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Method Article

Development of a sensitive analytical method for the simultaneous analysis of Benzophenone-type UV filters and paraben preservatives in umbilical cord blood



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A B S T R A C T

UV filters and parabens are compounds used in large quantities in modern societies and have become ubiquitous in the environment. They are considered compounds of emerging concern due to the unwanted effects they cause in the environment and their bioaccumulation potential in humans. Considering their endocrine disrupting activity and their so far unknown effects in newborns, a continuous monitoring of these substances is required. In this work, we developed and validated a new sensitive methodology for the analysis of 8 UV filters and metabolites, and 4 parabens in umbilical cord blood samples. The method consisted of a liquid-liquid extraction and phase separation by freezing. Then, the organic extract was further analyzed at alkaline pH using liquid chromatography coupled to tandem-mass spectrometry (LC-MS/MS) using a QqLIT hybrid mass spectrometer as analyzer. The low limits of detection achieved (0.01–0.42 ng/mL) allowed the reliable simultaneous quantification of UV filters and parabens in this complex biological matrix.

- Simple, fast and sensitive analysis of UV filters and parabens in cord blood samples.
- First simultaneous analysis of UV filters and parabens in cord blood.
- Allows the evaluation of perinatal transfer of UV filters and parabens from the mother to the fetus.

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Method details

Background

The industrial production and the use of personal care products (PCPs) have increased in recent years. Among these compounds are UV filters and parabens, which are extensively used as sunscreens and as preservatives, respectively. They are present in cosmetics, sunscreens, lotions, hygiene products, but also in foodstuff, plastics, rubbers, and textiles [9]. These compounds are considered contaminants of emerging concern (CECs) for the negative effects they can cause in the environment, including their potential for bioaccumulation [5,6] and biomagnification through the food web [3]. Their bioaccumulation in humans has also been reported [8,12,15,19,20]. This fact combined with their endocrine disrupting activity [1,2,10,13,14] make a regular monitoring of their occurrence necessary. This is even more important in crucial stages of life like pregnancy [4], where the exposure of the unborn to these substances might have short- and long-term consequences in the development of the fetuses. Similar works are reported for the analysis of benzophenones or parabens in cord blood [7,12,16–18]. However, most of these methods use a solid-phase extraction [7,16,18] implying time-consuming and tedious steps, in addition to other steps such as long incubation, and derivatization. Kruse et al. used a laborious method, including an incubation of 3 h. This method was developed to detect benzophenone derivatives in serum (from the mothers and the fetuses) but all the cord blood samples analyzed were below the method limit of detection. Recently Song et al. presented a simpler method, however, it included time-consuming steps (incubation of 12 h and shaking for 60 min). Despite that, only benzophenone-type compounds could be determined. This work describes a sensitive method for the simultaneous analysis of UV filters and paraben preservatives in umbilical cord blood in order to achieve a better understanding of the bioaccumulation of these compounds and their maternal transfer. To this end, a method used for the analysis of bisphenols and parabens [11] was adapted and significantly simplified for the simultaneous analysis of eight benzophenone-type UV filters and metabolites, and four parabens in human cord blood.

Chemicals and reagents

Table 1 lists the selected compounds. The UV filters avobenzene (AVO), benzophenone-2 (BP2), benzophenone-4 (BP4), benzophenone-3 (BP3) and their main metabolites namely benzophenone-1 (BP1), 4-hydroxybenzophenone (4HB), 4,4'-dihydroxybenzophenone (4DHB), and 2,2'-dihydroxy-4-methoxybenzophenone (DHMB, BP8), and the paraben preservatives methyl paraben (MePB), propyl paraben (PrPB), benzyl paraben (BePB), and butyl paraben (BuPB) were purchased from Sigma Aldrich (Darmstadt, Germany). The isotopically labelled compounds 2-hydroxy-4-methoxy-2',3',4',5',6'-d5 (BP3-d5), benzyl paraben-d4 (BePB-d4), and 5-(2,5-dimethylphenoxy)-2,2-

bis(trideuteriomethyl)pentanoic acid (Gemfibrozil-d6) were purchased from CDN isotopes (Quebec, Canada). Water and methanol (MeOH) of high performance liquid chromatography (HPLC) grade were obtained from J.T. Backer (Deventer, The Netherlands) and the nitrogen (99.995% purity) was supplied by Air Liquide (Barcelona, Spain). Formic acid (HCOOH) and ammonium acetate (AcNH₄) were from Merck (Darmstadt, Germany). For the extraction process methyl tert-butyl ether (MTBE), sodium chloride (NaCl), sodium hydrogen-carbonate (NaHCO₃) from Sigma Aldrich, and ammonium formate (NH₄HCO₂) from Fisher Scientific (Fair Lawn, New Jersey, EEUU) were used.

A mix of isotopically labelled internal standards containing BP3-d5, BePB-d4 and gemfibrozil-d6 was prepared in MeOH with the appropriate volume of the standard stock solutions at a concentration of 200 ng/mL, and was stored at -20° C.

Ethical aspects

Cord blood samples were provided by the Sant Joan de Déu Hospital (Barcelona, Spain), and were donated voluntarily by the mothers, who were asked to sign an informed consent to participate in the study, well before delivery. The present study was approved by the Ethics Review Board of the University of Barcelona and Sant Joan de Déu Hospital. All the data compiled were saved following the current regulation on Protection of Personal Data and guarantee of digital rights (Ley Orgánica 3/2018).

Sampling and sample extraction

Umbilical cord blood samples were collected in metal-free serum tubes (to have the serum component of the blood) after direct extraction by venipuncture from the umbilical cords obtained immediately after delivery. The biological samples were stored at Sant Joan de Déu Hospital following the Spanish Law of Biomedical Investigation of 2007 (Law 14/2007) until shipment via urgent courier to the IDAEA-CSIC laboratories for analysis. All samples were received in perfect conditions and correctly codified, and were preserved frozen until analysis.

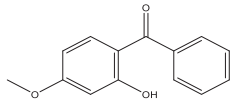
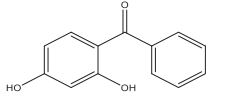
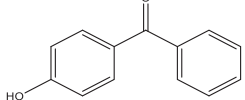
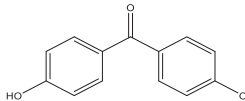
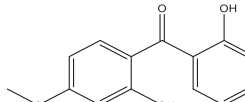
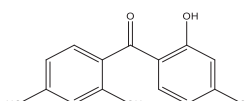
Samples were centrifuged at 3500 rpm during 5 min to remove cell debris and the serum was collected with a Pasteur pipette for further analysis. Then, 500 µL of each serum sample were spiked with 100 µL of the mix of internal standards solution and 500 µL of a physiological solution of NaCl previously prepared with MeOH (0.137 M). Isolation of the target analytes was carried out by liquid-liquid extraction adding 2 mL of MTBE. The mix was vigorously shaken and the samples were frozen until the organic and aqueous phases were separated. The organic phases were transferred with a Pasteur pipette to 2 mL HPLC-vials and further evaporated until almost dryness under a gentle current of nitrogen. Then, 0.5 mL of NaHCO₃ (100 mM) were added up to pH 10.5 and the samples were incubated at 60 °C for 5 min. Further, the samples were evaporated again under a stream of nitrogen until near dryness and then, 0.3 mL of the buffer NH₄HCO₂ (10 mM) and 0.3 mL of MeOH were added to dilute the samples up to 1:1 (v:v) proportion. Finally, the extracts were brought to dryness and further reconstituted with 1 mL of MeOH. The extracts were stored at -20°C until HPLC-MS/MS analysis.

Instrumental analysis

The chromatographic separation of the compounds was performed in a Hibar Purospher® STAR® HR R-18 (50 mm × 2.0 mm, 5 µm) column using a Symbiosis™ Pico instrument from Spark Holland (Emmen, The Netherlands). Detection was carried out in a 4000 Q TRAP™ hybrid quadrupole-linear ion trap mass spectrometer from Applied Biosystems-Sciex (Foster City, CA, USA). Mobile phases consisted of MeOH and H₂O 0.1% HCOOH in positive ionization mode determination, and MeOH and H₂O 5 mM AcNH₄ in negative ionization mode, respectively. The detailed gradient profiles are shown in [Tables 2](#) and [3](#). The injection volume was set up to 20 µL. Electrospray ionization in positive (ESI+) and negative (ESI-) modes were selected. Tandem-mass spectrometry detection (MS/MS) was performed under selected reaction monitoring (SRM) mode for improved sensitivity and selectivity. The two most intense transitions were selected and used for the quantification (most intense, 1st

Table 1

Target compounds name, acronym, family, CAS number, molecular mass, chemical structure and log octanol-water partition coefficient.

Compound	Other names	Family	CAS number	Molecular mass (g/mol)	Structure	log K_{ow}
Benzophenone-3 (BP3)	Oxybenzone; 2-Hydroxy-4-methoxybenzophenone	Benzophenones	131-57-7	228.24		3.79
Benzophenone-1 (BP1)	2,4-Dihydroxybenzophenone	Benzophenones	131-56-6	214.22		3.15
4-Hydroxybenzophenone (4HB)	-	Benzophenones	1137-42-4	193.18		2.92
4,4'-Dihydroxybenzophenone (DHB)	-	Benzophenones	611-99-4	214.22		2.19
2,2'-Dihydroxy-4-methoxybenzophenone (DHMB, BP8)	Benzophenone-8; Dioxybenzone	Benzophenones	131-53-3	244.25		3.82
Benzophenone-2 (BP2)	2,2',4,4'-Tetrahydroxybenzophenone	Benzophenones	131-55-5	246.22		2.78

(continued on next page)

Table 1 (continued)

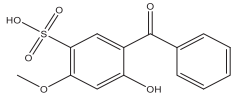
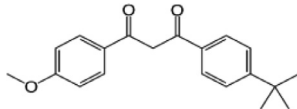
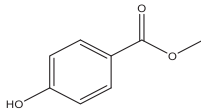
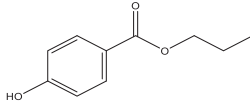
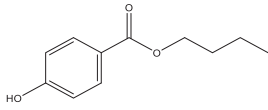
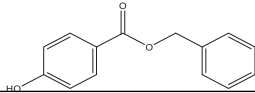
Compound	Other names	Family	CAS number	Molecular mass (g/mol)	Structure	log K_{ow}
Benzophenone-4 (BP4)	5-benzoyl-4-hydroxy-2-methoxybenzene sulfonic acid; HMBS; Sulisobenzone	Benzophenones	4065-45-6	308.31		0.88
Avobenzone (AVO)	1-(4-tert-butylphenyl)-3-(4-methoxyphenyl)propane-1,3-dione	Benzophenones	70,356-09-1	31,017		4.51
Methyl paraben (MePB)	Methyl 4-hydroxybenzoate	Parabens	99-76-3	152		2
Propyl paraben (PrPB)	Propyl 4-hydroxybenzoate	Parabens	94-13-3	180.2		2.98
Butyl paraben (BuPB)	Butyl 4-hydroxybenzoate	Parabens	94-26-8	194.23		3.47
Benzyl paraben (BePB)	Benzyl 4-hydroxybenzoate	Parabens	94-18-8	228.24		3.7

Table 2

Mobile phases used in positive mode, with its gradient flow and time.

Positive ionization			
Time (min)	% Mobile Phase A*	% Mobile Phase B [^]	Flow (mL/min)
0	95	5	0.3
7	25	75	0.3
10	0	100	0.3
15	0	100	0.3
17	95	5	0.3
23	95	5	0.3

* A: H₂O 0,1% in HCOOH;[^] B: MeOH 0,1% in HCOOH.**Table 3**

Mobile phases used in negative mode, with its gradient flow and time.

Negative ionization			
Time (min)	% Mobile Phase A*	% Mobile Phase B [^]	Flow (mL/min)
0	95	5	0.3
3	50	50	0.3
6	10	90	0.3
13	0	100	0.3
17	0	100	0.3
18	95	5	0.3
20	95	5	0.3

* A: H₂O 5 mM AcNH₄.[^] B: MeOH 5 mM AcNH₄.**Table 4**Retention time (t_R), selected MS/MS transitions, internal standard (IS) used, and ionization parameters for each compound. (-) for those analyzed in negative ionization mode.

Compound	t_R	1st transition	DP (V)	CE (eV)	CxP (eV)	2nd transition	DP (V)	CE (eV)	CxP (eV)	IS
BP3	12.12	229>151	40	25	12	229>105	40	27	16	BP3-d ₅
BP1	11.39	215>137	40	27	10	215>105	40	29	6	BP3-d ₅
4HB	11.36	199>121	40	25	8	199>105	40	27	8	BP3-d ₅
4DHB	10.41	215>121	45	27	8	215>93	45	45	6	BP3-d ₅
DHMB	11.93	245>121	43	29	8	245>151	43	27	12	BP3-d ₅
BP2	10.89	247>137	46	25	8	247>109	46	45	8	BP3-d ₅
BP4 (-)	8.42	307>227	-50	-34	-15	307>211	-70	-40	-9	Gemfibrozil-d ₆
AVO	13.04	311>135	40	25	15	311>161	40	25	15	BP3-d ₅
BePB (-)	9.5	227>92	-65	-26	-9	227>136	-65	-22	-1	BePB-d ₄
BuPB (-)	9.54	193>137	-55	-22	-5	193>92	-55	-34	-13	BePB-d ₄
PrPB (-)	9.22	179>92	-60	-30	-13	179>137	-60	-24	-5	BePB-d ₄
MePB (-)	8.5	151 > 92	-45	-28	-7	151>136	-45	-20	-9	BePB-d ₄

DP: Declustering potential (V); CE: Collision energy (eV); CxP: Collision cell exit potencial (eV);

transition) and confirmation (second most intense, 2nd transition) of each compound. The principal parameters of the developed HPLC-MS/MS method, including chromatographic retention time (t_R), selected transitions and ionization parameters are compiled in Table 4. Analytical standards, reagent blank samples, and quality control solutions were included in each analysis batch together with the serum extracts. The Analyst v. 1.4.2 software package (Applied Biosystems) was used for acquisition and data analysis processing

Table 5

Limits of detection (MLODs) and quantification (MLOQs) of the method (expressed in ng/ml blood sample) and determination coefficient (r^2) for each compound.

	MLOD (ng/ml)	MLOQ (ng/mL)	r^2
BP3	0.3	1.01	0.9997
BP1	0.08	0.28	0.9984
4HB	0.42	1.39	0.9982
DHB	0.05	0.18	0.9982
DHMB	0.14	0.48	0.9995
BP2	0.16	0.53	0.9974
BP4 (-)	0.26	0.85	0.9988
AVO	0.35	1.17	0.9992
MePB (-)	0.41	1.38	0.9993
PrPB (-)	0.23	0.75	0.9991
BuPB (-)	0.18	0.61	0.9969
BePB (-)	0.01	0.04	0.9986

MLOD: Limit of detection of the method; MLOQ: Limit of quantification of the method.

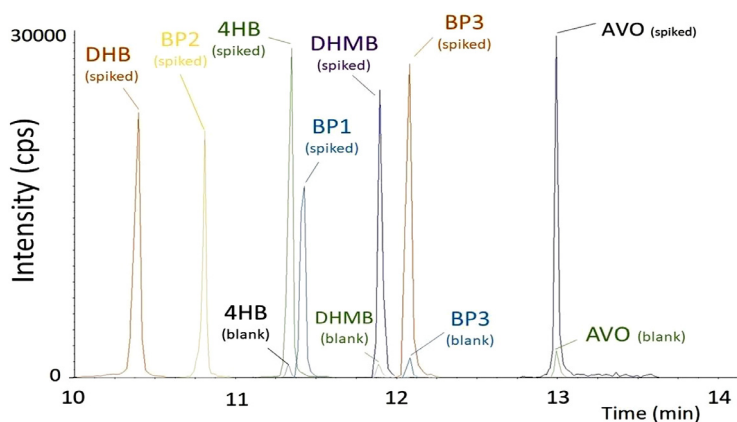


Fig. 1. Reconstructed ion chromatograms showing the SRM 1st transition obtained in the spiked samples at 5 ng/mL and in the procedural blanks using positive ionization (ESI+).

Quality assurance and quality control

One of the most common problems in trace analysis is background contamination. Therefore, procedural blanks were processed and analyzed. The procedural blanks were prepared using 500 μ L of HPLC water and submitted to all the steps in the sample analysis. No quantifiable peaks of the target analytes were measured, as shown in Figs. 1 and 2, where the peak area of the spiked samples at 5 ng/mL are notably higher than those of the blanks. Furthermore, all the glass material was cleaned with MeOH and acetone and dried at 400 $^{\circ}$ C overnight before use. Quality controls (mix of standards at known concentrations) were randomly measured along the samples' analysis sequence to ensure a reliable determination. The t_R of the compounds were compared at a tolerance of 2.5% maximum, and the relative ion intensities of the two SRM transitions (1st transition / 2nd transition) were compared at a tolerance level below 15% with those of the standards. The target compounds were identified following EU normative (Commission Decision 2002/657/EC). Isotopically labelled standards for each family of compounds were used to overcome potential matrix effects and thus, for proper quantification. The calibration curves were built through ten mix standard solutions at 1, 3, 5, 10, 30, 50, 100, 300, 500 and 700 ng/mL spiked in the matrix (matrix matched standards).

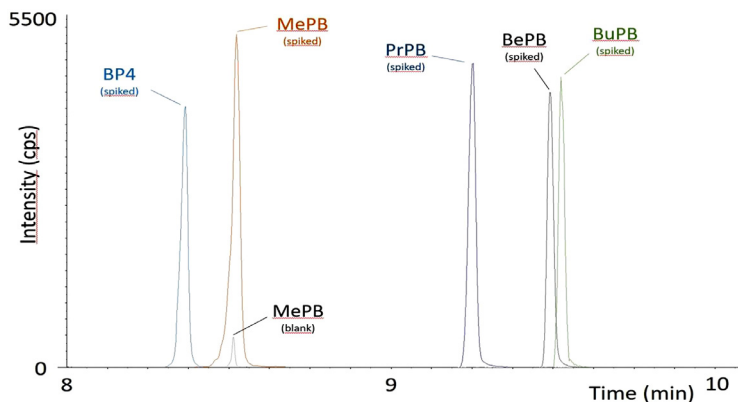


Fig. 2. Reconstructed ion chromatograms showing the SRM 1st transition obtained in the spiked samples at 5 ng/mL and in the procedural blanks using negative ionization (ESI⁻).

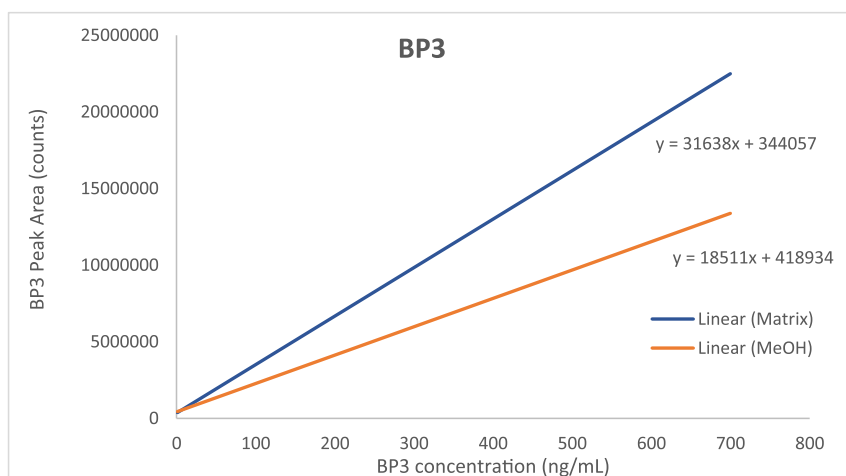


Fig. 3. Calibration curves for BP3 showing the enhancement of the signal in the serum matrix in comparison with MeOH.

Method validation

A number of the received samples was pooled to obtain a representative mixture of the umbilical cord serum, that was needed to validate the proposed method. Ten aliquots of 500 μ L of the pool samples were collected to elaborate the validation samples. These 10 samples were spiked at two concentrations (50 and 400 ng/mL) with the mix of the target compounds. The developed method was evaluated under optimized conditions in terms of linearity range, sensitivity, accuracy, precision, and matrix effects.

The method limits of detection (MLODs) and quantification (MLOQs), and the coefficient of determination (r^2) are listed in Table 5. MLODs and MLOQs were calculated as the concentration of each compound giving a signal-to noise ratio of 3 and 10, respectively. A wide linearity interval 1–700 ng/mL was obtained for all the compounds, with $r^2 > 0.9969$. The method was highly sensitive, with MLODs in the range 0.01–0.42 ng/mL blood.

Considering the high complexity of the sample composition, matrix effects were expected, and consequently, evaluated. Two representative examples of the calibration curves in the matrix extract

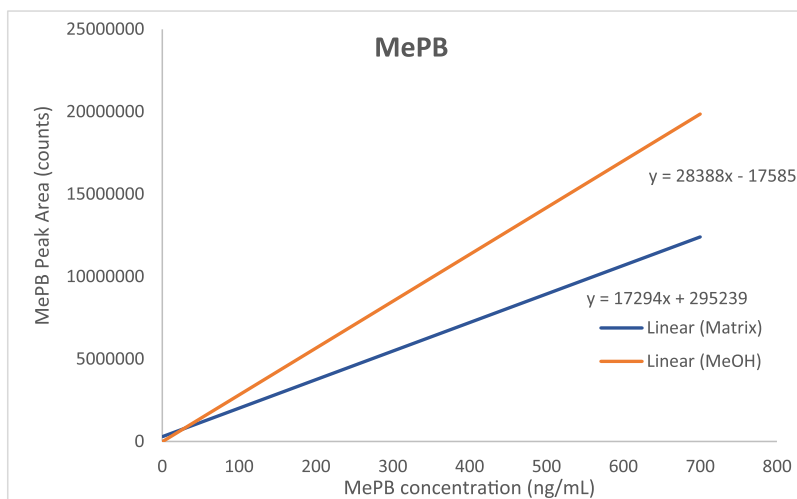


Fig. 4. Calibration curves for MePB showing the suppression of the signal in the serum matrix in comparison with MeOH in comp.

Table 6

Recovery rates (%) obtained from the spiked samples at the two concentration levels tested.

Validation sample	BP3	BP1	4HB	DHB	DHMB	BP2	BP4 (-)	AVO	BePB (-)	BuPB (-)	PrPB (-)	MEPB (-)
50 ng/mL (1)	89.8	134.4	109.4	94.2	107.4	94.4	17.08	31.2	86.4	100.2	111	121.6
50 ng/mL (2)	83.4	101.2	110.4	87	114.4	72.6	28.4	31.4	87.8	97.4	108	110.6
50 ng/mL (3)	83.8	142.8	123.6	128.8	82.6	82.8	14.28	24.8	81.6	93.8	105.4	114.2
50 ng/mL (4)	85.6	131.2	136.4	101.2	110.8	100.4	19.3	23.6	81.4	93.2	103.4	111.6
50 ng/mL (5)	90.6	146.4	120.4	121.2	121.4	106.4	16.58	21.6	80.4	92.4	104.8	118.6
400 ng/mL (1)	91.5	95	104	98.75	74.5	21.6	68.25	15.52	85.75	101.2	91	77
400 ng/mL (2)	106	96.25	97.5	99.75	65	27.25	66.25	21.77	84.5	103.5	91.75	74.5
400 ng/mL (3)	110	92	104.2	103.2	57.75	20.5	68	25.25	88.75	100	95.25	75.75
400 ng/mL (4)	106.5	93	94.5	84.75	63.5	14.75	82.75	15.8	90.5	97.75	97.75	72.25
400 ng/mL (5)	113.7	96	103.7	105.2	74.5	18.57	74.25	19.17	86.75	101.5	92.75	74.75
Average 50 ng/mL	86.6	131.2	120.0	106.5	107.3	91.3	19.1	26.5	83.5	95.4	106.5	115.3
Average 400 ng/mL	105.5	94.45	100.8	98.35	67.05	20.53	71.9	19.50	87.25	100.8	93.7	74.85

(1), (2), (3), (4), (5): Number of replica; (-): Analyzed in negative mode.

Table 7

Relative standard deviation (RSD%) for inter- and intra-day precision.

	RSD% Intra C1	RSD% Intra C2	RSD% Inter C1	RSD% Inter C2
BP3	1.68	33.8	8.45	10.41
BP1	8.93	7.5	2.56	15.07
4HB	5.51	18.05	0.72	12.09
DHB	8.91	32.17	2.7	2.8
DHMB	7.38	29.28	0.46	15.47
BP2	6.81	18.3	7.04	18.49
BP4 (-)	1.66	9.56	4.45	15.77
AVO	2.25	16.47	1.59	0.82
MePB (-)	1.64	8.47	3.1	7.68
PrPB (-)	1.5	11.1	7.21	14.21
BuPB (-)	2.34	7.02	5.99	11.61
BePB (-)	2.74	27.11	9.25	17.84

C1: Spiked concentration 1; C2: Spiked concentration 2; RSD%: Relative standard deviation; Intra: Intra-day; Inter: Inter-day.

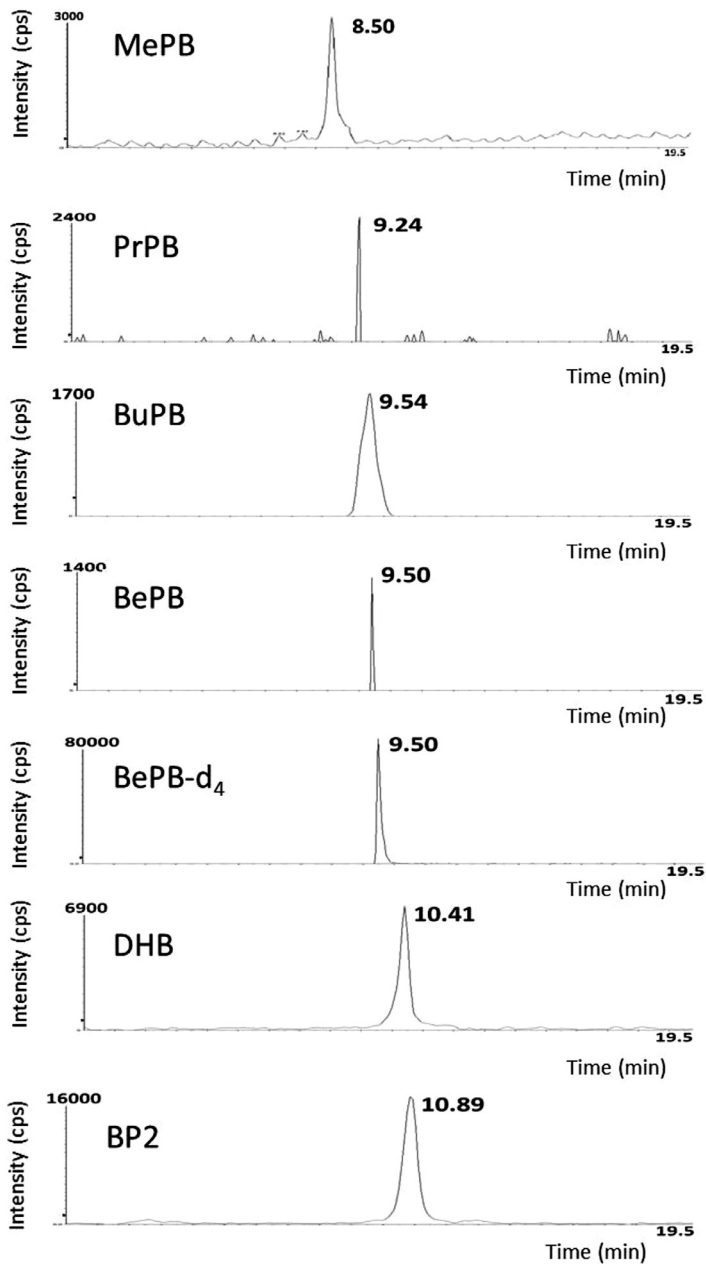


Fig. 5. Reconstructed ion chromatograms showing the SMR first selected transition, in ascendant chromatographic retention time (t_R) order, corresponding to a cord serum sample.

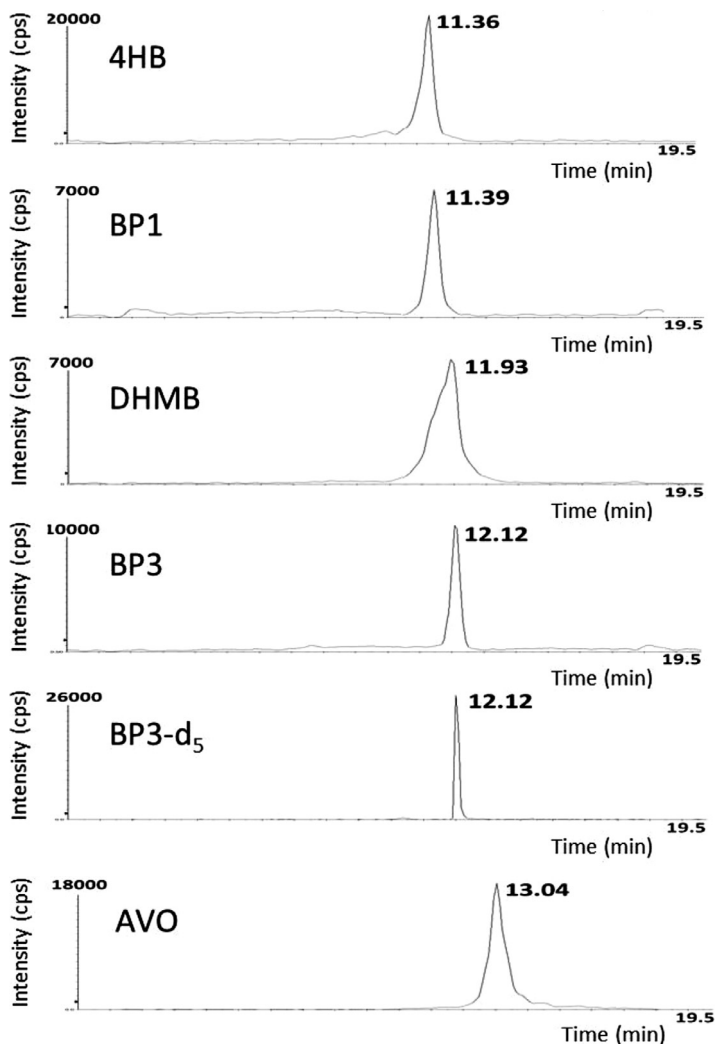


Fig. 5. Continued

(matrix-matched standards) and in the organic solvent are shown in Figs. 3 and 4. The large differences in the slope of the curves showed that, in these cases, BP3 signal suffers from signal enhancement in the presence of the matrix, and MePB experienced signal suppression, as indicated by the different slope obtained in the two media. Therefore, the matrix effects observed were significant, and demanded consideration. Thus, matrix matched calibration curves were used for all the analytes studied and were prepared using the pool of the samples created for the validation of the method.

Table 6 lists the recovery rates obtained at the two spiked concentration levels. Despite generally good recoveries were obtained, between 80 and 120%, BP2 was scarcely recovered (c.a. 20%) at the higher spike level (400 ng/mL); however, at low concentration the recovery was quite good ($\approx 91.3\%$). Considering the complexity of the samples analyzed, occurrence levels are not expected to reach this high concentration, and thus BP2 was also included in the method. AVO, on the other hand, presented medium-to-low recoveries (15.5–31.4%) at both concentrations, so it was also included in the method, but the obtained concentration values were considered semi-quantitative. Finally, BP4

had the opposite behavior than BP2. It showed a good recovery at high concentration (c.a. 71.9%), but small recovery at the low concentration (c.a.19%), and, therefore we decided to proceed as for AVO.

Repeatability and reproducibility were evaluated (Table 7). Intra-day RSD values (1.5–32%) and inter-day RSD values (0.5–18%) indicated quite good precision for the complex matrix.

As an applicability example of the developed method, Fig. 5 shows the reconstructed ion chromatograms corresponding to the UV filters and parabens detected in the serum of a cord blood sample. All the target compounds were detected and quantifiable, at concentrations from 0.20 to 53.3 ng/mL.

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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