-5	*			EVA 4
40	11.30_559.5181	[MNa] ⁺	C34H68N2O2	Hexadecanamide, N,N'-1,2-ethanediylbis-CAS: 5518-18-3	282.2787/254.2466/ 299.3060/271.2755	263.3 ± 3.4		EVA 4
41	11.82_587.5502	[MNa] ⁺	C36H72N2O2	Heptadecanamide, N,N'-1,2-ethanediylbis-CAS: 173862-96-9	*	270.2 ± 3.8		EVA 4
42	13.18_639.5806	[MNa] ⁺	C40H80N2O2	Nonadecanamide, N,N'-1,2-ethanediylbisCAS: 29271-29-2	*			EVA 4
43	9.42_685.4369	[MNa] ⁺	C42H63O4P	Irgafos 168 OXO CAS: 95906-11-9	495.2657/551.3289/ 439.2037/607.3921	290.1 ± 2.9	Confirmed with standard	EVA 1,2,3,4

(*) These compounds were not found in the Chemspider library.

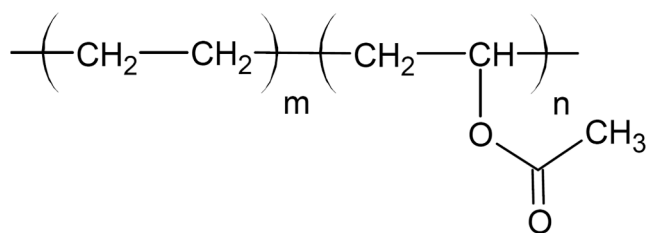


Fig. 2. Structure of ethylene vinyl acetate (EVA) copolymer.

position with 4 molecules of ethylene monomer, $n = 4$, (A-A-B-B-B-B). For compound 26 (Fig. 3b), $m = 3$ and $n = 5$ (A-A-A-B-B-B-B). A common feature between both sequences of cyclic oligomers is the fact that the most intense fragments have a mass difference of 18.0153 m/z , which can be attributed to the loss of one neutral molecule of water. Additionally, both fragments had the cleavage of one acetate group in common.

A family of NIAS found in addition to the oligomers, are formed by two amides of the same acid bonded by ethylene (family 2, compounds 39–42 in Table 1). Their molecular formula have the form $C_xH_{2x}N_2O_2$ and the mass difference between the consecutive molecules was 28.0312 m/z , corresponding to the loss of C_2H_4 (two bonded methyl groups of each chain of amides). All of these compounds were found to have two common adducts, $[M + O + H]^+$ produced by their oxidation reaction, and $[2M + Na]^+$. These products had also been identified in previous work on polypropylene materials (Vera, Canellas, & Nerin, 2018) as possible degradation products or impurities from the lubricant Octadecanamide, N,N'-1,2-ethanediylbis.

Finally, Irgafos 168 OXO ($C_{42}H_{63}O_4P$) was also detected and can also be classified as NIAS (compound 43 in Table 1), originating from the oxidation of Irgafos 168 ($C_{42}H_{63}O_3P$). The identification was confirmed by oxidizing the Irgafos 168 with tetrahydrofuran solvent for 1 day at 40 °C (Vera et al., 2019; Vera et al. (2018)). This compound together with Irganox 1010 and Irgafos 168, appeared in most of the EVA samples.

3.1.2. Identification of volatile compounds

Seven volatile compounds were found to migrate from the EVA samples tested. Fig. 4 compares the SPME-GC-MS chromatograms of 20% ethanol exposed to the EVA 1 to its blank and the difference due to migration is clear. The migrating compounds are listed in Table 2, with their retention times, main remarks and the samples where they were detected with a signal-to-noise value > 10. Six of seven compounds were NIAS with the seventh compound being identified as the antioxidant butylated hydroxytoluene (BHT). Compounds 45 and 46 could not be identified (since their library match scores were below 80% when compared to the NIST library). It appears clear though, that they include branched alkanes due to their characteristic spectra with abundant fragment masses (57, 71 and 60 m/z) and similar breakdown to the alkanes. Two branched alkanes (heptane 2,2,4,6,6-pentamethyl and nonane, 2,2,4,4,6,8,8-heptamethyl) were identified with a spectral match above 90% and may come from the production process of ethylene.

The identified antioxidant butylated hydroxytoluene (BHT) was confirmed by its commercial standard, whilst phenol, 2,6-bis(1,1-dimethylethyl)-4-ethyl was also detected in the samples EVA 4 and 5. The latter shares the same scaffold as BHT, but has an additional methyl group, which makes the association of an impurity of the antioxidant a plausible hypothesis.

Finally, the compound 7,9-ditert-butyl-1-oxaspiro[4.5]deca-6,9-diene-2,8-dione was also detected and the identification confirmed by UHPLC-IM-HRMS.

On comparing the results from all samples, the compounds found to migrate most readily were heptane 2,2,4,6,6-pentamethyl and BHT. No compounds were found to migrate to wither of the simulants from the EVA 6 and EVA 8 samples and only BHT was found to migrate from the EVA 7 sample.

3.2. Quantification of migration and risk assessment

Following the identification of the migrating compounds, a calibration curve for each compound was derived, over the relevant intensity range, using an analytical standard. The concentrations of the migrating compounds were subsequently determined from the calibration curves

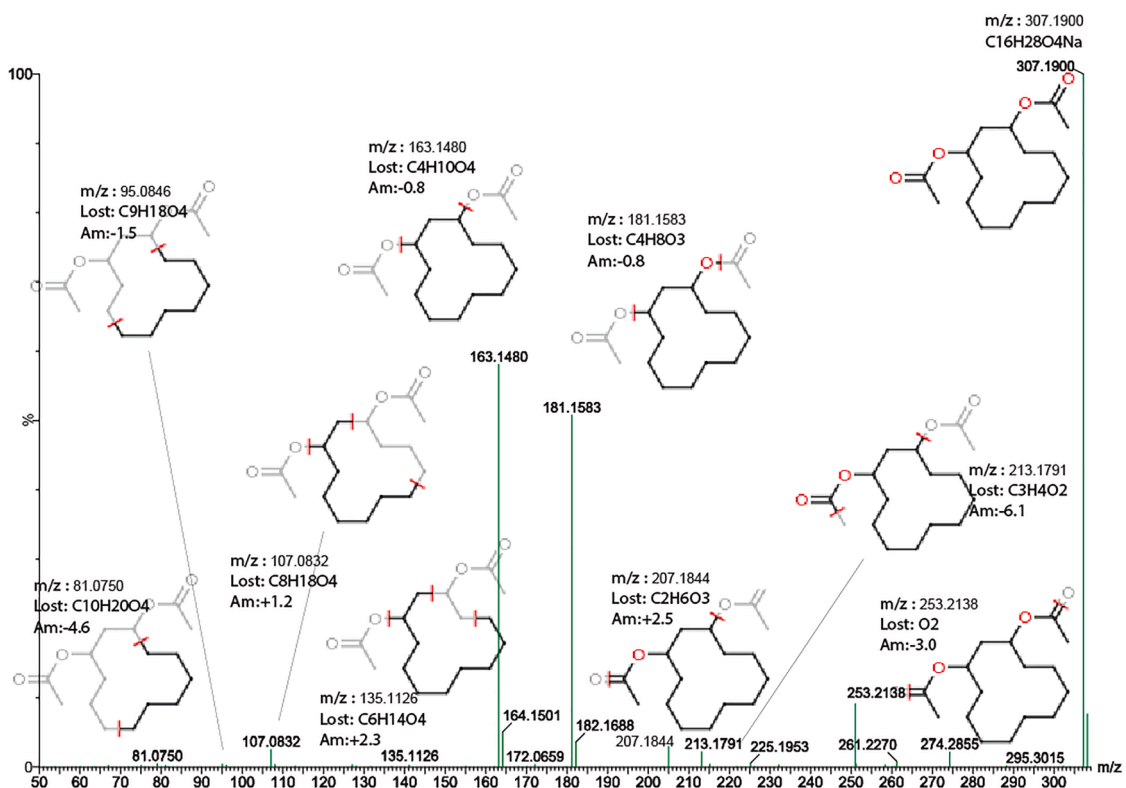


Fig. 3a. High energy spectra of the cyclic co-oligomer $n = 4$, $m = 2$ and sub-structure assignment by the Fragment Match tool.

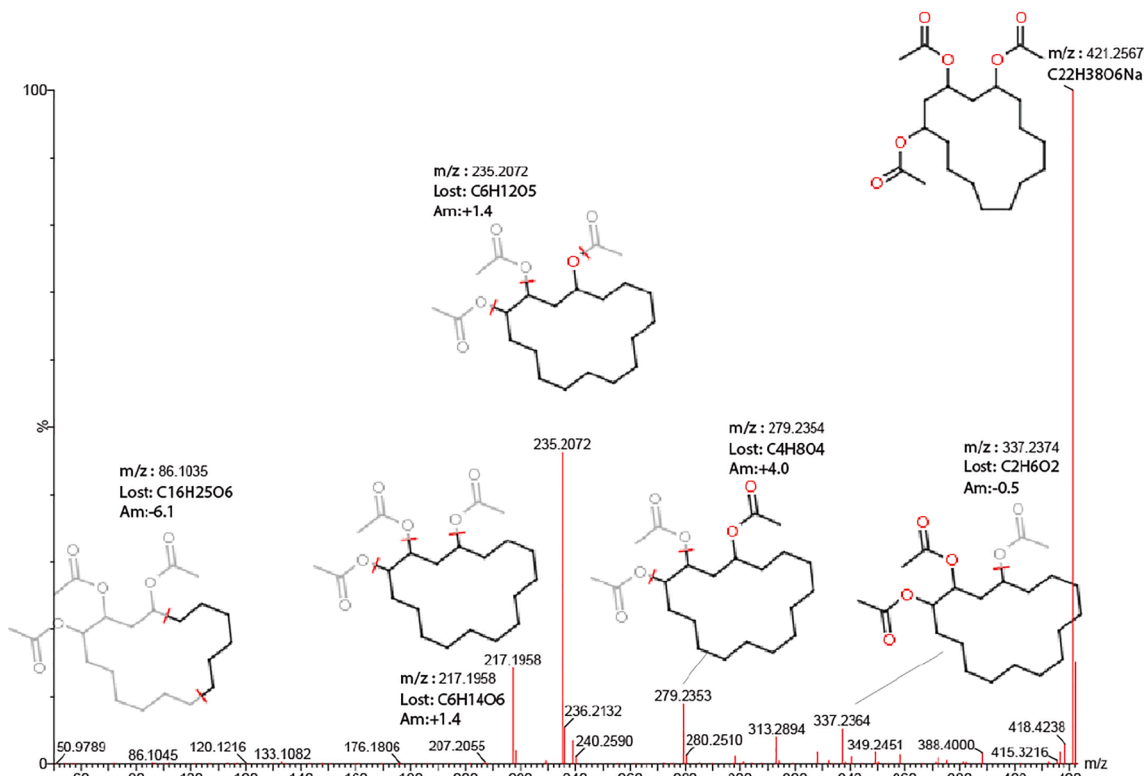


Fig. 3b. High energy spectra of the cyclic co-oligomer $n = 5$, $m = 3$ and sub-structure assignment by the Fragment Match tool.

for each sample and are presented in Table 3, together with the limits of detection and quantification for each compound. For those compounds for which a standard was not available a suitable analogue was used for

the quantification. The analogues used in such cases are detailed in Table 3.

The limits of detection for the compounds identified in the UHPLC-

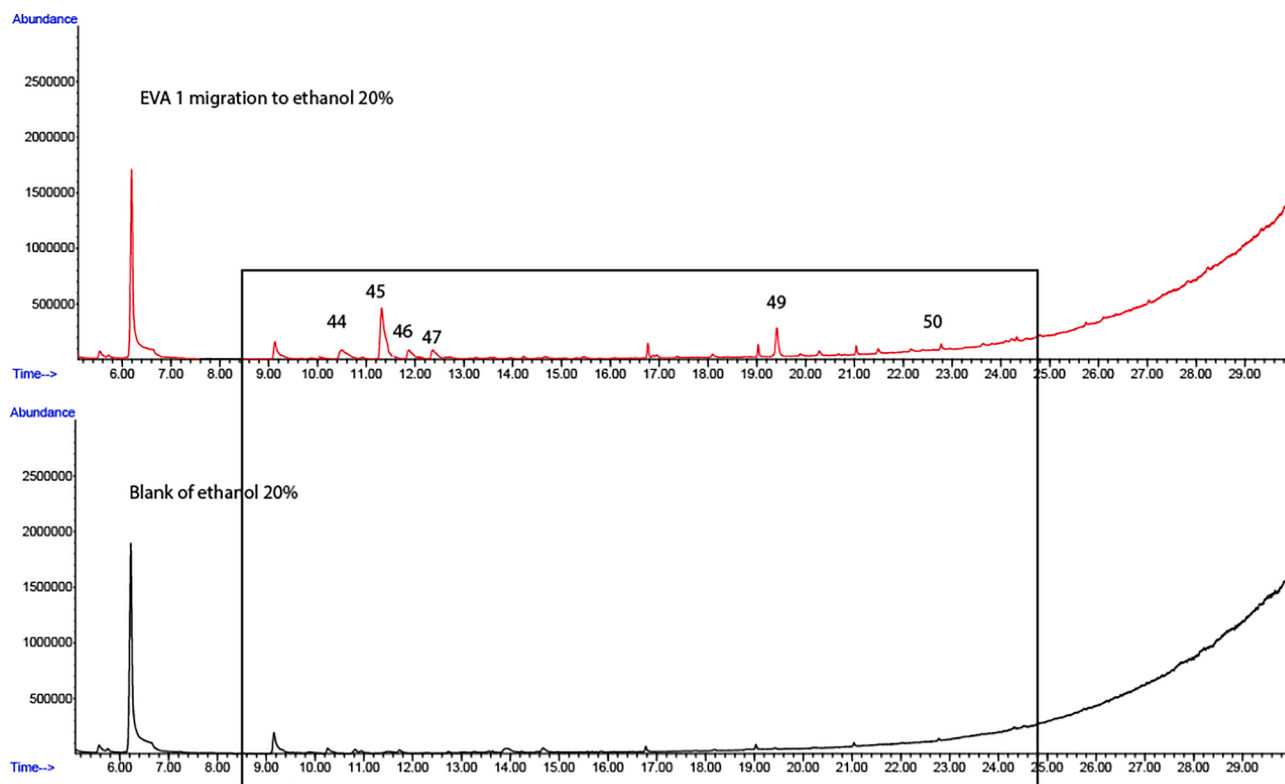


Fig. 4. Comparison of SPME-GC-MS chromatograms of 20% ethanol exposed to EVA 1 and the blank of 20% ethanol, highlighting potential migrating compounds.

Table 2

Volatile compounds from EVA corks detected in migration solutions analyzed by SPME immersion-GC-MS, retention time (RT), compound name and CAS number, remarks and samples.

N	RT	Compound /CAS	Remarks	Samples (simulants)
44	10.7	Heptane 2,2,4,6,6-pentamethylCAS: 13475-82-6	Library Match: 96	EVA 1,2,3,4,5 (both simulants)
45	11.5	Branched alkane (1)		EVA 1 (EtOH 20%), EVA 3,4,5 (both simulants)
46	11.9	Branched alkane (2)		EVA 1,3 (EtOH 20%), EVA 4,5 (both simulants)
47	12.2	Nonane, 2,2,4,4,6,8,8-heptamethylCAS: 4390-04-9	Library Match: 92	EVA 1 (both simulants)
48	19.3	Phenol, 2,6-bis(1,1-dimethylethyl)-4-ethyl CAS: 4130-42-1	NIAS confirmed with standard	EVA 4,5 (EtOH 20%)
49	19.4	BHT CAS:128-37-0	Antioxidant	EVA 1,2,3,4,5,7 (both simulants)
50	22.1	7,9-ditert-butyl-1-oxaspiro[4.5]deca-6,9-diene-2,8-dione CAS:82304-66-3	NIAS confirmed with standard	EVA 1,2,3,4 (EtOH 20%)

IM-HRMS experiments ranged from 5.5 µg/kg for butyl 4-hydroxybenzoate up to 22 µg/kg for Irganox 1010. For the SPME-GC-MS analyses, the compounds identified had very low detection limits, ranging between 0.3 µg/kg for dodecane up to 0.5 µg/kg for phenol, 2,6-bis(1,1-dimethylethyl)-4-ethyl.

The migration to 20% ethanol was generally higher compared to the migration to 3% acetic acid. The mean predicted octanol/water partition coefficients (XLogP) were about 6.5 and 3.5 for ethanol and 3% acetic acid food simulants, respectively. Hence, high XLogP compounds have higher potential to migrate into 20% ethanol while low XLogP substances to 3% acetic acid (Su, Vera, Nerin, Lin, & Zhong, 2021). For example, XLogP of irganox 1010 (15.33), EBO (15.76), octadecanamide,

N,N'-1,2-ethanediybis- (16.76), hexadecanamide, N,N'-1,2-ethanediybis- (14.51) and BHT (4.6) with higher tendency to migrate to 20% ethanol

It should be also emphasized that the concentration of most of the migrants found were below their limits of quantification in many of the samples. For the volatile compounds, the migration values were quite low and most of them were below 10 µg/kg. Only two compounds were above this value, namely heptane 2,2,4,6,6-pentamethyl for EVA 2 (18 µg/kg) and BHT for EVA 7 (15 µg/kg).

Sixty percent of the compounds quantified were included in the positive list of Regulation <https://doi.org/10/2011/EU> ("COMMISSION REGULATION (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food,"). Some compounds are authorized without specific migration limits (SML) whilst others such as Irganox 1076, phenol, 2,6-bis(1,1-dimethylethyl)-4-ethyl and BHT do have an SML. In all cases the concentrations of the migrating compounds included in the positive list of Regulation <https://doi.org/10/2011/EU>, were far below the corresponding SML (Table 3).

For the compounds not present in the EU positive list, a Cramer classification was applied ("Threshold of toxicological concern (TTC). ILSI Europe concise monograph series (2005)"). The group of two amides bonded by ethylene, were considered to be most toxic to human health and classified as class III. The 7,9-ditert-butyl-1-oxaspiro[4.5]deca-6,9-diene-2,8-dione was assigned class II, and the other seven compounds, methacrylic acid, diester with triethylene glycol, butyl 4-hydroxybenzoate, the cyclic co-oligomers and the branch alkanes were classified as class I. The migration concentration of most of these compounds were found to be below the values recommended by Cramer for class III, II and I which have limits of 0.09, 0.54 and 1.8 mg/kg, respectively. However, the migration of 7,9-ditert-butyl-1-oxaspiro[4.5]deca-6,9-diene-2,8-dione, heptadecanamide N,N'-1,2-ethanediybis- and nonadecanamide N,N'-1,2-ethanediybis- from EVA 4 to 20% ethanol was at a concentration level above the recommended limits by Cramer for their respective toxicity classes.

Table 3

Migrant concentrations in different simulants (20% ethanol and 3% acetic acid) expressed as mg/kg of simulant, standard used for the quantification, limits of detection and quantification (expressed in $\mu\text{g}/\text{kg}$) and their specific migrant limits or Cramer classification.

Migrant	Standard used/LOD/LOQ ($\mu\text{g}/\text{kg}$)	Sample	Migration to different simulants ($\mu\text{g}/\text{kg}$)		EU/11/2011 (mg/kg) or Cramer class	
			EtOH 20%	AA 3%		
Non-volatile compounds						
Methacrylic acid, diester with triethylene glycol	16/153	EVA4	140 \pm 11	<LOQ	I	
Butyl 4-hydroxybenzoate	1/4.5	EVA4	105 \pm 9.3	83 \pm 4.1	I	
Irganox 1010	22/73	EVA5	45 \pm 3.3	<LOD	Authorized without SML	
		EVA1	<LOQ	<LOD		
		EVA2	<LOQ	<LOD		
		EVA3	<LOQ	<LOD		
		EVA4	115 \pm 13	<LOD		
Irganox 1076	11/37	EVA5	<LOQ	<LOD	SML = 6	
		EVA7	<LOQ	<LOD		
		EVA8	<LOQ	<LOD		
		EVA1	140 \pm 11	<LOQ		
EBO	6.8/ 23	EVA3	<LOQ	<LOD	Authorized without SML	
Octadecanamide, N,N'-1,2-ethanediybis-	18/ 63	EVA4	213 \pm 11	65.8 \pm 5.2	Authorized without SML	
Irgafos 168	8.5/ 28.3	EVA1	53.4 \pm 3.7	<LOQ	Authorized without SML	
		EVA2	<LOQ	<LOD		
		EVA3	33.1 \pm 1.6	<LOD		
		EVA4	<LOQ	<LOD		
7,9-ditert-butyl-1-oxaspiro[4.5]deca-6,9-diene-2,8-dione	5.5/ 18	EVA1	53 \pm 3.8	<LOD	II	
		EVA2	<LOQ	<LOQ		
		EVA3	157 \pm 11	<LOD		
		EVA4	654 \pm 49	102 \pm 5.1		
		EVA5	269 \pm 24	47 \pm 3.8		
Sum of all cyclic co-oligomers	Poly(ethylene-co-vinyl acetate)9.8/ 32	EVA4	315 \pm 92	52 \pm 3.6	I	
Pentadecanamide, N,N'-1,2-ethanediybis-	Octadecanamide, N,N'-1,2-ethanediybis-	EVA4	<LOQ	<LOD	III	
Hexadecanamide, N,N'-1,2-ethanediybis-		18/63	EVA4	152 \pm 12	64.1 \pm 3.8	Authorized without SML
Heptadecanamide, N,N'-1,2-ethanediybis-	15/ 50	EVA4	115 \pm 13	<LOD	III	
Nonadecanamide, N,N'-1,2-ethanediybis-		EVA4	91.5 \pm 6.4	<LOQ	III	
Irgafos 168 OXO		EVA1	75.2 \pm 3.4	<LOQ	Authorized without SML	
		EVA2	<LOQ	<LOD		
		EVA3	<LOQ	<LOD		
	EVA4	87.4 \pm 2.5	52.1 \pm 3.6			
Volatile compounds						
Heptane 2,2,4,4,6,6-pentamethyl	Dodecane0.3/1.1	EVA1	6.2 \pm 0.4	2.8 \pm 0.6	I	
		EVA2	18.2 \pm 0.7	11.5 \pm 0.1		
		EVA3	0.9 \pm 0.1	0.9 \pm 0.3		
		EVA4	8.7 \pm 0.7	<LOQ		
		EVA5	3.3 \pm 0.2	<LOQ		
Branched alkane (1)		EVA1	1.3 \pm 0.1	<LOD		
		EVA3	0.7 \pm 0.1	0.8 \pm 0.1		
		EVA4	<LOQ	<LOQ		
		EVA5	<LOQ	<LOQ		
		EVA1	1.6 \pm 0.1	<LOD		
Branched alkane (2)		EVA3	<LOQ	<LOD		
		EVA4	<LOQ	<LOQ		
		EVA5	<LOQ	<LOQ		
		EVA1	2.3 \pm 0.1	<LOQ		
		EVA4	6.8 \pm 0.6	<LOD		
Nonane, 2,2,4,4,6,8,8-heptamethyl	0.5/1.6	EVA5	3.1 \pm 0.2	<LOD	SML = 4.8	
Phenol, 2,6-bis(1,1-dimethylethyl)-4-ethyl		EVA1	3.4 \pm 0.1	2.2 \pm 0.1		
		EVA2	1.7 \pm 0.2	<LOD		
BHT	0.4/1.2	EVA3	1.4 \pm 0.1	<LOD	SML = 3	
		EVA4	10.3 \pm 0.4	6.2 \pm 0.4		
		EVA5	3.7 \pm 0.1	<LOQ		
		EVA7	15.0 \pm 0.3	11.3 \pm 0.3		

4. Conclusion

A non-targeted migration study of eight corks made from an ethylene-vinyl acetate copolymer has been carried out using the analytical techniques of UHPLC-IMS-QTOF and SPME-GC-MS in order to identify the non-volatile and volatile compounds migrating to the simulants 20%

ethanol and 3% acetic acid. The use of an in-house spectral library, allowed us to perform an extractables and leachables study using statistical tools to isolate the unique markers migrating from the samples. The ion mobility incorporated into the QTOF mass analyzer provided clean spectra and improved resolution, thus reducing the number of possible interferences. We successfully integrated the CCS values as an

additional characteristic parameter, which allowed increased confidence level of the identification process.

A total of fifty compounds including non-volatiles and volatiles were identified, nine of which were additives such as antioxidants and crosslinking agents. The remaining compounds identified were NIAS, and included a group of cyclic co-oligomers, with different chain sequences, resulting from the copolymerization of ethylene and vinyl acetate monomers to produce the EVA copolymer. Potential chemical impurities were also found, such as a group of two amides bonded by ethylene.

For all compounds, the migration values were higher to 20% ethanol compared to those to 3% acetic acid. While the concentration of most of the migrants were below their respective SML or maximum values recommended by the Cramer toxicity scheme, three compounds from one of the corks were found to migrate to 20% ethanol at a concentration in excess of the level permitted by their Cramer classification. This implies that one of the tested corks is not suitable as food contact material.

This study presents a general overview of compounds (NIAS and additives) present in EVA materials intended to be into contact with food. It shows that these compounds can migrate from the product into the food it is contact with. The study provides important insights into the nature and potential origin of these compounds and can help producers of FCMs to reduce the prevalence of these compounds in the formulation of the final product.

CRedit authorship contribution statement

Paula Vera: Conceptualization, Investigation, Supervision. **Elena Canellas:** Investigation, Supervision. **Cristina Nerin:** Funding acquisition, Supervision. **Nicola Dreolin:** Investigation, Supervision. **Jeff Goshawk:** Investigation, Supervision.

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.

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