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Method for analysis of 68 organic contaminants in food contact paper using gas and liquid chromatography coupled with tandem mass spectrometry

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ABSTRACT

Food contact materials (FCMs) have been reported as a source of various xenobiotics. This study investigates the possibility of simultaneous analysis of 68 potential contaminants in paper FCMs, specifically phthalates, polycyclic aromatic hydrocarbons, photoinitiators, bisphenols, and polyfluorinated compounds. Target compounds were co-isolated using a technique based on ultrasonic extraction by mixture of acetonitrile and water followed by QuEChERS-like liquid–liquid partition in the presence of inorganic salts. Resulting extracts were analyzed using gas and high performance liquid chromatography coupled with tandem mass spectrometry (GC–MS/MS, HPLC–MS/MS). Acceptable recoveries (70–120%) and RSDs (<20%) were achieved for most of the analytes at spiking levels of 0.05, 0.2 and 1 mg/kg. LOQs ranged from 0.0013 to 0.22 mg/kg. The proposed method was successfully applied to analysis of 15 real samples. Complex mixtures of contaminants reaching levels up to 48 mg/kg were identified in the samples.

1. Introduction

Food contact materials (FCM) in the EU are subject of the Regulation (EC) No 1935/2004 stating FCM should not endanger human health or bring about an unacceptable change in the composition and a deterioration in organoleptic properties of food. There is a list of 17 types of FCM, which may be covered by specific measures, but only in the case of plastics, ceramics, regenerated cellulose films, active and intelligent materials detailed legislative requirements on EU-level have been introduced to date. However, some EU member countries regulated paper FCM on national level by implementing e.g. lists of approved substances.

An important question is which unintentional and probably harmful substances may enter the food chain via paper FCM. European Food Safety Authority (EFSA, 2009) identified paper and board along with other non-regulated items, e.g. coatings, adhesives, printing inks and rubber, as an important source of chemical contamination of food. Recent articles have reported occurrence of phthalates (Bononi & Tateo, 2009; Zhang, Noonan, & Begley, 2008), bisphenols (Pérez-Palacios, Fernández-Recio, Moreta, & Tena, 2012), ink photoinitiators (Bugey, Janin, Edder, & Bieri, 2013; Koivikko et al., 2010), fluorescent whitening agents (Chen & Ding, 2006), polyfluorinated compounds (PFC) (Begley et al., 2005; Poothong, Boontanon, & Boontanon, 2012; Trier, Granby, & Christensen, 2011) and biocides (Domeño, Munizza, & Nerín, 2005; Votavová, Hanušová, Vápenka, Dobiáš, & Kvasnička, 2014). Furthermore, EFSA (2012) believes that recycled paper and board represent an important source of mineral oil hydrocarbons (MOH) including both saturated and aromatic fractions (MOSH and MOAH, respectively).

Chemical contaminants in paper may contribute to overall human xenobiotic intake due to their capability of transfer into food. In cases, where paper contacts dry food, the migration takes place primarily via gas phase as it was demonstrated e.g. on an example of MOH (Moret, Grob, & Conte, 1997), phthalates (Poças, Oliveira, Pereira, Brandsch, & Hogg, 2011), or selected volatile organic pollutants (Triantafyllou, Akrida-Demertzi, & Demertzis, 2007).

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Despite the fact that the vapor pressures of compounds decrease with decreasing temperature, Johns, Jickells, Read, and Castle (2000) found that model ink components (b.p. between 223 °C and 305 °C) transfer from cardboard into food even in a frozen state (−20 °C). PFC do not volatilize easily but they readily migrate into directly contacted water-ethanol food simulants, fast food, butter and oily materials (Begley, Hsu, Noonan, & Diachenko, 2008; Begley et al., 2005; Trier et al., 2011). In fact, the number of substances migrating from paper packages can be so high as it seems impossible to bring all of them under control (Biedermann & Grob, 2013).

The presented study focused on 68 model contaminants of paper belonging into five different groups: phthalates, PAH, photoinitiators, bisphenols, and PFC, more specifically perfluoroalkylcarboxylic acids (PFCA), perfluoroalkylsulfonates (PFAS), perfluoroalkylphosphonic acids (PFAPA), polyfluorinated phosphate esters (PAP) and perfluoroctylsulfonamide (FOSA). Several multicomponent analytical studies have been published to date in this field, but in most cases, their scope is limited to analytes with similar physicochemical properties. This fact gives rise to a theoretical situation, where each paper article has to be analyzed using several quantitative methods in order to gain complex information about present contaminants resulting in inacceptable time, labor, and economic requirements. For this reason, we aimed to develop a simultaneous strategy for all the analytes.

Chromatographic techniques coupled with MS represent a predominant determination practice nowadays. GC–MS has been frequently used for the analysis of phthalates (Bononi & Tateo, 2009; Zhang et al., 2008) and PAH or MOAH (Biedermann & Grob, 2015; Bordajandi, Dabrio, Ulberth, & Emons, 2008; Chalbot, Vei, Lykoudis, & Kavouras, 2006), HPLC–MS/MS for bisphenols (Gallart-Ayala, Moyano, & Galceran, 2010; Pérez-Palacios et al., 2012) and PFC (Begley et al., 2005, 2008; Poothong et al., 2012; Trier et al., 2011), whereas ink photoinitiators have been analyzed by both techniques (Bugey et al., 2013; Sagratini et al., 2008; Shen, Lian, Ding, Xu, & Shen, 2009). Derivatization procedures were also developed for bisphenols and PFCA to make them amenable for GC–MS (Dufková, Čabala, & Ševčík, 2012; Viñas, Campillo, Martínez-Castillo, & Hernández-Córdoba, 2010). Another work describes the analysis of PAH by means of HPLC–MS using a silver nitrate post column reagent promoting ionization in an electrospray interface (Takino, Daishima, Yamaguchi, & Nakahara, 2001). In our study, simultaneous use of both chromatographic tools was preferred to the development of derivatization techniques. Triple quadrupole tandem MS instruments were employed for detection with expectation of providing excellent sensitivity and selectivity.

Solvent extraction using e.g. ethanol-water or methanol-water mixtures for PFC (Begley et al., 2005; Poothong et al., 2012; Trier et al., 2011), methanol for bisphenols (Pérez-Palacios et al., 2012), acetonitrile for photoinitiators (Bugey et al., 2013; Koivikko et al., 2010) and dichloromethane for phthalates (Zhang et al., 2008) has served for the isolation of target compounds from paper matrix. Headspace SPME application for the GC–MS analysis of diisobutyl phthalate in pizza boxes was also described by Bononi and Tateo (2009). Published methods typically involve no or minimum sample cleanup. In this study, various solvents and conditions were examined in order to find single extraction procedure for all of the analytes. Possible co-extracts were screened in real paper FCM prior to considering whether a cleanup is required or not.

2. Materials and methods

2.1. Chemicals

The mixture solution of 16 PAH (100 μg/ml) was purchased from Sigma–Aldrich. The individual solutions (50 μg/ml) of selected PFC were supplied by Wellington Laboratories. Other reference standards were neat or >95% purity compounds obtained from Sigma–Aldrich, Dr. Ehrenstorfer and Tokyo Chemical Industry. Isotopically labeled anthracene (D_{10}), benzophenone (D_{10}), bis(2-ethylhexyl) phthalate (D_4), bisphenol A (D_{14}) from Sigma–Aldrich and PFOA ($^{13}C_2$) from Wellington Laboratories served as internal standards. The detailed list of target compounds is given in Table 1.

All solvents used were high purity grade for trace analysis obtained from Sigma–Aldrich. Eluent aditive grade ammonium acetate and ammonium formate as well as monobasic sodium phosphate monohydrate were from Sigma–Aldrich. Sodium chloride (NaCl) and anhydrous magnesium sulfate ($MgSO_4$) were supplied by Merck. All chemicals were used as received except for NaCl and $MgSO_4$ which were baked at 400 °C for at least 4 h before use. Water was purified using a Purelab Classic system (ELGA LabWater).

Neat standards were dissolved in ethylacetate (PAH) or acetonitrile (other analytes) to form stock solutions (1 mg/ml). Working mixtures (1 μg/ml) were prepared from stock or purchased solutions in acetonitrile. Analyte concentrations in matrix-matched calibrations were 0.1, 0.3, 1, 3, 10, 30, 100, 200 and 300 ng/ml.

2.2. Samples

Real samples of paper FCM were acquired from the market in the Czech Republic (Table 2). Samples were cut into small pieces (approximately 2 × 10 mm) and stored in screw cap polypropylene containers.

Laboratory filtration paper served as a blank material for method development and validation experiments. For recovery study, blanks were fortified to the levels of 0.05, 0.2 and 1 mg/kg using the standard solution of analytes and let to stand for 1 h in order to simulate analyte incorporation into matrix. Fortified samples were analyzed using the same procedure as the real samples.

2.3. Sample preparation

2.3.1. Ultrasonic solvent extraction

The aliquots of paper samples (1.0–1.5 g) were precisely weighed into 50 ml disposable polypropylene tubes, into which 20 ml extraction solvent (acetonitrile, acetone or 2-propanol) and 100 μl internal standard solution were added. Each tube was capped and its contents mixed by short shaking. The sample was extracted using a Sonorex ultrasonic bath (Bandelin electronic) for 15 min at room temperature. The same extraction procedure using acetonitrile-water 1:1, 2-propanol-water 1:1 (*v*/*v*) or the buffered varieties of both containing 5 g/l monobasic sodium phosphate was employed prior to a liquid–liquid extraction (LLE, Section 2.3.2).

2.3.2. Liquid–liquid extraction

Liquid–liquid partition was achieved according to the procedure known as “quick, easy, cheap, effective, rugged and safe” (QuEChERS; Anastassiades & Lehotay, 2003) by adding 4 g $MgSO_4$ and 1 g NaCl into a tube containing the sample and the solvent-water extract. Each tube was hand-shaken for 1 min and centrifuged using an Universal 320R centrifuge (Hettich) at 3000 r/min for 3 min. The upper solvent layer was taken for further processing. Acetone was omitted from LLE experiments due to its low boiling point which is easily reached during the exothermic reaction between $MgSO_4$ and water.

2.3.3. Processing of raw extracts

Prior to HPLC–MS/MS, all extracts in organic solvents were diluted using an equal volume of ultrapure water and centrifuged

Table 1
Target compounds and detection parameters tabled in retention order: Retention times (RTs), collision energies (CIs).

Analyte	CAS	Abbreviation	RT (min)	MS/MS transition 1			MS/MS transition 2		
				Parent *m/z*	Product *m/z*	CI (eV)	Parent *m/z*	Product *m/z*	CI (eV)
GC–MS/MS method									
Naphtalene	91-20-3	Na	5.19	128.06	102.03	20	128.06	77.04	30
2-Methylnaphthalene	91-57-6	2MNa	5.73	142.08	115.05	25	142.08	141.07	25
1-Methylnaphthalene	90-12-0	1MNa	5.87	142.08	115.05	25	142.08	141.07	25
2,6-Dimethylnaphthalene	581-42-0	26DMNa	6.35	156.09	141.07	20	156.09	115.05	20
1,6-Dimethylnaphthalene	575-43-9	16DMNa	6.52	156.09	141.07	20	156.09	115.05	20
1,4-Dimethylnaphthalene	571-58-4	14DMNa	6.69	156.09	141.07	20	156.09	115.05	20
1,2-Dimethylnaphthalene	573-98-8	12DMNa	6.82	156.09	141.07	20	156.09	115.05	20
Acenaphthylene	208-96-8	Acy	7.01	152.06	126.05	20	152.06	102.05	30
Dimethyl phthalate	131-11-3	DMP	7.02	163.04	77.04	20	163.04	135.04	10
Acenaphthene	83-32-9	Ace	7.21	153.07	126.05	40	153.07	151.05	40
Diethyl phtalate	84-66-2	DEP	7.97	149.06	65.04	22	149.06	93.03	16
Fluorene	86-73-7	Fln	8.05	165.07	163.05	30	165.07	139.05	30
2,7-Diisopropylnaphthalene	40458-98-8	27DiPNa	8.39	212.16	197.13	10	212.16	155.09	20
2,6-Diisopropylnaphtalene	24157-81-1	26DiPNa	8.43	212.16	197.13	10	212.16	155.09	20
Benzophenone (D_{10})	–	BFN (D_{10})	8.57	192.14	110.06	15	192.14	82.07	20
Benzophenone	119-61-9	BFN	8.59	182.07	105.03	15	182.07	77.04	20
1-Methylfluorene	1730-37-6	1MFln	9.11	180.09	165.07	20	180.09	178.08	25
Ethyl-4-dimethylamino benzoate	10287-53-3	EDB	9.19	193.11	165.08	10	193.11	148.07	10
4-Methylbenzophenone	134-84-9	4MBFN	9.72	196.09	181.07	5	196.09	119.05	10
Diisobutyl phtalate	84-69-5	DiBP	10.02	149.06	65.04	22	149.06	93.03	16
Phenanthrene	85-01-8	Phe	10.18	178.08	176.07	20	178.08	152.06	20
Anthracene (D_{10})	1719-06-8	Ant (D_{10})	10.24	188.14	184.11	30	188.14	160.11	15
Anthracene	120-12-7	Ant	10.26	178.08	176.07	20	178.08	152.06	20
Dibutyl phthalate	84-74-2	DBP	10.94	149.06	65.04	22	149.06	93.03	16
2-Methylanthracene	613-12-7	2MAnt	11.17	192.09	190.08	25	192.09	165.07	30
9-Methylanthracene	779-02-2	9MAnt	11.70	192.09	190.08	25	192.09	165.07	30
Anthraquinone	84-65-1	–	12.09	208.05	180.06	10	208.05	152.06	15
Dipentyl phthalate	131-18-0	DnPP	12.15	149.06	65.04	22	149.06	93.03	16
Fluoranthene	206-44-0	Flt	12.48	202.08	200.06	30	202.08	176.06	30
Bis(2-ethylhexyl) adipate	103-23-1	DEHA	12.83	147.06	129.03	5	147.06	111.00	10
Pyrene	129-00-0	Pyr	12.93	202.08	200.06	30	202.08	176.06	30
2-Ethylhexyl-4-dimethylamino benzoate	21245-02-3	EHDB	12.94	277.20	165.07	10	277.20	148.07	20
Bis(2-ethylhexyl) phthalate (D_4)	93951-87-2	DEHP (D_4)	13.93	153.05	97.06	20	153.05	69.06	25
Bis(2-ethylhexyl) phthalate	117-81-7	DEHP	13.97	149.06	65.04	22	149.06	93.03	16
Diisononyl phthalate	28553-12-0	DiNP	14–17	293.14	149.06	10	293.14	167.03	5
Diheptyl phthalate	3648-21-3	DHpP	14.12	265.14	149.06	5	149.06	93.03	16
4-Isopropylthioxanthone	83846-86-0	4ITX	14.20	254.08	239.05	15	254.08	196.00	25
2-Isopropylthioxanthone	5495-84-1	2ITX	14.29	254.08	239.05	15	254.08	196.00	25
Diisodecyl phthalate	26761-40-0	DiDP	15–18	307.20	149.06	10	307.20	167.10	8
Benzo(*a*)anthracene	56-55-3	BaA	15.13	228.09	226.08	30	228.09	202.08	30
Dioctyl phthalate	117-84-0	DnOP	15.27	149.06	65.04	22	149.06	93.03	16
Chrysene	218-01-9	Chr	15.30	228.09	226.08	30	228.09	202.08	30
Benzo(*b*)fluoranthene	205-99-2	BbF	18.15	252.09	226.08	30	252.09	250.09	30
Benzo(*k*)fluoranthene	207-08-9	BkF	18.23	252.09	226.08	30	252.09	250.09	30
Benzo(*a*)pyrene	50-32-8	BaP	19.25	252.09	226.08	30	252.09	250.09	30
Dibenzo(*ah*)anthracene	53-70-3	DBahA	21.25	278.11	276.08	30	278.11	274.08	60
Indeno(1,2,3-*cd*)pyrene	193-39-5	IcdP	21.25	276.09	274.08	40	276.09	272.08	60
Benzo(*ghi*)perylene	191-24-2	BghiP	22.31	276.09	274.08	40	276.09	272.08	60
HPLC–MS/MS method									
Perfluorobutanoic acid	375-22-4	PFBA	3.86	213.0	119.0	8	213.0	169.0	10
Bisphenol S	80-09-1	BPS	3.99	249.0	92.1	36	249.0	108.0	28
Perfluorohexanephosphonic acid	–	PFHxPA	4.54	398.8	79.0	30	–	–	–
Perfluoropentanoic acid	2706-90-3	PFPA	4.57	219.0	69.0	36	262.8	218.8	4
Perfluorobutanesulfonic acid	375-73-5	PFBS	4.65	298.9	80.0	45	298.9	98.9	32
Bisphenol F	620-92-8	BPF	5.23	199.0	92.7	20	199.0	105.0	18
Perfluorohexanoic acid	307-24-4	PFHxA	5.39	269.0	119.0	18	312.9	268.9	4
Bisphenol A (D_{14})	–	BPA (D_{14})	6.19	241.0	222.9	16	241.0	142.0	24
Perfluoroheptanoic acid	375-85-9	PFHpA	6.24	319.0	118.9	16	363.0	318.9	6
Perfluorooctanephosphonic acid	–	PFOPA	6.24	498.7	79.0	35	–	–	–
Perfluorohexanesulphonic acid	355-46-4	PFHxS	6.25	399.0	80.0	50	399.0	99.0	36
Bisphenol A	80-05-7	BPA	6.26	227.1	133.0	24	227.1	212.0	16
Sodium 1H,1H,2H,2H-perfluorooctyl phosphate	–	6:2PAP	6.79	442.8	79.0	62	442.8	97.0	16
Perfluorooctanoic acid	335-67-1	PFOA	7.05	368.9	169.0	16	412.9	368.9	6
Perfluorooctanoic acid ($^{13}C_2$)	–	PFOA ($^{13}C_2$)	7.06	415.0	370.0	6	–	–	–
Perfluorooctanesulphonic acid	1763-23-1	PFOS	7.74	498.8	80.0	56	498.8	98.9	52
Perfluorononanoic acid	375-95-1	PFNA	7.78	419.0	169.0	16	419.0	219.0	14
Perfluorodecanephosphonic acid	–	PFDPA	7.89	598.7	79.0	74	–	–	–
Sodium 1H,1H,2H,2H-perfluorodecyl phosphate	–	8:2PAP	8.28	542.8	79.0	76	542.8	97.0	18
Perfluorodecanoic acid	335-76-2	PFDA	8.42	468.9	218.9	16	512.8	468.9	8
Perfluoroundecanoic acid	2058-94-8	PFUnA	8.96	518.9	268.9	16	562.9	518.9	8
Perfluoroctylsulfonamide	754-91-6	FOSA	9.01	497.9	47.9	80	497.9	78.0	38

(*continued on next page*)

Table 1 (*continued*)

Analyte	CAS	Abbreviation	RT (min)	MS/MS transition 1			MS/MS transition 2		
				Parent *m/z*	Product *m/z*	CI (eV)	Parent *m/z*	Product *m/z*	CI (eV)
Perfluorododecanoic acid	307-55-1	PFDoA	9.44	613.0	169.0	35	613.0	569.0	17
Sodium bis(1H,1H,2H,2H-perfluorooctyl) phosphate	–	6:2diPAP	10.00	788.8	96.9	32	788.8	442.9	20
Sodium bis(1H,1H,2H,2H-perfluorodecyl) phosphate	–	8:2diPAP	10.90	988.8	96.9	38	988.8	542.9	24

Table 2
Description of real samples, distribution of analyte concentrations and maximum levels found (Max.).

Sample description	Sample	Type of food contact	Analyte count			Max. (mg/kg)
			LOQ–1 mg/kg	1–10 mg/kg	>10 mg/kg	
Paper packages of wheat flour	1	Direct	13	0	0	0.43 (DiBP)
	2	Direct	16	1	0	1.5 (4MBFN)
Paper bags for bakery products	3	Direct	35	2	3	31 (DiBP)
	4	Direct	34	7	3	25 (DBP)
Sheets of paper for food packaging in food stores	5	Indirect	28	8	1	19 (DEHP)
	6	Indirect	23	4	0	8.6 (DiBP)
Cardboard boxes for packaging of various foodstufs	7	Indirect (cheese)	27	8	3	12 (DiBP)
	8	Direct (pizza)	31	10	3	48 (DiBP)
	9	Indirect (chocolates)	31	9	1	13 (DEHP)
Coated bakery release papers for oven baking at temperatures up to 220 °C	10	Direct	5	0	0	0.24 (DiBP)
	11	Direct	8	1	0	2.3 (DEHA)
	12	Direct	8	0	1	18 (BFN)
Paper filters for coffee preparation	13	Direct	9	2	0	2.0 (DiBP)
	14	Direct	9	1	0	1.0 (DiBP)
	15	Direct	18	0	0	0.72 (DiBP)

at −10 °C and 9000 r/min for 10 min. Prior to GC injection, the raw solvent extracts obtained by the LLE required treatment by $MgSO_4$ in order to reduce the residual amount of water. The acetonitrile extracts were shaken with 150 mg $MgSO_4$ per each ml, while the 2-propanol extracts were first diluted using an equal volume of *n*-hexane and then shaken with 150 mg $MgSO_4$ per each ml of resulting solution. $MgSO_4$ was subsequently removed by centrifugation at 3000 r/min for 3 min. Pure solvent extracts were injected directly into GC.

2.4. Instrumental analysis

2.4.1. HPLC–MS/MS

HPLC analyses were carried out using an Agilent 1290 HPLC system connected to an Agilent 6490 triple quadrupole MS/MS via a Jetstream electrospray ionization (ESI) source (Agilent Technologies). Experiments used a reverse-phase Poroshell 120 EC-C18 column (150 mm long, 3.0 mm i.d., 2.7 μm particle size; Agilent Technologies) maintained at 40 °C. Sample aliquots (20 μl) were injected into 0.4 ml/min flow of the mobile phase consisting of (A) 2 mmol/l ammonium acetate in ultrapure water and (B) 2 mmol/l ammonium acetate in methanol. The initial proportion of 20% (B) was linearly ramped to 60% (B) at 2 min, then linearly ramped to 100% (B) at 10 min and finally held at 100% (B) for 2 min. The system was equilibrated using the initial composition for at least 4 min prior to each analysis.

The conditions of the ESI source operating in the negative polarity mode were set as follows: 200 °C drying gas temperature, 20 l/min drying gas flow, 40 psi nebulizer pressure, 325 °C sheath gas temperature, 10 l/min sheath gas flow, 3000 V capillary voltage and 1000 V nozzle voltage. Dwell time 10 ms was set to each MS/MS transition acquired in multiple reaction monitoring (MRM) mode.

2.4.2. GC–MS/MS

GC–MS analyses employed a system consisting of a Trace 1310 GC, a Triplus RSH autosampler and a TSQ Quantum XLS Ultra triple quadrupole MS (Thermo Scientific). Sample aliquots (5 μl) were introduced into a programmable temperature vaporizer (PTV) injector equipped with a 2 mm deactivated multiple-baffle liner heated to 40 °C. The sample solvent was evaporated by 40 ml/min helium flow to a split vent. Solvent vent time was determined in repeated injection experiments as the shortest time required for avoiding peak distortion resulting from solvent overflow: 0.60 min was used for acetonitrile, 0.50 min for 2-propanol, 0.25 min for 2-propanol-hexane mixture and 0.15 min for acetone. The analytes were transferred on a Rxi-PAH column (30 m long, 0.25 mm i.d., 0.10 μm film thickness, Restek) after heating the PTV to 280 °C at 14.5 °C/s in splitless mode (splitless time 1 min). Oven temperature was initially held at 50 °C for 2 min, then ramped at 50 °C/min to 150 °C, 10 °C/min to 210 °C, 20 °C/min to 270 °C, 3 °C/min to 285 °C, 20 °C/min to 325 °C and finally held at 325 °C for 3 min. Helium carrier gas flow was maintained at 1 ml/min.

Electron ionization (EI) was carried out under following conditions: −70 eV ionization energy, 50 μA emission current and 200 °C source temperature. Pressure of collision gas (argon) and acquisition cycle time were set to 1 mTorr and 0.2 s, respectively. GC–MS screening of major matrix components was performed using the full scan mode acquiring *m/z* from 50 to 650.

3. Results and discussion

3.1. Sample preparation

The key objective of our work was to develop a simultaneous sample preparation strategy for the isolation of 68 analytes from paper matrix. When attempting to recover compounds ranging from relatively polar PFC to apolar PAH, medium polarity solvents acetone, acetonitrile and 2-propanol were selected in the first place. In order to examine extraction efficiency, solvents were added to paper matrix fortified with 0.2 mg/kg target compounds and the extraction took place in the ultrasonic bath. As Fig. 1 shows, acetone and 2-propanol yielded comparable amounts of spiked analytes, while there was a higher proportion of lower recoveries when using acetonitrile thus confirming its lower efficiency. Mono-

PAP and PFAPA were, however, not detected at all regardless the extractant used. Esparza, Moyano, De Boer, Galceran, and Van Leeuwen (2011) also reported difficulties when recovering PFAPA from sewage sludge or sediments and concluded that tetrahydrofuran-water (1:3) was the optimum solvent composition. Organic solvents with a certain proportion of water frequently serve for extraction of other PFC as mentioned in Section 1, but in this application, undesired complications were expected to take place when injecting such solvent into the GC system. Samples were, therefore, first extracted by solvent-water 1:1 (*v*/*v*) mixture and subsequently $MgSO_4$ and NaCl were added in order to separate organic phase from aqueous. Prior to GC injection, residual amount of water was removed by $MgSO_4$. Consequently, recoveries of all spiked compounds including mono-PAP and PFAPA improved significantly when using acetonitrile (Fig. 1). This observation may be explained as a result of both salting-out effect, which is an important feature of QuEChERS method, and matrix hydration effect, which plays a crucial role e.g. when recovering incurred pesticide residues (Poulsen, Christensen, & Herrmann, 2009). Rather surprisingly, 2-propanol provided even poorer results in the LLE process.

Our experiments also explored the effect of monobasic sodium phosphate which was expected to shift the acid-base equilibria of PFC towards protonated forms and enhance their transfer into the organic phase. Yet, the results show no additional benefit of the buffer.

Acetonitrile extracts of 15 real samples were subjected to analysis by means of GC–MS operating in scan mode in order to learn about possible interferents. The signals of aliphatic hydrocarbons C_{24}–C_{38} (probably residues of waxes) were identified in sample 5 (Fig. 2). Mineral oils may act as another source of aliphatic hydrocarbons in recycled papers as discussed in Section 1. The main problem with these compounds is that they may contaminate the reversed-phase HPLC system and make its operating backpressure grow (Kumar, Verma, & Gaur, 2014). Because HPLC was employed in this study as one of the determination paths, the possibility of hydrocarbon elimination was investigated.

When an equal volume of ultrapure water was added to the raw acetonitrile extract as proposed by Mawn et al. (2005), the solid matter precipitated out of the solution and after centrifugation, the signals of aliphatic hydrocarbons disappeared from the GC–MS scan. However, even after this treatment, precipitation of some real extracts was observed to continue during the storage at 4 °C in a HPLC autosampler. For this reason, lowered temperature (−10 °C) was applied during centrifugation of diluted extracts.

In the final method, samples were isolated using unbuffered

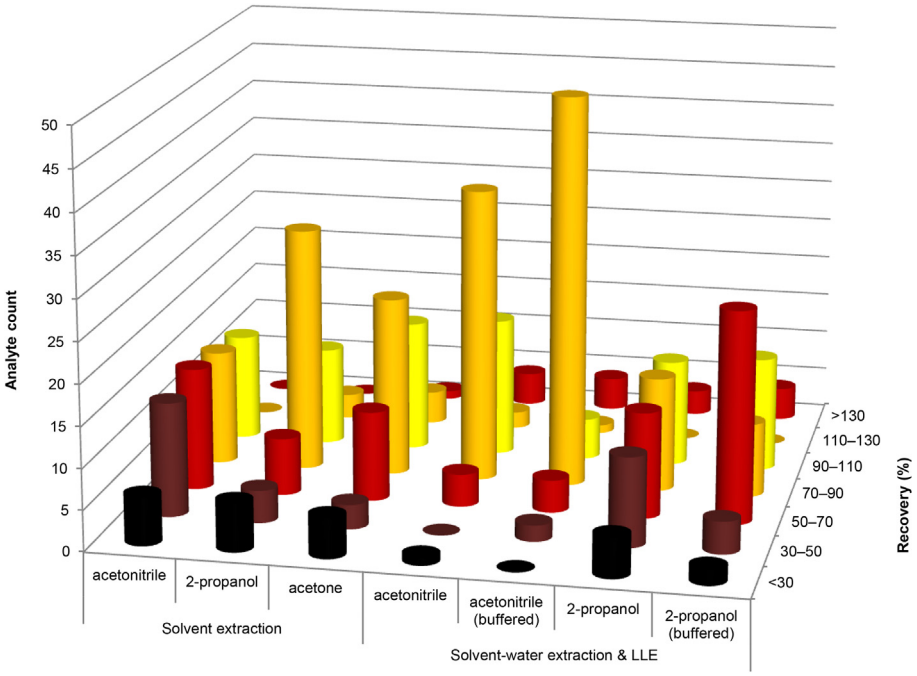

Fig. 1. Distributions of analyte recoveries at 0.2 mg/kg ($n = 3$) when using various extraction techniques and solvents.

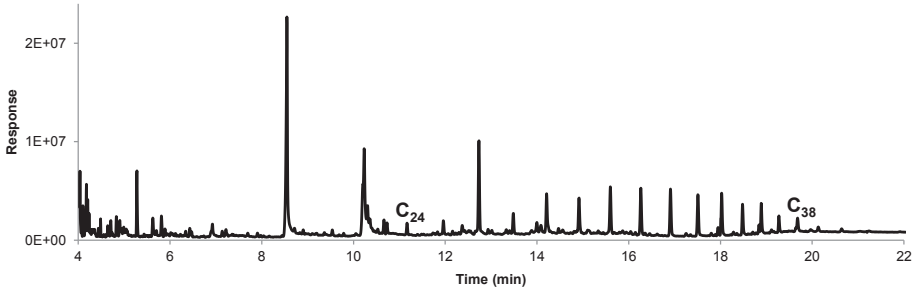

Fig. 2. Chromatographic profile of C_{24}–C_{38} *n*-alkanes in sample 5 (*m*/*z* 85).

acetonitrile LLE process (Section 2.3.2). Obtained extracts were dried prior to GC, whereas prior to HPLC, the extract was mixed with additional amount of water and centrifuged at −10 °C.

3.2. Chromatographic and MS/MS conditions

PAH, phthalates and photoinitiators were determined simultaneously by means of GC–MS/MS. The Rxi-PAH column was selected for the separation as the mix of 16 PAH and 11 alkylated analogs of PAH was included in the scope of this method. Aside Phe, Ant, BbF and BkF, separation of which is generally considered problematic (Bordajandi et al., 2008), two additional critical pairs (26DiPNa and 27DiPNa, 2ITX and 4ITX) were identified in the scope of this study. Fig. 3 shows the chromatographic resolution of these compounds achieved by the optimized GC gradient. Moreover, additional non-targeted signals frequently occurred nearby the elution zones of alkylated PAH in real samples. This probably results from either high complexity of present mineral oils (Biedermann & Grob, 2015), or components of carbonless copy paper in case of DiPNa (Sturaro, Parvoli, Rella, Bardati, & Doretti, 1994). However, quantitative determination was still possible thanks to sufficient chromatographic separation of interfering signals from target compounds as demonstrated on example of DiPNa (Fig. 4).

No critical pairs were identified among bisphenols and PFC allocated into HPLC run due to the complete spectral resolution of the analytes. Mobile phase solvents (acetonitrile and methanol) and additives (0.1% formic acid, 0.1% acetic acid, 2 mmol/l ammonium formate and 2 mmol/l ammonium acetate) were examined in a full factorial experiment, since the published literature lacks general agreement. H. Gallart-Ayala et al. (2010) recommended methanol mobile phase containing no additives in order to avoid ion suppression of BPA. On the other hand, the signal of BPA was reported to increase after the addition of acetic acid into acetonitrile mobile phase (Pérez-Palacios et al., 2012) or ammonium acetate into methanol mobile phase (Chu, Haffner, & Letcher, 2005) which is consistent with our results (Fig. 5). Consequently, the highest signals of three studied bisphenols, on average, were obtained with ammonium acetate, no matter what the solvent was.

Ammonium acetate, ammonium formate or ammonium hydroxide typically find use in mobile phases for analysis of PFC. In this study, most of PFC showed best responses in methanol containing neither buffers, nor acids. Nevertheless, the peak shapes of PAP, PFAPA and late eluting PFCA were notably distorted. The addition of ammonium acetate substantially improved the peak shapes and provided still acceptable responses as documented in Fig. 6 which made this composition a good choice for the final method.

During the development of the MS/MS methods, precursor ions were selected from acquired full MS spectrum; $[M - H]^-$ ions characteristically formed in the ESI interface. Product ion scans at the collision energies of 0, 20, 40 and 60 eV (HPLC–MS/MS) and 5, 10, 15, 20, 25, 30, 35 and 40 eV (GC–MS/MS) were performed in order to select at least 2 transitions per analyte. This common identification criterion could not have been met by PFAPA since their $[M - H]^-$ yield only a single fragment (PO_3^-, m/z 79). Collision energies were finally optimized in MRM experiments.

3.3. Validation study

Analysis of phthalates frequently encounters a problem with raised blanks. Since especially DBP and DEHP are known to abound the environment including the air, which allows them to contaminate all laboratory equipment, (Fankhauser-Noti & Grob, 2007)

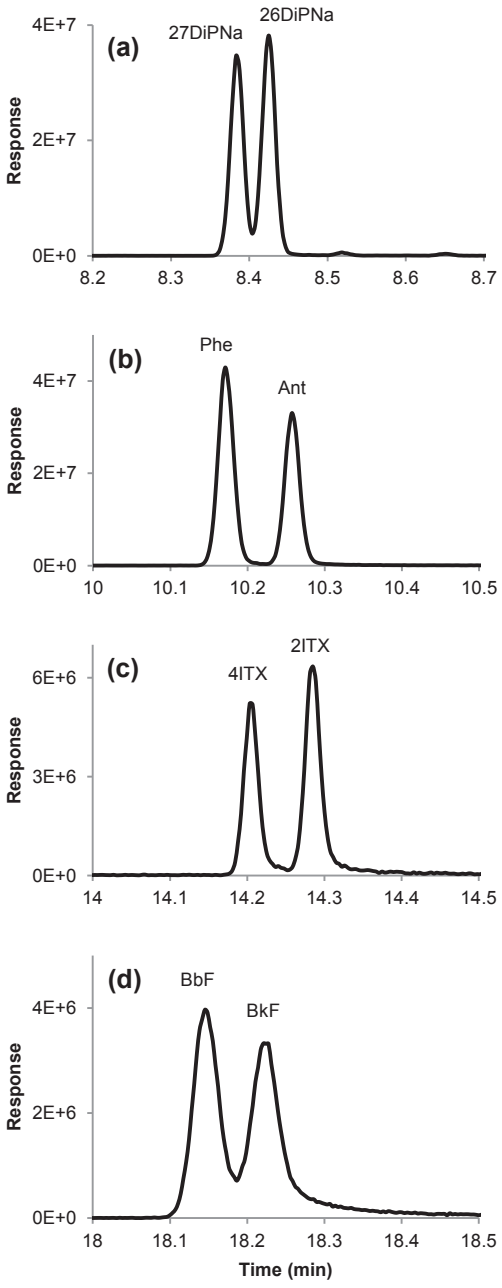

Fig. 3. Typical chromatograms of four critical pairs on Rxi–PAH column (a) m/z 212.16 → 197.13, (b) m/z 178.08 → 176.07, (c) m/z 254.08 → 239.05, (d) m/z 252.09 → 250.09.

proposed several measures to avoid their undesired presence. In this study, all laboratory glassware, $MgSO_4$ and NaCl were baked at 400 °C prior to use but even after implementing this precaution, procedure blanks of DiNP, DBP, DiDP, DEHP, DiBP and DEP remained at the levels of 18, 15, 8.5, 6.4, 5.8 and 2.2 μg/kg, respectively. The blank responses of DEHA, PAP and PFAPA were noted as well. Owing to the fact that common signal-to-noise practice for estimation of LOQ was useless in this situation, LOQs were determined from linear regressions. Six independent measurements of the matrix-matched calibrations were performed and LOQs were expressed as $LOQ = 10\, s_a/b$, where s_a is standard deviation of intercept and b is average slope. The resulting values show evident relation to blank levels (Table 3). This phenomenon can be demonstrated on the example of phthalates, most of which are quantified using the same

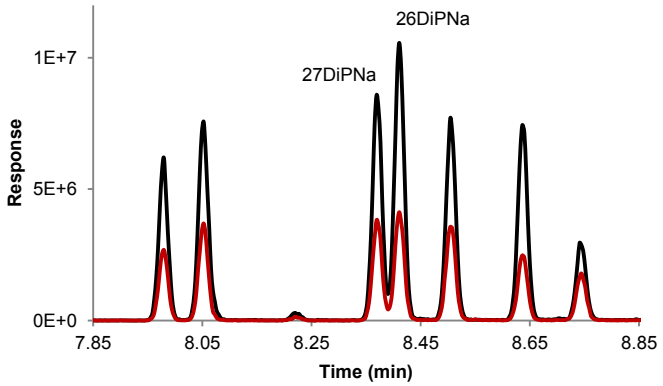

Fig. 4. Chromatographic profile of sample 5 showing 26DiPNa, 27DiPNa and interfering signals, (▬) *m/z* 212.16 → 197.13, (▬) *m/z* 212.16 → 155.09.

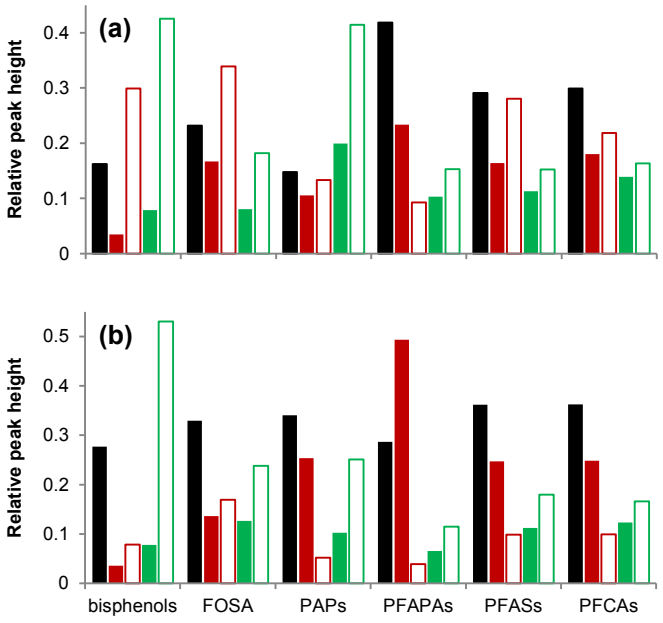

Fig. 5. Relative peak heights of LC analytes in (a) acetonitrile and (b) methanol mobile phases containing (■) no additives, (■) 0.1% formic acid, (□) 0.1% acetic acid, (■) 2 mmol/l ammonium formate, (□) 2 mmol/l ammonium acetate. Responses of individual compounds in each group were averaged.

MS/MS transition (*m/z* 149.06 → 65.04) with a comparable sensitivity, although corresponding LOQs spread in a 110-fold range.

Six replicates of each level of fortified samples (0.05, 0.2, 1 mg/kg) were analyzed in order to evaluate recovery and RSD of the proposed procedure. Resulting RSDs were below 20% with only exception (BPF, 1 mg/kg). Recoveries of some compounds, mostly phthalates, exceeded 120% when the spiking level was close to LOQ. Since the higher levels of the same compounds were recovered normally, this was probably again a result of the blank contribution. By contrast, less than 70% of spiked amount of low molecular weight PAH (Na, 1MNa and 2MNa) was recovered at 0.05 mg/kg. Yields of PFHxPA ranged around 50% at all spiking levels denoting this single compound was not fully recovered during the extraction.

3.4. Real samples

In order to further explore the applicability of the validated method, a total of 15 real food packages were analyzed. Table 3 summarizes minimum and maximum levels of the identified analytes. There were 17 analytes with maximum levels beyond 1 mg/kg; even the level of 10 mg/kg was exceeded in case of BFN, DiBP, DBP, DEHP, and BPA. The maximum levels of e.g. DBP, BPA and 26DiPNa were still lower than published values 55, 25.4, and 62.5 mg/kg, respectively (Pérez-Palacios et al., 2012; University of Rome 'La Sapienza', 1995; Zhang et al., 2008), however, our multi-analyte approach revealed that complex mixtures of xenobiotics are typically present in samples. This applies especially to cardboard boxes, wrapping papers and bags for bakery products. As Table 2 documents, up to 44 compounds were identified per sample (samples 4 and 8). On the other hand, notably lower levels of less frequent analytes were found in baking papers and coffee filters.

4. Conclusions

We developed a novel method based on GC–MS/MS and HPLC–MS/MS for simultaneous determination of 68 contaminants in paper FCM. The sample preparation process based on QuEChERS approach provides acceptable recoveries and RSDs for most of phthalates, PAH, photoinitiators, bisphenols and PFC. LOQs were sometimes affected by the presence of the target compounds in the laboratory environment but, at the same time, low enough to allow quantification of 56 of the target compounds in 15 real samples. Our results show that paper FCM are frequently contaminated by complex "chemical cocktails", which represent a potential health

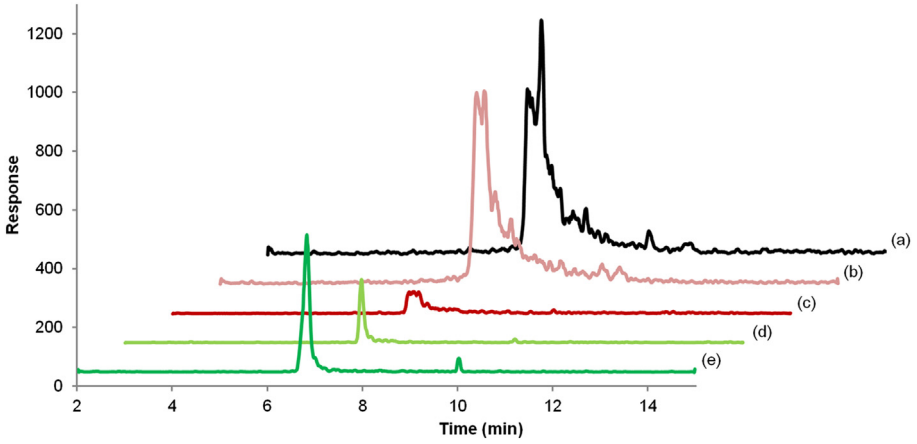

Fig. 6. Chromatographic profiles of 6:2 PAP in methanol-water mobile phase containing (a) no additives, (b) 0.1% formic acid, (c) 0.1% acetic acid, (d) 2 mmol/l ammonium formate, (e) 2 mmol/l ammonium acetate (*m/z* 442.8 → 79.0).

Table 3
Results of the validation study and the analysis of 15 real samples: limits of quantification (LOQs), relative standard deviations (RSDs), mean recoveries (Rec.), counts of positive samples (*n*), minimum and maximum concentrations found (Min., Max.).

Compound	LOQ[a] (mg/kg)	Level 0.05 mg/kg		Level 0.2 mg/kg		Level 1 mg/kg		Occurences in real samples		
		RSD (%)	Rec. (%)	RSD (%)	Rec. (%)	RSD (%)	Rec. (%)	*n*	Min. (mg/kg)	Max. (mg/kg)
Anthraquinone	0.018	2.9	135	2.4	115	0.95	97	9	0.062	1.2
DEHA	0.22	–	–	–	–	2.6	97	9	0.26	7.8
Phthalates										
DBP	0.19	–	–	10	96	4.3	95	12	0.16	28
DEHP	0.10	–	–	16	133	6.7	90	14	0.13	19
DEP	0.031	8.2	128	4.5	111	1.1	98	13	0.025	1.1
DHpP	0.0023	5.3	88	5.2	79	2.8	99	7	0.0064	0.036
DiBP	0.11	–	–	7.7	122	4.1	102	15	0.21	48
DiDP	0.19	–	–	13	117	11	86	7	0.62	3.4
DiNP	0.20	–	–	16	92	9.6	73	7	1.2	8.5
DMP	0.0065	4.4	132	3.1	117	1.9	99	9	0.011	1.0
DnOP	0.011	8.3	127	7.9	95	6.1	97	7	0.061	0.36
DnPP	0.0018	3.4	92	1.7	92	1.5	102	1	0.015	0.015
PAH										
12DMNa	0.0037	6.3	78	2.9	86	2.0	99	3	0.0032	0.013
14DMNa	0.0039	7.3	74	2.5	86	2.5	99	3	0.0039	0.014
16DMNa	0.0046	5.9	79	3.5	88	2.2	100	8	0.0031	0.068
1MFln	0.0034	1.5	94	1.4	94	1.2	99	13	0.0039	1.1
1MNa	0.0075	8.1	65	7.9	83	2.4	100	6	0.0074	0.028
26DiPNa	0.0063	4.4	101	2.3	94	1.8	98	15	0.017	2.5
26DMNa	0.0038	7.3	76	3.3	88	2.3	99	7	0.0034	0.045
27DiPNa	0.0085	3.4	105	2.8	100	2.1	98	15	0.013	2.3
2MAnt	0.0061	1.1	102	1.2	102	1.0	99	7	0.0064	0.12
2MNa	0.0087	8.9	64	6.4	85	2.8	100	5	0.0081	0.036
9MAnt	0.0046	5.1	103	1.9	103	1.1	100	0	–	–
Ace	0.0072	7.0	79	2.4	93	1.9	99	0	–	–
Acy	0.0040	8.1	82	4.0	94	1.9	100	1	0.012	0.012
Ant	0.0057	1.9	93	1.9	93	0.85	100	4	0.0061	0.014
BaA	0.0042	3.6	105	3.0	105	0.67	98	7	0.0043	0.027
BaP	0.0070	5.8	111	3.6	111	2.1	97	0	–	–
BbF	0.0051	4.6	107	4.9	110	1.4	99	6	0.013	0.035
BghiP	0.0083	7.2	96	4.9	93	8.7	95	8	0.0067	0.080
BkF	0.0064	5.5	113	3.3	114	1.0	98	6	0.0076	0.014
DBahA	0.013	5.9	97	5.4	93	9.6	95	1	0.012	0.012
Fln	0.0056	6.5	94	2.3	96	0.93	99	6	0.0096	0.054
Flt	0.0053	2.3	107	1.9	103	1.1	99	10	0.0043	0.11
Chr	0.0060	6.4	102	3.3	99	1.5	96	9	0.0058	0.14
IcdP	0.0093	3.7	99	5.5	95	8.9	94	5	0.0088	0.022
Na	0.029	5.8	52	15	79	3.5	101	3	0.027	0.033
Phe	0.0076	1.5	129	1.3	101	0.99	100	9	0.0074	0.24
Pyr	0.0051	2.2	105	2.6	102	1.3	99	9	0.013	0.12
Photoinitiators										
2ITX	0.0095	2.2	117	2.1	110	1.0	99	7	0.014	1.9
4ITX	0.0050	4.4	124	3.1	113	1.2	99	8	0.013	0.23
4MBFN	0.0077	3.1	114	2.6	106	1.0	100	12	0.0084	1.5
BFN	0.015	2.8	120	1.3	100	1.1	99	15	0.021	18
EDB	0.0041	12	115	4.6	113	2.4	96	9	0.0062	0.25
EHDB	0.0051	9.1	109	2.9	115	1.7	95	7	0.0047	0.23
Bisphenols										
BPA	0.059	–	–	7.7	108	17	120	7	0.22	12
BPF	0.070	–	–	14	108	21	85	3	0.082	0.13
BPS	0.0042	6.5	86	12	86	8.6	88	4	0.13	1.1
PFC										
6:2diPAP	0.0079	8.7	98	8.6	97	6.1	76	6	0.010	0.055
6:2PAP	0.13	–	–	15	84	9.3	78	1	0.13	0.13
8:2diPAP	0.019	11	143	5.9	114	6.1	85	3	0.019	0.12
8:2PAP	0.10	–	–	12	85	4.6	70	3	0.10	0.23
FOSA	0.0027	4.6	86	5.1	85	5.8	77	1	0.0050	0.0050
PFBA	0.0053	9.2	90	8.0	82	5.1	78	0	–	–
PFBS	0.0013	7.6	99	6.2	97	6.0	86	0	–	–
PFDA	0.0031	7.8	88	7.8	92	9.0	87	0	–	–
PFDoA	0.0032	7.2	92	11	90	6.3	89	0	–	–
PFDPA	0.046	15	107	11	101	6.8	78	0	–	–
PFHpA	0.0038	8.0	100	7.8	112	9.0	106	0	–	–
PFHxA	0.0035	7.5	85	7.3	88	6.5	79	1	0.010	0.010
PFHxPA	0.031	19	56	7.8	46	9.4	59	0	–	–
PFHxS	0.0030	14	81	11	82	7.9	78	0	–	–
PFNA	0.0047	5.5	109	5.9	111	9.8	105	0	–	–
PFOA	0.0031	5.7	88	14	101	8.7	93	0	–	–
PFOPA	0.038	13	85	11	80	5.7	79	0	–	–
PFOS	0.0056	12	75	13	77	13	75	0	–	–
PFPA	0.052	–	–	11	96	7.8	79	0	–	–
PFUnA	0.0034	6.3	103	2.8	104	6.6	99	0	–	–

[a] Presented LOQs correspond to typical sample aliquot 0.1 g/ml. Note that aliquots ranging between 0.1 and 0.15 g/ml were used when analyzing real samples.

risk for consumers and make paper FCM worthy of control. The method presented here perfectly suits this task, because it offers a cost effective and high throughput alternative to implementing several methods with a limited scope.

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