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Quick and simple sample treatment for multiresidue analysis of bisphenols, bisphenol diglycidyl ethers and their derivatives in canned food prior to liquid chromatography and fluorescence detection

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ABSTRACT

We report herein a multiresidue method for canned food determination of 12 bisphenols [bisphenol A (BPA), bisphenol B (BPB), bisphenol F (BPF), bisphenol E (BPE)], bisphenol diglycidyl ethers [bisphenol F diglycidyl ether (BFDGE), bisphenol A diglycidyl ether (BADGE)] and their derivatives [BADGE·2H_2O, BADGE·H_2O, BADGE·HCl·H_2O, BADGE·HCl, BADGE·2HCl and BFDGE·2HCl]. The method was based on the microextraction of the target contaminants in 200 mg food sample with 600 μL of a supramolecular solvent made up of inverse aggregates of tetradecanol, followed by analysis of the extract by liquid chromatography/fluorescence detection using external calibration. Chromatographic separation of all target compounds, including the *ortho–ortho, ortho–para and para–para* isomers of BFDGE and BFDGE·2HCl, was achieved with baseline separation (Resolution ≥ 1.52). No concentration of the extracts was required, the microextraction took about 30 min and several samples could be simultaneous treated. Method validation was carried out according to the recommendations of the European Commission Decision 2002/657/EC. Quantitation limits for the different analytes ranged between 0.9 and 3.5 μg kg^{-1}. Repeatability and reproducibility, expressed as relative standard deviation, were in the ranges 1.8–6.8% and 4.4–8.1%. The method was applied to the analysis of the target compounds in different food categories including vegetables, legumes, fruits, fish and seafood, meat product and grain. Recoveries in samples were within the range 80–110%. Only BPF and BPE were undetected in the canned food analyzed. The concentration found for the rest of bisphenols, diglycidyl ethers and derivatives was in the range 7.1–959 μg kg^{-1}. The study of the isomeric distribution of BFDGE and BFDGE·2HCl in food showed that they are preferentially present as one of the isomeric forms, that highlighting for further studies. The analytical and operational characteristics of this multiresidue method make it suitable for monitoring programs intended for the assessment of human exposure to bisphenols, diglycidyl ethers and derivatives from diet.

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1. Introduction

Epoxy phenolic resins are widely used as protective linings for food and beverage cans. Bisphenol A (BPA) is the core substrate to produce bisphenol A diglycidyl ether (BADGE), the main monomer used in the epoxy resin industry [1]. Both BPA and BADGE can migrate from the protective lining into food and the latter can generate different derivatives during food storage by hydrolysis of epoxy groups (e.g. BADGE·2HCl, BADGE·HCl, BADGE·H_2O, BADGE·2H_2O and BADGE·HCl·H_2O) [2]. Table 1 shows the structure and some physicochemical properties of these compounds.

Occurrence of BPA in food has been widely documented in scientific literature and an interesting analysis of the data published from 2006 onwards has been included in the European Food Safety Authority (EFSA) draft scientific opinion on the risks to public health related to the presence of BPA in foodstuffs, which is scheduled for completion in mid-2014 [3]. Minimal and maximal average concentrations for BPA in the 17 canned food categories considered by EFSA were 0.2 μg kg^{-1} and 52 μg kg^{-1} for sugar and confectionary and snack and desserts, respectively. Data were extracted from a total of 2521 samples and BPA concentrations varied in a wide interval (i.e. 0.1–395 μg kg^{-1}). Occurrence of BADGE and derivatives in canned food has been also well documented, the concentrations ranging from undetected to 860 μg kg^{-1} [4–7]. To protect human health, a tolerable day intake (TDI) of 0.05 mg kg^{-1} of body weight for BPA was set by the European Commission (EC) in 2006 [8]

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Table 1
Chemical structure, ionization constants, octanol–water partition coefficients and number of proton donors and acceptors for the target bisphenols.

Compound name	Structure	pKa_1 [a]	pKa_2 [a]	Log K_{ow} [a]	Sum of hydrogen donors and acceptors [a]
2,2-Bis(4-hydroxyphenyl)propane (BPA)		10.29	10.93	3.46	4
2,2-Bis(4-glycidyloxyphenyl)propane (BADGE)		–	–	3.59	4
2-[4-(2,3-Dihydroxypropyloxy)phenyl]-2-[4-(glycidyloxy)phenyl]propane (BADGE·H2O)		13.53	15.02	2.47	7
2,2-Bis[4-(2,3-dihydroxypropoxy)phenyl]propane (BADGE·$2H_2O$)		14.72	15.32	2.05	10
2-[4-(3-Chloro-2-hydroxypropyloxy)pheny]-2-[4-(glycidyloxy)phenyl]propane (BADGE·HCl)		13.13	–	4.27	5
2,2-Bis[4-(3-chloro-2-hydroxypropoxy)phenyl]propane (BADGE·2HCl)		12.83	13.48	4.34	6
2-[4-(3-Chloro-2-hydroxypropyloxy)phenyl]-2-[4-(2,3-dihydroxypropyloxy)phenyl]propane (BADGE·HCl·H_2O)		13.53	15.02	2.89	8

Table 1 (*Continued*)

Compound name	Structure	pKa_1[a]	pKa_2[a]	Log K_{ow}[a]	Sum of hydrogen donors and acceptors[a]
Bis[4-(glycidyloxy)phenyl]methane (BFDGE)		–	–	2.96	4
Bis[4-(3-chloro-2-hydroxypropoxy)phenyl]methane (BFDGE·2HCl)		12.82	13.42	3.8	6
2,2-Bis(4-hydroxyphenyl)butane (BPB)		10.27	10.91	3.82	4
4,4′-Ethylidenebisphenol (BPE)		10.10	10.74	2.86	4
4,4′-Dihydroxydiphenylmethane (BPF)		9.91	10.50	2.93	4

[a] Data's calculated from http://ilab.acdlabs.com/ilab2 (ACD LABS, 2013).

and a migration limit of 9 mg kg^{-1} for BADGE and its hydrolytic derivatives and 1 mg kg^{-1} for the chlorinated derivatives has been proposed by the EC for food contact applications [9].

The health risks to the general population related to the endocrine disruptive effects of BPA has been a bone of contention in the scientific community. On the one hand, it has been considered that the health risk is very low owing to three reasons; first, the affinity of BPA for estrogen receptors is 10,000- to 100,000-fold weaker than that of estradiol, second, the human dietary exposure to BPA is below the set TDI and third, BPA undergoes biotransformation in the liver to harmless BPA-glucoronide [8]. On the other hand, different reports have shown that there are recognized effects in animals (effects on reproduction, on the mammary gland, on metabolism, the brain and behavior) and other suspected effects in humans (on reproduction, metabolism and cardiovascular diseases) at very low levels of exposure, during sensitive phases of the development of individuals [10]. The French Agency for Food, Environmental and Occupational Health and Safety (ANSES) has recommended a reduction in exposure, mainly through substitution of BPA in food contact materials, especially for the most vulnerable populations (infants, young children and pregnant or breastfeeding women) [11]. Also BADGE has been reported to form DNA adducts [12], to elicit teratogenic and mutagenic effects in vitro [13], and to produce cytotoxicity, developmental, and reproductive toxicity in laboratory animals [14].

Due to these effects, other bisphenols such as bisphenol F (BPF), bisphenol B (BPB) bisphenol E (BPE) and bisphenol F diglycidyl ether (BFDGE) are starting to be used by the industry for the production of epoxy resins (Table 1). Very few data are available for the occurrence of these bisphenols in canned food (e.g. 141–218 ng L^{-1} for BPF in soft drinks [15], 27.1–85.7 μg kg^{-1} for BPB in peeled tomatoes [16], 110–420 μg kg^{-1} for BFDGE for vegetables [7], etc) and additional toxicokinetic, reproductive and mechanistic studies are needed to adequately assess the effect on human health of these other substitutes for BPA [11].

Because canned food is the main source for population exposure to bisphenols, the study of their occurrence in the different foodstuffs is required for human exposure assessment and establishment of subsequent legislation and control. So, the development of quick and simple multiresidue methods able to quantify most of bisphenols and derivatives with potential to migrate from the can to the food is highly desirable. Multiresidue methods give

a more realistic whole intake of bisphenols – the study of the combined effect on endocrine active substances is a hot topic – and permit labs to quantify them while saving costs and analysis time.

Mass spectrometry (MS) combined with both LC and gas chromatography (GC) as well as LC/FD have been reported for the determination of bisphenols and/or their diglycidyl derivatives in food [15,17–23]. The use of GC/MS has reduced lately because it requires derivatization that is labour intensive and a source of contamination. Also, analytical performance of GC is greatly reduced by lipids hence requiring laborious cleanup for fatty foods [24]. LC offers simplicity over GC. Bisphenols are usually analyzed by ESI in negative mode, which produces $[M-H]^-$ ions that are used as diagnostic ions in LC/MS or precursor ions in LC/MS^2 [17]. Bisphenol diglycidyl ethers show poor signal or even no signal in negative ion mode [4] and they have high tendency to form adducts in positive mode (e.g. $[M+NH_4]^+$, $[M+Na]^+$, $[M+K]^+$, etc) that fragment easily. For this reason, mobiles phases require the presence of additives such as sodium acetate, ammonium formate, etc. However, the presence of additives cause signal suppression for bisphenols, so it is difficult to find a mobile phase composition that permit to obtain optimal sensitivity for the determination of both bisphenols and bisphenol diglycidyl ethers [17].

Repetitive solvent extraction involving solvent consumption between 40 and 300 mL and extraction times of 10–120 min is the most frequent technique used for isolation of bisphenols and their diglycidyl derivatives from foodstuffs, often the extraction efficiency being matrix dependent [17]. Other extraction techniques reported in the literature include pressurized liquid extraction [25–27], microwave assisted extraction [28] and matrix solid phase dispersion extraction [29] but they have not been proved to work with a wide range of foodstuffs. In most cases, additional sample cleanup with SPE or immunoaffinity columns and concentration steps are required to achieve the desired selectivity and sensitivity [17].

The aim of this study was to develop a multiresidue method for the determination of 12 bisphenols, bisphenol diglycidyl ethers and their derivatives in canned food (Table 1), able to meet the following criteria: (1) simple, fast, cheap and environmentally friendly; (2) applicable to a wide range of foodstuffs; (3) its performance should fit the guidelines of the European Commission Decision (2002/657/EC) [30] and (4) useful for the monitoring a large number of samples as required in risk assessment studies. For this purpose we investigated the suitability of a supramolecular solvent made up of inverse aggregates of tetradecanol [31] for developing a generalized and simplified sample treatment, and LC/FD for reliable quantification of the target bisphenols and derivatives.

Supramolecular solvents (SUPRASs) are nanostructured liquids generated from aqueous or hydroorganic solutions of amphiphiles through spontaneous self-assembly processes that are induced by pH, temperature, salt or a poor solvent for the amphiphile [32]. The production of these solvents occurs through the formation of oily droplets that flocculate as conglomerates of individual droplets and finally separate from the solution as an immiscible liquid named SUPRAS.

2. Experimental

2.1. Chemicals

Reagents (analytical grade) and solvents were used as received. Tetrahydrofuran was obtained from Panreac (Barcelona, Spain), methanol from Carlo Erba (Madrid, Spain), acetonitrile from VWR-Prolabo (Bois, France), 1-tetradecanol from Sigma-Aldrich (Steinheim, Germany) and ultra-high-quality water from Milli-Q water purification Millipore setup (Madrid, Spain). Bisphenol A (BPA), bisphenol F (BPF) and bisphenol A diglycidyl ether (BADGE) were purchased from Aldrich (St. Louis, USA), bisphenol E (BPE) and bisphenol B (BPB) were obtained from TCI Europe (Zwijndrecht, Belgium), while $BADGE{\cdot}H_2O$, $BADGE{\cdot}2H_2O$, BADGE·HCl, BADGE·2HCl, $BADGE{\cdot}HCl{\cdot}H_2O$, BFDGE and BFDGE·2HCl were all supplied by Fluka Chemika (Bushs, Switzerland). Both BFDGE and BFDGE·2HCl were mixtures of *ortho–ortho, ortho–para and para–para* isomers. Stock solutions of 10 mg L^{-1} of individual bisphenols and derivatives were prepared in acetonitrile and refrigerated at 4 °C. Intermediate solutions were prepared monthly from the stock standard solution by appropriate dilution in acetonitrile. Calibration standard solutions ranging from 1 to 500 μg L^{-1} were prepared daily.

2.2. Apparatus

The liquid chromatography assembly (HPLC-Breeze, Waters Milford, USA) was made up of a 717 automated injector, a 1525 binary pump, a column heater of 1500 series and a 2475 multi-wavelength fluorescence detector. The stationary phase was an Ultrabase C-18 column (particle size 5 μm, length 250 mm, i.d. 4.6 mm) from Análisis Vínicos (Tomelloso, Spain). Apparatus for sample preparation were a vortex shaker from Reax Heidolph (Schwabach, Germany), an Ultra-Turrax T25 basic from Ika-Werke (Staufen im Breisgau, Germany) and a MPW-350R brushless centrifuge from MPW Medical Instruments (Warszawa, Poland). A Basicmagmix magnetic stirrer from Ovan (Barcelona, Spain) and a Mixtasel centrifuge from JP-Selecta (Abrera, Spain) were used for production of the supramolecular solvent.

2.3. Supramolecular solvent synthesis

The procedure below detailed, which permits to obtain a SUPRAS volume around 4 mL able to treat six food samples, was routinely followed. Tetradecanol (1.2 g) was dissolved in THF (12 mL) in a centrifuge tube and stirred magnetically up to complete dissolution (∼1–2 min). Then 18 mL of ultrapure water were added and the mixture was subjected to centrifugation at 3500 rpm for 10 min to allow for effective separation of the SUPRAS as supernatant. The SUPRAS was then collected carefully with a 5 mL-glass syringe, transferred to a hermetically closed storage glass vial to avoid THF losses and stored at 4 °C until use. Under these conditions, the solvent produced was stable for at least one month.

2.4. Multiresidue determination of bisphenols and their diglycidyl derivatives in canned food

2.4.1. Sample collection and pretreatment

Canned foodstuffs belonging to different categories were analyzed, namely vegetables (mushroom, red pepper, olive, green beans, asparagus), legumes (chickpeas, lentils), fruits (pineapple, peach), fish and other seafood (mackerel, mussels, tuna, cockles), meat products (tripe, meat ball) and grains (sweet corn). All foodstuffs were purchased in local supermarkets in Córdoba, Spain, in June 2013. Samples were selected to encompass a broad range of compositions regarding the content of carbohydrate (0–21.8%, *w*/*w*), protein (0–35.3%, *w*/*w*) and fat (0.1–42.7%, *w*/*w*). Table 2 shows the nutritional composition obtained from the label information of the foodstuffs analyzed. Cans were left at room temperature until they were opened and their liquid content poured off. The whole solid content of the can or a portion of 100 g was chopped and homogenized using an Ultra-Turrax T25 basic. Then, aliquots of about 200 mg were taken for analysis and recovery experiments, which were performed in triplicate. Samples not immediately analyzed were stored at −20 °C. Spiking of chopped samples (200 mg) was done by adding 25 μL of a solution containing bisphenols and

Table 2
Nutritional composition of the foodstuffs analyzed.

Food category	Food	Nutritional composition (g/100 g)[a]			Best before
		Protein	Carbohydrate	Fat	
Vegetables	Mushroom	1.9	2.7	0.29	02-2018
	Red pepper	0.8	5.0	0.2	01-2015
	Green beans	1.7	3.8	0.1	08-2015
	Olive	1.3	0	16.2	04-2016
	Asparagus	0.8	2.1	0.3	12-2018
Legumes	Lentils	3.7	10.5	2.4	03-2018
	Chickpeas	3.5	10.8	2.6	01-2018
Fruits	Pineapple	0.4	12.2	0.1	05-2017
	Peaches	0.4	18.5	0.1	01-2016
Fish and Seafood	Mussels	17.0	4.0	9.0	12-2016
	Cockles	14.0	0.0	1.0	01-2016
	Mackerel	23.1	0.0	4.0	12-2017
	Tuna-olive oil	26.0	0.0	16.0	12-2019
Meat products	Tripe	0.0	3.9	36.1	03-2018
	Meat ball	35.3	23.2	42.7	04-2018
Grain	Sweet corn	3.1	21.8	1.6	08-2016

[a] As specified on labels of individual canned food.

derivatives (0.1–10 mg L^{-1} each) in acetonitrile. They were analyzed after solvent evaporation which took around 1 h at room temperature.

2.4.2. SUPRAS-based microextraction

A food aliquot (200 mg) was mixed with 600 μL of supramolecular solvent in a 2 mL safe-lock microtube purchased from Eppendorf Iberica (Madrid, Spain). The mixture was shaken with a vortex at 2500 rpm for 10 min and then centrifuged at 15,000 rpm with the temperature set at 17 °C for 15 min. The supramolecular extract was withdrawn with a glass-syringe and transferred to an auto-sampler vial for chromatographic analysis. Fig. 1 shows a schematic of the sample treatment and microextraction procedure.

2.4.3. Liquid chromatography-fluorescence detection

Fluorescent measurement of bisphenols and derivatives was performed at 276/303 nm excitation/emission wavelengths. The mobile phase was made up of water (A) and acetonitrile (B) and the gradient elution profile used was: (1) isocratic conditions for the first 7 min: 50% A and 50%B at 0.6 mL min^{-1}; (2) linear gradient from 7 to 8 min with the final conditions being 45%A and 55%B at 1 mL min^{-1} and then isocratic conditions from 8 to 28 min; (3) linear gradient from 28 to 28.5 min with the final conditions being 100%B at 1.0 mL min^{-1} and then isocratic conditions from 28.5 to 33.5 min. After each run, initial elution conditions (50%A, 50%B, 0.6 mL min^{-1}) were restored using a linear gradient from 33.5 to 34 min and these conditions were kept for 1 min before the next injection. The delay time for recording the next chromatogram was 10 min. The temperature of the column and injector were maintained at 40 °C and 25 °C, respectively. Calibrations were run by injecting 20 μL of standard solutions containing a mixture of target analytes at concentrations in the range of 1–500 μg L^{-1}. Background contamination with bisphenols and derivatives arising from labware was avoided by rising glassware and eppendorf microtubes with methanol before their use.

3. Results and discussion

3.1. Chromatographic separation of bisphenols and their diglycidyl derivatives

Mobile phases made up of different water/methanol ratios used in both isocratic and gradient elution did not give satisfactory peak resolution for the separation of the 12 bisphenols and diglycidyl ethers selected as well as the isomers of BFDGE and BFDGE·2HCl. The mixture of water and acetonitrile under isocratic conditions improved resolution but it was not enough for analyte separation. The use of gradient elution with an additional gradient regulation of flow rate (see Section 2.4.3) permitted baseline separation (resolution in the interval 1.52–4.52) with retention factors in the interval 1.53–11.08. Fig. 2A shows a chromatogram for the mixture of the analytes in acetonitrile. Because of the lack of standards, no precise assignment or quantification of individual BFDGE and BFDGE·2HCl isomers was performed. Multiple-stage mass spectrometry has been previously used to establish the elution order of the three positional isomers of BFDGE in reversed phase chromatography using water:methanol as the mobile phase [33]. However, it has

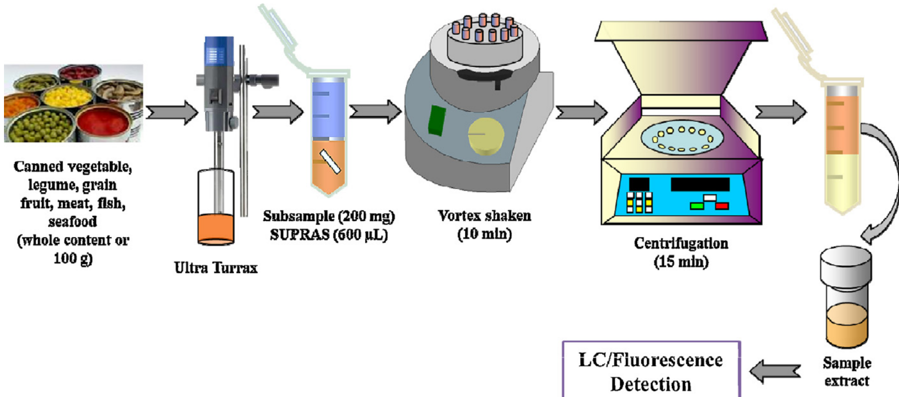

Fig. 1. Schematic of the generalized sample treatment proposed for the extraction of bisphenols, bisphenol diglycidyl ethers and derivatives in canned food.

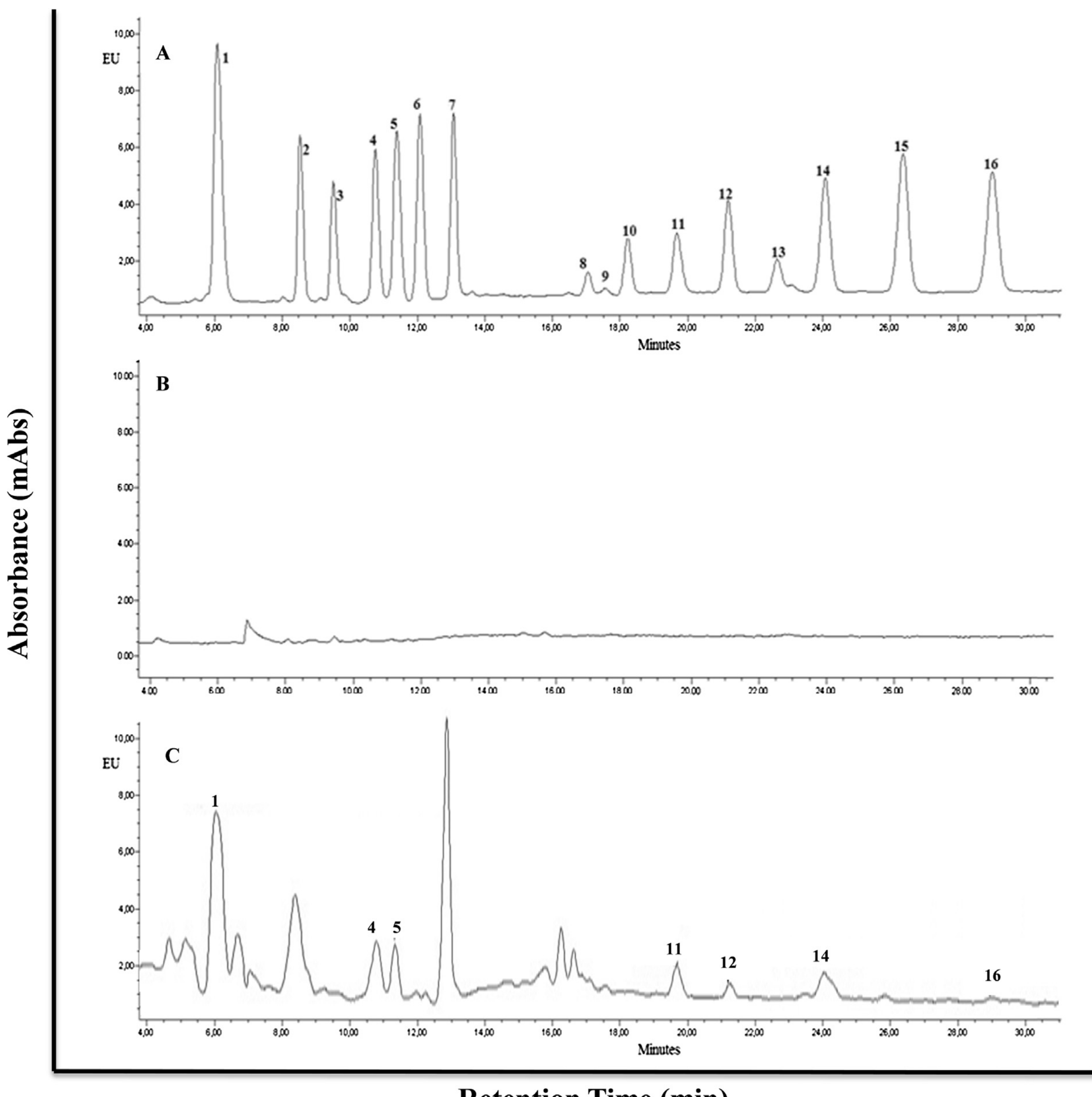

Fig. 2. HPLC/FLD chromatograms of (A) a standard solution containing the analytes at a concentration of 100 μg L^{-1} in acetonitrile, (B) tetradecanol based SUPRAS and (C) a mushroom sample. Working conditions as indicated in Section 2.4.3. 1 = BADGE·$2H_2O$, 2 = BPF, 3 = BPE, 4 = BPA, 5 = BADGE·H_2O·HCl, 6 = BADGE·H_2O, 7 = BPB, 8–10=BFDGE·2HCl isomers 11–13 = BFDGE isomers, 14 = BADGE·2HCl, 15 = BADGE·HCL, 16 = BADGE.

been repeatedly proved that elution order of both bisphenols and diglycidyl ethers changes as moving from methanol to acetonitrile [34], so we avoided to assign the chromatographic peaks in Fig. 2A to individual BFDGE since the mobile phase in this study consisted of acetonitrile and water. On the other hand, no identification of BFDGE·2HCl isomers has been reported owing to their identical product ion spectra by multiple-stage MS [33]. So, quantification of both BFDGE and BFDGE·2HCl was carried out as the sum of the three isomers, although their chromatographic separation was considered interesting in order to know isomer distribution in food samples.

3.2. Supramolecular solvent-based microextraction of bisphenols and their diglycidyl derivatives

3.2.1. Solvent description and extraction capabilities

Alkanols have been recently reported to give environment-responsive SUPRASs in water/THF solutions [31]. They are synthesized by adding water, as a self-assembly inductor, to solutions of (C_7–C_{14}) alkyl alcohols in THF. These solvents are made up of hexagonal droplets in which alkanols arrange as inverted hexagonal aggregates where the polar groups surround aqueous cavities and the hydrocarbon chains are dispersed in THF.

There are different characteristics of alkanol-based SUPRASs that, a priori, render them ideal to develop generalized sample treatments able to deal with a broad range of food types and bisphenols. Thus, they provide mixed-mode mechanisms for analyte solubilization since they can establish both dispersion and hydrogen bond interactions. Also, the concentration of alkanol in the SUPRAS can be so high such as 0.68 mg μL^{-1}, that involving that many binding sites are available and, consequently, very low volumes of solvent will be required for efficient extraction [31]. On the other hand, the size of the aqueous cavities of these solvents can be tailored by controlling the THF:water ratio in the bulk solution where alkanols self-assemble. So these SUPRAS have the potential to behave as restricted access properties liquids and this means that

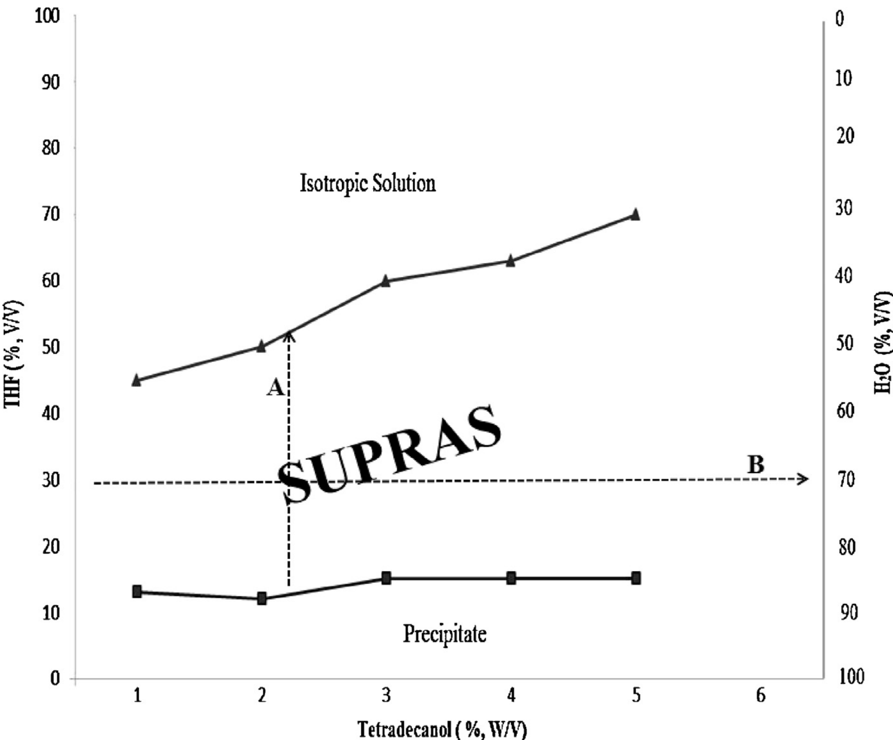

Fig. 3. Phase diagram for ternary mixtures of THF, water and tetradecanol at room temperature.

they can exclude the extraction of macromolecules such as proteins and polysaccharides thus making easier sample treatment. Efficient extraction of carcinogenic chlorophenols in environmental waters [31] and endocrine disruptors in sediments [35] using alkanols-based SUPRASs have been recently reported, so they are very promising as extractants of contaminants in food.

3.2.2. Optimization

Optimization of SUPRAS extraction was carried out using blank tuna (200 mg) spiked with all the target bisphenols and diglycidyl ethers at a concentration of 125 $\mu g\,kg^{-1}$ each. Because of canned tuna always contains some of these compounds at quantifiable concentrations, blank samples were obtained from commercially available tuna in olive oil glass bottles. To avoid the potential contamination coming from the metallic lid, the upper content of the bottle was discarded. Recovery experiments were made in triplicate. Selection of the optimal conditions was based on the recoveries and precision obtained. After solvent selection, the variables investigated were composition and volume of extractant, pH for extraction and time required to reach equilibrium conditions.

The extraction efficiency for bisphenols and diglycidyl ethers provided by SUPRASs synthesized from solutions containing 1% (w/v) C_7–C_{14} alkanols, 20% THF (v/v) and 80% water (v/v) was investigated. There were no significant differences for the recoveries obtained for the SUPRASs tested, so selection was based on the chromatographic profile of the SUPRAS extracts. In this respect, tetradecanol-based SUPRAS was the most suitable solvent because it eluted after the analytes, gave the lowest baseline and did not show any interfering peaks for bisphenols or derivatives (Fig. 2B). Retention times and peak areas for analytes in the SUPRAS and acetonitrile were not statistically different by applying a student t-test at $P = 0.05$ using the Statgraphics Centurion XVI program. So, the SUPRAS did not influence the chromatographic behavior of analytes.

Fig. 3 depicts the phase diagram for the formation of the tetradecanol-based SUPRAS. Outside the boundaries of the SUPRAS region, tetradecanol precipitated or gave isotropic solutions at low and high percentages of THF, respectively. Isotropic solutions were the consequence of the similar density of the SUPRAS and the respective equilibrium solution.

SUPRAS composition can be tailored by controlling the environment, that is the THF:water ratio in the bulk solution where tetradecanol self-assembles. The exact composition of the solvent can be calculated from the following previously derived equations [31]:

$$Y_{ws} = 42.2 - 0.31X_{wb} - 0.998Z_a \quad (1)$$

$$Y_{ts} = 6.3 + 2.4X_{tb} - 0.024X_{tb}^2 \quad (2)$$

where Y_{ws} and X_{wb} are the percentage (w/w) of water in the SUPRAS and bulk solution, respectively, Z_a is the number of carbon atoms in the alkanol and Y_{ts} and X_{tb} are the percentage (w/w) of THF in the SUPRAS and bulk solution, respectively.

On the other hand, the volume of solvent produced (Y, μL) is linearly and exponentially dependent on the amount of tetradecanol (X, mg) and percentage of THF (Z, v/v), respectively, according to the equation:

$$Y = X[0.17 + e^{0.0389Z}] \quad (3)$$

As is derived from Eqs. (1) and (2), SUPRASs with increasing contents of water and THF will be produced as the percentage of THF in the bulk solution increases. So, the composition of the SUPRASs synthesized from a constant concentration of tetradecanol and variable THF/water ratios (dotted line A in Fig. 3) is different and the volume of solvent produced will be exponentially dependent on the percentage of THF (Eq. (3)). On the other hand, the composition of the SUPRAS synthesized from variable concentrations of tetradecanol and constant THF/water ratios (dotted line B in Fig. 3) remains unchanged and the volume of solvent produced will be linearly dependent on the amount of tetradecanol (Eq. (3)).

Tetradecanol-based SUPRASs of different compositions were prepared from bulk solutions containing variable water/THF ratios

Table 3
Mean recoveries and standard deviations obtained for the target bisphenols and derivatives as a function of the composition of the tetradecanol-based SUPRAS.

Analyte	Mean recoveries ± Standard deviation (%)[a]		
	Tetradecanol: 40.4, THF: 52.9, water: 6.7[b]	Tetradecanol:29.1, THF: 61.4, water:9.5[c]	Tetradecanol: 18.8, THF: 65.7, Water: 15.5[d]
BADGE·2H_2O	70 ± 7	80 ± 5	70 ± 5
BPF	99 ± 4	100 ± 2	95 ± 7
BPE	92 ± 9	107 ± 4	87 ± 4
BPA	68 ± 10	77 ± 5	71 ± 3
BADGE·H_2O·HCl	70 ± 6	80 ± 3	67 ± 2
BADGE·H_2O	77 ± 4	99 ± 4	75 ± 6
BPB	75 ± 8	103 ± 6	69 ± 3
BFDGE·2HCl	79 ± 11	80 ± 6	75 ± 2
BFDGE	68 ± 4	89 ± 3	63 ± 4
BADGE·2HCl	70 ± 9	96 ± 2	72 ± 3
BADGE·HCL	66 ± 8	97 ± 4	69 ± 7
BADGE	68 ± 3	90 ± 3	79 ± 3

[a] $n = 3$.
[b–d] SUPRAS composition, expressed as percentages (w/w) and calculated from Eqs. (1) and (2). The SUPRASs were obtained from 4% (w/v) tetradecanol in solutions containing water and THF at the following water/THF ratios (v/v): [b] 70/30, [c] 60/40 and [d] 40/60.

from 70/30 to 40/60 (v/v) and a constant tetradecanol concentration (4%, w/v). A volume of 400 μL of the different solvents produced was used to extract bisphenols and their derivatives from 200 mg of tuna samples spiked at 125 $\mu g\,kg^{-1}$ each. Table 3 shows the recoveries obtained and the corresponding standard deviation for representative compositions of the SUPRASs investigated for extraction. Both the content of tetradecanol and water in the SUPRAS seemed to influence the recoveries for bisphenols and derivatives; the former determines the number of binding sites for analytes while the latter influences the size of the aqueous cavities of the inverted hexagonal aggregates in which tetradecanol self-assembles. Maximal recoveries were obtained for intermediate concentrations of water and tetradecanol, so the SUPRAS selected had the following composition, expressed as mass fraction, tetradecanol 29.1%; THF 61.4% and water 9.5%.

The volume of supramolecular solvent required for optimal extraction was determined by extracting a constant amount of sample (200 mg of blank tuna spiked with bisphenols and derivatives at 125 $\mu g\,kg^{-1}$ each) with variable volumes (400–1000 μL) of the selected SUPRAS. Recoveries above 85% with relative standards deviations in the range 4–6% were obtained for all the target bisphenols and derivatives for solvent volumes equal and above 600 μL. So, this volume was selected as optimal.

The pH had not influence on the extraction of bisphenols and derivatives. This variable was investigated by producing the SUPRAS from water solutions in which the pH was adjusted between 2 and 10. The time required to reach equilibrium conditions for extraction was investigated in the interval 5–45 min. About 10 min of extraction were required to achieve recoveries above 85% for all analytes. Such a short extraction time is a valuable asset of SUPRAS-based extractions and it is a consequence of both the different types of interactions that these solvents can establish with analytes and the high number of sites available for solubilization, which facilitates the breakdown of analyte–matrix interactions.

3.3. Validation

The developed method was subjected to validation according to the guidelines established by the European Commission decision 2002/657/EC [30], which provides admissible performance criteria to evaluate if an analytical method is fit for the purpose.

3.3.1. Sensitivity and linearity

Calibration parameters and method detection (MDLs) and quantitation (MQLs) limits for the determination of bisphenols and derivatives are shown in Table 4. Calibration curves were run using seven standard solutions prepared in acetonitrile. The maximal concentration tested was 500 $\mu g\,L^{-1}$. The range of linearity was confirmed by visual inspection of residual plots versus analyte concentration [36]; the residuals were randomly scattered within a horizontal band and a random sequence of positive and negative residuals was obtained. The MDLs were calculated from six independent complete analyses of blank tuna samples, according to

Table 4
Analytical figures of merit of the proposed method.

Bisphenol	Calibration parameters			MDL ($\mu g\,kg^{-1}$)[d]	MQL ($\mu g\,kg^{-1}$)[e]
	Linear range ($L\,\mu g^{-1}$)[a]	Slope ± S (×10^3) ($L\,\mu g^{-1}$)[b]	r[c]		
BADGE·2H_2O	0.2–500	13.6 ± 0.4	0.9998	0.3	0.9
BPF	0.6–500	5.5 ± 0.1	0.9992	0.8	2.6
BPE	0.7–500	4.1 ± 0.1	0.9992	1.1	3.5
BPA	0.6–500	5.9 ± 0.1	0.9995	0.8	2.9
BADGE·H_2O·HCl	0.4–500	7.4 ± 0.2	0.9998	0.4	1.5
BADGE·H_2O	0.4–500	7.8 ± 0.2	0.9995	0.4	1.4
BPB	0.4–500	7.6 ± 0.2	0.9993	0.6	2.0
BFDGE·2HCl	0.8–500	3.32 ± 0.03	0.9998	1.0	3.2
BFDGE	0.3–500	9.4 ± 0.1	0.9995	0.3	1.2
BADGE·2HCl	0.5–500	6.8 ± 0.1	0.9992	0.5	1.6
BADGE·HCL	0.3–500	9.1 ± 0.2	0.9991	0.3	0.9
BADGE	0.4–500	8.7 ± 0.2	0.9990	0.4	1.2

[a] Instrumental quantitation limit calculated by using a signal-to-noise ratio of 10.
[b] Standard error of the estimate.
[c] Correlation coefficient.
[d] Method detection limits.
[e] Method quantification limits obtained for the determination of analytes in tuna.

Table 5
Mean concentrations and recoveries obtained for the determination of bisphenols and derivatives in unfortified and fortified foodstuffs, respectively.

Bisphenol	Concentration found[a] ± S (μg kg^{-1})[b] (Recoveries[c] ± RSD, %)[d]							
	Red pepper	Peaches	Green beans	Pine apple	Meat balls	Chickpeas	Lentils	Tripe
BADGE·2H_2O	102 ± 2 (86 ± 6)	nd (101 ± 1)	354 ± 24 (92 ± 1)	nd (98 ± 1)	341 ± 20 (91 ± 4)	616 ± 40 (97 ± 5)	227 ± 5 (93 ± 7)	630 ± 24 (88 ± 4)
BPF	nd (110 ± 1)	nd (94 ± 2)	nd (101 ± 2)	nd (92 ± 4)	nd (103 ± 1)	nd (98 ± 2)	nd (105 ± 2)	nd (102 ± 1)
BPE	Nd (104 ± 1)	nd (103 ± 1)	nd (105 ± 2)	nd (100 ± 4)	nd (104 ± 1)	nd (102 ± 1)	nd (98 ± 1)	nd (100 ± 1)
BPA	241 ± 2 (106 ± 3)	nd (89 ± 3)	60 ± 3 (103 ± 1)	13 ± 1 (94 ± 3)	82 ± 3 (96 ± 6)	116 ± 4 (81 ± 1)	83 ± 1 (81 ± 1)	62 ± 2 (99 ± 2)
BADGE·H_2O·HCl	31 ± 1 (87 ± 3)	nd (80 ± 1)	171 ± 11 (92 ± 4)	6.1 ± 0.2 (86 ± 2)	90 ± 7 (90 ± 2)	80 ± 3 (97 ± 1)	41 ± 1 (90 ± 4)	53 ± 1 (82 ± 4)
BADGE·H_2O	nd (89 ± 6)	nd (88 ± 3)	nd (87 ± 3)	nd (96 ± 2)	60 ± 2 (92 ± 2)	50 ± 1 (94 ± 1)	30 ± 1 (86 ± 3)	179 ± 12 (85 ± 2)
BPB	nd (104 ± 8)	nd (87 ± 2)	25 ± 1 (99 ± 9)	nd (96 ± 4)	nd (105 ± 1)	nd (104 ± 2)	nd (101 ± 1)	39 ± 1 (91 ± 1)
BFDGE·2HCl	nd (91 ± 2)	nd (91 ± 1)	19 ±1 (97 ± 5)	nd (88 ± 6)	nd (107 ± 1)	120 ± 10 (97 ± 1)	nd (102 ± 10)	nd (89 ± 2)
BFDGE	nd (107 ± 9)	nd (99 ± 1)	29 ± 2 (96 ± 7)	nd (98 ± 1)	240 ± 16 (102 ± 5)	22 ± 1 (92 ± 1)	21 ± 1 (103 ± 4)	314 ± 19 (106 ± 2)
BADGE·2HCl	25 ± 1 (103 ± 3)	nd (91 ± 1)	110 ± 6 (102 ± 5)	nd (91 ± 4)	32 ± 1 (83 ± 2)	215 ± 13 (84 ± 5)	141 ± 3 (86 ± 2)	110 ± 8 (100 ± 2)
BADGE·HCL	nd (106 ± 5)	nd (93 ± 2)	21 ± 1 (100 ± 12)	nd (88 ± 5)	9.2 ± 0.3 (95 ± 4)	nd (82 ± 2)	nd (89 ± 2)	nd (93 ± 1)
BADGE	nd (107 ± 1)	nd (95 ± 1)	nd (95 ± 8)	nd (92 ± 6)	nd (92 ± 1)	nd (84 ± 1)	nd (91 ± 2)	nd (98 ± 4)

Bisphenol	Mushroom	Asparagus	Mackerel	Cockles	Mussels	Sweet corn
BADGE·2H_2O	240 ± 13 (100 ± 4)	959 ± 18 (105 ± 10)	nd (89 ± 2)	311 ± 9 (97 ± 1)	662 ± 6 (86 ± 6)	nd (101 ± 1)
BPF	nd (107 ± 2)	nd (102 ± 1)	nd (108 ± 2)	nd (97 ± 2)	nd (98 ± 1)	nd (102 ± 1)
BPE	nd (103 ± 7)	nd (98 ± 2)	nd (102 ± 1)	nd (104 ± 1)	nd (93 ± 9)	nd (105 ± 6)
BPA	153 ± 6 (85 ± 6)	97 ± 4 (102 ± 5)	nd (86 ± 2)	182 ± 6 (108 ± 3)	117 ± 7 (88 ± 3)	142 ± 2 (81 ± 2)
BADGE·H_2O·HCl	88 ± 4 (96 ± 5)	533 ± 15 (80 ± 1)	nd (82 ± 3)	110 ± 4 (106 ± 2)	60 ± 2 (89 ± 4)	13 ± 1 (83 ± 1)
BADGE·H_2O	nd (84 ± 3)	nd (94 ± 6)	nd (85 ± 2)	29 ± 1 (96 ± 8)	85 ± 5 (88 ± 6)	22.3 ± 0.9 (86 ± 3)
BPB	nd (86 ± 5)	nd (85 ± 3)	nd (90 ± 2)	40 ± 3 (88 ± 3)	nd (93 ± 2)	nd (83 ± 2)
BFDGE·2HCl	nd (85 ± 1)	nd (97 ± 4)	nd (90 ± 1)	nd (105 ± 5)	nd (89 ± 2)	nd (90 ± 4)
BFDGE	190 ± 13 (86 ± 3)	nd (102 ± 10)	nd (95 ± 1)	nd (105 ± 1)	251 ± 1 (99 ± 9)	nd (86 ± 1)
BADGE·2HCl	80 ± 5 (98 ± 8)	73 ± 2 (94 ± 4)	nd (90 ± 1)	55 ± 1 (102 ± 6)	124 ± 6 (92 ± 2)	91 ± 4 (105 ± 2)
BADGE·HCL	nd (80 ± 1)	9.4 ± 0.4 (88 ± 5)	nd (91 ± 1)	7.2 ± 0.3 (100 ± 6)	nd (92 ± 10)	nd (80 ± 1)
BADGE	7.1 ± 0.3 (91 ± 4)	nd (89 ± 7)	nd (89 ± 3)	nd (89 ± 4)	nd (88 ± 5)	nd (103 ± 1)

[a] Mean of three independent determinations.
[b] Standard deviation.
[c] Fortification level for each analyte: 100 μg kg^{-1}.
[d] Relative standard deviation, $n = 3$.
nd is not detected.

the procedure detailed in Section 2.4, by using a signal-to-noise ratio of 3 (the ratio between the peak areas for each target analyte and peak area of noise). The MQLs were calculated alike with a signal-to-noise ratio of 10. They were in the range 0.9–3.5 μg kg^{-1}, which allows the quantification of bisphenols and dyglicydyl ether derivatives at the low content they are usually present in samples. These MQLs were far below the migration limits set for BPA (i.e. 600 mg kg^{-1}, [37]), BADGE and its hydrolytic derivatives (i.e. 9 mg kg^{-1}, [9]) and BADGE chlorinated derivatives (i.e. 1 mg kg^{-1}, [9]) from food contact plastic materials.

3.3.2. Selectivity

The possible interference from matrix components, including the effect of salt (ionic strength), was investigated by comparison of the slopes of the calibration curves obtained from standards in acetonitrile with those run from blank tuna fortified with known amounts of the target analytes (15–1500 μg kg^{-1}) analyzed using the whole recommended procedure (see Section 2.4). The slopes of the calibration curves obtained for the tuna and those obtained from standards in acetonitrile were not statistically different by applying a Student's *t*-test [38]. The experimental *t*-values were in the interval 1.53–3.25 and were below the critical *t*-value (3.36, significant level = 0.01). Chromatograms obtained for blank tuna samples did not show any peak near the retention times of analytes except for BPF. This peak did not affect the accuracy achieved for the determination of this bisphenol as it could be inferred from the results obtained from the analysis of spiked samples.

3.3.3. Trueness

Trueness, usually expressed as bias, is the degree of closeness and agreement between mean values obtained from multiple replicates of test results and an accepted reference value. Because of the unavailability of certified reference materials in this study, trueness for the method here developed was investigated by repetitive analysis ($n = 6$) of blank tuna samples fortified with a mixture of bisphenols and their derivatives at 2 and 5 times the respective MQLs (Table 4). The recoveries at 2xMQLs and 5xMQLs ranged between 91 and 107% and 87 and 103%, respectively with relative standard deviations between 3 and 8%. These results were consistent with the 2002/657/EC decision which consider that the mean recoveries for analyte concentrations in the range >1 μg kg^{-1} to 10 μg kg^{-1} should be in the interval 70–110%.

3.3.4. Precision

Precision was studied in terms of repeatability and within-laboratory reproducibility. For this purpose, 18 aliquots of a blank tuna sample spiked with analytes at five times the respective method quantification limits (Table 4) were analyzed in three days (six aliquots each) using freshly prepared SUPRAS, mobile phases and standard solutions. The repeatability, expressed as standard deviation, was calculated as the square root of the average value of the intra-day variances obtained and, the within laboratory reproducibility as the square root of the mean intra-day variance plus the inter-day variance. The relative standard deviations under repeatability and reproducibility conditions varied within the intervals 1.8–6.8% and 4.4–8.1%, respectively, which is in compliance with the 2002/657EC Commission Decision (i.e. the relative standard deviations for within-laboratory reproducibility conditions should not exceed 20% for analyte concentrations in the range >10–100 μg kg^{-1}).

3.4. Analysis of canned foodstuffs

The proposed method was applied to the determination of bisphenols and their diglycidyl ethers and derivatives in canned foodstuffs. Different food categories that encompassed a wide

Table 6
Isomeric distribution found for BDFGE.2HCl and BFDGE in the foodstuffs analyzed.

	Peak area (%)[a] ± RSD[b]						
Isomer[b]	Green beans	Meat balls	Chickpeas	Lentils	Tripe	Mushroom	Mussels
BFDGE·2HCl (isomer 1, peak 8)	nd	nd	nd	nd	nd	nd	nd
BFDGE·2HCl (isomer 2, peak 9)	nd	nd	nd	nd	nd	nd	nd
BFDGE·2HCl (isomer 3, peak 10)	100 ± 6	nd	100 ± 8	nd	nd	nd	nd
BFDGE (isomer 1, peak 11)	nd	8.0 ± 0.4	nd	nd	nd	89 ± 5	nd
BFDGE (isomer 2, peak 12)	100 ± 7	92 ± 6	100 ± 5	100 ± 4	100 ± 6	11.0 ± 0.5	100.0 ± 0.4
BFDGE (isomer 3, peak 13)	nd	nd	nd	nd	nd	nd	nd

[a] Mean of three independent determinations.
[b] Relative standard deviation.
nd is not detected.

range of compositions regarding proteins, carbohydrates and salts were analyzed (see Table 2). Both native and spiked samples (100 $\mu g\,kg^{-1}$ each analyte) were quantified. Table 5 shows the mean values obtained for the concentration ($\mu g\,kg^{-1}$) and recoveries (%) found from three independent determinations, besides their corresponding standard deviations and variation coefficient, respectively.

Among the target bisphenols, both BPA and BADGE hydrolytic and chlorinated derivatives were the most frequently detected and also they were present at the highest concentrations, that confirming the greater use of BADGE-based coatings. BADGE was only detected in the mushroom sample at low concentration probably because of its favorable transformation in the respective derivatives. No presence of BPF or BPE was detected in any of the samples analyzed, while BPB was only present in three samples at concentration equal or below 40 $\mu g\,kg^{-1}$. Regarding BFDGE and BFDGE·2HCl, the former was more frequently detected in the foodstuff analyzed and, in addition, it was present at higher concentration. Recoveries for analytes in the samples were all within the range 80–110%, as recommended for the 2002/657/EC decision for analyte concentrations >10 $\mu g\,kg^{-1}$.

Table 6 shows the isomeric distribution found for BFDGE and BFDGE·2HCl, expressed as percentage of peak area, in the different foodstuffs. BFDGE·2HCl was only present as isomer 3 in the two samples analyzed. Except for mushroom, BFDGE was almost exclusively present as isomer 2. No isomer 3 for BFDGE was detected in any of the samples analyzed. Because of the probable different toxicity of the isomers, these preliminary results highlight the need for the individual determination of the isomeric forms of bisphenols and their diglycidyl ether and derivatives.

Fig. 2c shows, as an example, the chromatogram obtained from an unfortified mushroom sample. Identification of analytes was performed by co-chromatography [30]. For this purpose, the retention time and the peak width at half-maximum height obtained for each analyte from non-spiked and spiked samples were compared. The peak width at half-maximum height should be within the 90–110% range and retention times should be identical within a margin of 5%. Differences between retention times and peak width for analytes measured from fortified and unfortified samples were lower than 1.5 and within the range 92–107%, respectively, in all cases.

4. Conclusions

The effect of bisphenols on human health, especially on vulnerable populations such as infants, young children, pregnant and breastfeeding women, continues as a matter of debate. The concentration of these compounds in food, considered as the main source for human exposure, has to be determined through extensive monitoring programmes for establishing the cause and effect relationship.

The multiresidue method here developed has valuable analytical and operational assets for the simultaneous determination of major bisphenols in canned food. Thus, recoveries within the range 80–110% were obtained for analytes in a wide polarity range (e.g. octanol water partition coefficients were between 2.05 and 4.34, Table 1) and different food categories (i.e. legumes, vegetables, fruits, seafood, meat products and grain) that encompassed a broad range of compositions (Table 2). So it would be reasonably expected that the supramolecular solvent-based extraction here proposed can be applied as a generalized sample treatment for the intended purpose. Such good extraction efficiency for the target bisphenols was the result of the mixed mode mechanism (i.e. hydrogen bonding and dispersion interaction) driving analyte isolation from the matrix. On the other hand, combination of SUPRAS-based extraction with LC/fluorescence detection provided sensitivity enough to quantify bisphenols, diglycidyl ethers and derivatives at the concentrations they usually are present in samples, and selectivity enough to allow the use of external calibration. The method could be extended to LC–MS^2 when further improvement in sensitivity and selectivity is to be required.

From a practical point of view, the sample treatment here proposed features low cost, it takes about 30 min, several samples can be simultanously treated and it requires conventional lab equipments. Main advantages on previous reported methods for determining the target bisphenols in canned solid food include a substantial reduction in solvent consumption, the simplification of the sample treatment (i.e. no cleanup or solvent evaporation is required) and/or the no need for using dedicated equipment.

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