Food Packaging and Shelf Life 28 (2021) 100671

Contents lists available at ScienceDirect

Food Packaging and Shelf Life

journal homepage: www.elsevier.com/locate/fpsl

Multi-analyte method for the quantification of bisphenol related compounds in canned food samples and exposure assessment of the Spanish adult population

Antía Lestido-Cardama [a], Raquel Sendón [a], Juana Bustos [b], Mª Isabel Santillana [b], Perfecto Paseiro Losada [a], Ana Rodríguez Bernaldo de Quirós [a,*]

[a] Department of Analytical Chemistry, Nutrition and Food Science, Faculty of Pharmacy, University of Santiago de Compostela, 15782, Santiago de Compostela, Spain
[b] National Food Centre, Spanish Agency for Food Safety and Nutrition, 28220, Majadahonda, Spain

ARTICLE INFO

Keywords:
HPLC-FLD
Canned food
Bisphenols
BADGE
LC–MS/MS
Exposure

ABSTRACT

Major types of internal can coatings used for food and beverages are made from synthetic polymers known as epoxy-based resins, mainly based on bisphenol A diglycidyl ether (BADGE). The migration of components from coatings to food is a concern for food safety. A multiresidue method was developed for the identification and quantification of six bisphenols, BADGE and its derivatives, and cyclo-di-BADGE in sixteen canned food samples based on HPLC-FLD. The method developed showed excellent validation data with an adequate linearity, low detection levels, good repeatability and acceptable recoveries. Confirmation of the obtained results was made by LC–MS/MS. The exposure of the adult population to these compounds through the consumption of canned food was assessed. In general, the results suggested a low dietary exposure to this type of compounds (0.003 to 0.985 μg/kg bw/day) with values lower than the established tolerable day intake (TDI). The highest mean concentration was observed for cyclo-di-BADGE in a sample of pickled mussels.

1. Introduction

Metal foodstuff packaging provides long term ambient stable storage with excellent damage and abuse resistance during distribution, sale and consumer handling, and protection from external contamination, both chemical and microbiological. The final objective is to ensure the safety and quality of the packed food during the whole shelf-life period, that ranges from one to five years. Although metal, whether steel or aluminium, is the primary component in the manufacture of cans providing strength and integrity, on many occasions additional materials are required to make a functional package (Whitaker, 2007). Most of cans present an internal protective coating on the food contact surface to avoid the possible interaction between the foodstuff and the metal. Coatings seek, on one hand, to protect the integrity of the metal package surface from the corrosive properties of the foodstuffs during filling, storage, and in some cases, heating (Whitaker, 2007); and, on the other hand, also to protect the foodstuffs from the metal (Guo et al., 2020). So, the coatings need to have some characteristics like very good substrate adhesion and flexibility to stand, without loss of integrity, during metal forming operations, high temperatures, the food contact products, and the abuse during distribution and sale. In addition, another important requirement is that coatings should not transfer constituents to food in quantities that can be harmful to human health (Whitaker, 2007).

Coating materials may contain several components such as resins, cross-linking agents, catalysts, lubricants, wetting agents, and solvents (Bradley, Driffield, Harmer, Oldring, & Castle, 2008). Usually, food industries purchase the packaging material already coated and the detailed compositional information of coating formulations is rarely available for reasons of confidentiality of the industries (Sendón García, Paseiro Losada, & Pérez Lamela, 2003; Whitaker, 2007). However, it is clear that the major types of can coatings used in foods and beverages are epoxy-based resins, often composed of phenolic polymers produced from bisphenol A (BPA) (Bradley et al., 2008; Noonan, Ackerman, & Begley, 2011). BPA is the core substrate to produce bisphenol A diglycidyl ether (BADGE), the main monomer used in the epoxy resin industry (Alabi, Caballero-Casero, & Rubio, 2014). If the chemical reaction in the production process of the coating is not complete, the coatings can release these compounds and migrate into the packaged

* Corresponding author.
E-mail address: ana.rodriguez.bernaldo@usc.es (A. Rodríguez Bernaldo de Quirós).

https://doi.org/10.1016/j.fpsl.2021.100671
Received 18 December 2020; Received in revised form 5 April 2021; Accepted 7 April 2021
Available online 23 May 2021

food (Paseiro-Cerraro, DeVries, & Begley, 2017). High temperatures, as those achieved during the process of sterilization of the can, or the contact with either acid or basic foodstuffs, can promote the release of these compounds into foods (Fasano, Bono-Blay, Cirillo, Montuori, & Lacorte, 2012). It has been shown that most of the migration of BPA mainly occur during can processing, sealing and sterilization; and to a less extend during storage or after can damage (Tzatzarakis et al., 2017).

Although there are several investigations that relate the BPA with endocrine disruptive effects in humans, it is not expected to be a risk for the consumer health. Several regulatory agencies, such as European Food Safety Authority (EFSA) concluded that BPA poses no health risk at the estimated levels of exposure in foods (EFSA, 2015). Anyhow, it is recommended a reduction in exposure, especially for the most vulnerable populations like infants, young children and pregnant or breast-feeding women (Alabi et al., 2014). In the Title 21, Part 175 of the U.S. Code of Federal Regulations (FDA), indirect food additives: adhesives and components of coatings are specifically regulated, but currently there is no EU harmonised specific legislation covering this sector, and there are only certain substance specific legislations. In the absence of specific regulation for coatings, EU national member state regulations may be used to show compliance with the Framework Regulation (1935/2004) and the legislation for plastic food contact materials can be used as a guide (Bradley et al., 2008; Whitaker, 2007). Recently, Regulation (European Commission, 2018) was adopted setting a specific migration limit (SML) of 0.05 mg/kg, from plastics and also from varnishes or coatings applied to materials, while no migration of BPA is permitted from plastic materials or varnishes or coatings applied to materials and articles specifically intended to infants and young children up to 3 years old. The SMLs fixed by the European Commission No. 1895/2005 were 9 mg/kg or 9 mg/6 dm^2 in food or food simulant for BADGE and its hydroxyl derivatives and 1 mg/kg or 1 mg/6 dm^2 for its chlorinated derivatives. EFSA has established a tolerable day intake (TDI) of 0.15 mg/kg of body weight/day for BADGE and its hydrolysis products (EFSA, 2004). More recently, in 2015, EFSA reported in the Scientific Opinion on the risk to public health related to the presence of BPA in foodstuffs a temporary tolerable day intake (t-TDI) of 4 μg/kg of body weight/day (EFSA, 2015).

Some authors have reported that, as a consequence of these restrictions on the use of BPA in food contact materials, plastic and canning industries have been seeking alternatives to replace the use of BPA by other bisphenol analogues with similar physicochemical properties (Xiong et al., 2018). Bisphenols analogues (hereafter "bisphenols") are a group of organic compounds that share the basic structure of two phenol ring, with hydroxy moieties at the *para* positions, and joined by a carbon or sulfur bridge depending on the analogue (Xue, Wan, & Kannan, 2016). Unfortunately, this similarity is also expected to result in potentially harmful toxicological profiles (Xiong et al., 2018). In fact, available studies have reported various toxic effects, including endocrine disruption, cytotoxicity, genotoxicity, reproductive toxicity, dioxin-like effects, and neurotoxicity, of bisphenol analogues (Chen et al., 2016).

The development of multi residue methods able to quantify several bisphenols and bisphenol diglycidyl ethers (BADGEs), with potential to migrate from the can into the food, is desirable as a straightforward way to estimate the overall dietary exposure of this family of chemical compounds. Regarding food packaging, canned food is the main source for population exposure to these compounds compared to foods sold in glass, paper or plastic packaging. Therefore, the study of their occurrence in different canned foodstuffs is required for an evaluation of human dietary exposure in order to protect human health (Alabi et al., 2014; Liao & Kannan, 2013). Current detection methods for bisphenol related compounds are based on instrumental techniques such as gas chromatography-mass spectrometry (GC–MS), liquid chromatography with fluorescence detection (HPLC-FLD) and liquid chromatography-mass spectrometry (LC–MS) (Xiong et al., 2018). Due to the low volatility of these compounds, for the analysis by GC–MS samples are subjected to some derivatization pre-treatment by alkylation, silylation or acylation, prior to chromatographic separation (Arar & Alawi, 2019); which involves additional manipulation, increasing the analysis time, reducing the reproducibility of the method and adding a source of contamination (Alabi et al., 2014; Gallart-Ayala, Moyano, & Galceran, 2010). HPLC-FLD has great potential for simultaneous determination of bisphenols due to its advantages such as simple operation, rapid, highly efficient and low cost analysis (Guo et al., 2020; Xiong et al., 2018). Fluorescence detection was found to be highly sensitive and to present a similar response for all bisphenol-type compounds (Biedermann, Zurfluh, Grob, Vedani, & Brüschweiler, 2013). Tandem mass spectrometry is the detection method used to improve selectivity and sensitivity in the analysis of these compounds at low concentration levels in complex matrices. Triple quadrupole mass detectors are the most popular instruments, due to the sensitivity and selectivity achieved when operated in selected reaction monitoring (SRM) mode (Gallart-Ayala et al., 2010). Bisphenols are usually analysed in negative mode, which produces $[M-H]^-$ ions, while BADGEs show poor signal or even no signal in negative ion mode, and have a high tendency to form adducts in positive mode. The use of additives in the mobile phase to increase the signal response of BADGEs compounds may, however, cause signal suppression for bisphenols; therefore, it is difficult to find a mobile phase composition allowing the optimal sensitivity for the determination of both type of compounds (Alabi et al., 2014). Other alternative methods like molecular imprinting polymers (MIP), enzyme linked immune sorbent assay (ELISA), electrochemical analysis method or biosensor methods have been used for rapid detection of bisphenols, but only few bisphenols, such as, BPA can be tested with these techniques (Xiong et al., 2018).

This study is a continuation of the results published in a previous article by Lestido Cardama et al. (2019) where different can packaging materials were characterized by ATR (attenuated total reflectance)-FTIR spectrometer, and a screening approach was presented to identify potential migrants present in the polymeric coating of food cans. In the present study, the first objective has been to develop a multiresidue method for the identification and quantification of six bisphenols (BPA; bisphenol B, BPB; bisphenol C, BPC; bisphenol E, BPE; bisphenol F, BPF; bisphenol G, BPG), BADGEs (BADGE, BADGE.H_2O, BADGE.$2H_2O$, BADGE.HCl, BADGE.2HCl, BADGE.H_2O.HCl) and cyclo-di-BADGE, applicable to a wide range of canned food products and based on HPLC-FLD. Confirmation of the obtained results was performed by LC–MS/MS. The second objective was to carry out an initial assessment of the exposure of the Spanish adult population to these compounds in the diet, using the concentration of these compounds measured in the canned foods and consumption data from ENALIA. To the best of our knowledge, there is limited information regarding the assessment of the exposure to several bisphenol analogues and BADGEs from canned foods.

2. Materials and methods

2.1. Reagents and standard solutions

Acetonitrile (ACN) HPLC grade and LC–MS grade, methanol (MeOH) HPLC grade and LC–MS grade, tetrahydrofuran (THF) HPLC grade, absolute ethanol (EtOH) for analysis, and heptane HPLC grade were provided from Merck. Ethyl acetate HPLC grade was purchased from Sigma-Aldrich. Ultrapure water was obtained from an Autwomatic Plus purification system.

High purity analytical standards were used in the study, they are described in the previous work (Lestido Cardama et al., 2019).

Single stock solutions of individual compounds containing 1000 mg/L were prepared by dissolving the analytical standard in acetonitrile, except for the CdB, for which a solution of 200 mg/L was prepared in ACN:THF (60:40, v/v). An intermediate mix solution in 90 % ACN:H_2O (v/v) was prepared by diluting appropriate volumes of the stock

solutions to yield a final concentration of 10 mg/L. Calibration solutions ranging from 0.005 to 0.25 mg/L were prepared daily in 45 % ACN.

Another intermediate mix solution of 10 mg/L in ACN was prepared. From this, a 5 mg/L dilution in EtOH was obtained, by evaporation of 10 mL of the 10 mg/L mix solution in ACN, and reconstitution in 20 mL of EtOH. From this solution, three calibration solutions of 0.5, 1 and 2 mg/L in heptane were prepared for spiking tests on the oily sample.

2.2. Samples

A total of twelve canned food samples were purchased in a local supermarket of Santiago de Compostela (Galicia, Spain). It must be taken into account that Spain is the fourth canned fish producer in the world, and Galicia is responsible for almost the 80 % of canned fish manufactured in Spain destined to exportation to the European Union and the US (Míguez et al., 2012). These samples covered a variety of food categories including fish (tuna, sardines), seafood (clams, mussels), vegetables (olives, asparagus, tomato), grains (sweet corn) and fruit (peach in syrup). The covering liquids were analysed when they were oily in nature (AAL, MEL, SRL), and also the peaches syrup since this is frequently consumed (MAL). Labelling detailed information about all the samples included in this study is presented in Table 1. As can be seen, the fat content ranged between 0% in the peach and 33 % in the light tuna in extra virgin olive oil.

Determination of the pH of each sample was carried out following the FDA recommendations (Part 114 - Acidified foods, Subpart E – Production and Process Controls) with pH meter (Mettler Toledo) using 5 g of food and the proportional part of the covering liquid, except if the covering liquid contained oil that could cause electrode fouling after homogenisation. In this case, the oil layer was discarded, and 1 mL of distilled water was added. The reported result in Table 1 is the average of two experimental measurements in each sample at room temperature. All samples showed an acidic character (pH 3.7–6.5).

Table 1
Characteristics of the canned food samples included in the study.

Code	Type of sample	Weight (g)*	Fat content*	pH
ES	White asparagus buds	Net: 155 Drained: 100	0.1 g/100 g (Satur.: 0.0 g)	5.0
TO1	Fried tomato	140	3.3 g/100 g (Satur.: 0.4 g)	4.0
TO2	Fried tomato (home style)	100	7.0 g/100 g (Satur.: 0.9 g)	4.0
AH	Chamomile olive with bone	Net: 350 Drained: 185	18 g/100 g (Satur.: 3.3 g)	3.7
AL	Natural clams	Net: 115 Drained: 63	2.7 g/100 g (Satur.: 0.9 g)	6.2
AA/AAL	Light tuna in extra virgin olive oil	Net: 112 Drained: 82	33 g/100 g (Satur.: 4.8 g)	5.5
ME/ MEL	Pickled mussels	Net: 111 Drained: 69	6.2 g/100 g (Satur.: 1.6 g)	4.7
SR/SRL	Sardines in olive oil	Net: 120 Drained: 84	28 g/100 g (Satur.: 4.2 g)	5.9
AN	Natural light tuna	Net: 80 Drained: 56	1.4 g/100 g (Satur.: 0.3 g)	5.7
AR	Olives stuffed with anchovy pasta	Net: 120 Drained: 50	16.9 g/100 g (Satur.: 3.0 g)	4.1
MA/ MAL	Peaches in syrup	Net: 200 Drained: 115	0 g/100 g (Satur.: 0.0 g)	3.8
MZ	Naturally sweet corn. without salt	Net: 160 Drained: 140	1.7 g/100 g (Satur.: 0.4 g)	6.5

* The weight and fat content are indicated as specified on the labeling of the food.

2.3. Sample preparation

Cans were maintained at room temperature until they were opened. The solid food and the covering liquid were separated and analysed as an independent sample. Solid samples were chopped and homogenized using an ultra-turrax (IKA T25 digital). The covering liquid was analysed when it was oily in nature (AAL, MEL, SRL). Also the peaches syrup was analysed since this is frequently consumed (MAL).

The extraction method established in this study was based on the procedure described by Sendón García et al. (2003) for olive oil with some modifications. Aliquots of 5 g of each food previously homogenized were taken for analysis and prepared in duplicate. A volume of 5 mL of heptane solution was added to the sample and manually stirred 1 min for fat removal. Then 10 mL of ACN 90 % in water were added and manually stirred during 10 min, followed by centrifugation at 1357 × g for 10 min at 4 °C (Hettich Zentrifugen Universal 320R). Finally, 250 μL of the ACN/aqueous phase were taken and transferred into a vial containing 250 μL of ultrapure water. The vial was stirred with a vortex mixer (VELP Scientifica) and the extract filtered through a PTFE 0.22 μm filter, prior to injection in the HPLC system.

To perform recovery tests, the sample of asparagus (ES) and the oil in the tuna (AAL) were selected as representative examples of aqueous and fatty food respectively. The recovery was evaluated by spiking these samples at three different concentrations (0.05, 0.1 and 0.2 μg/g). For this, mix standard solutions in heptane and in 90 % ACN were used for the oily and aqueous samples, respectively. The standard solutions added were allowed to infuse into the sample (15 min) before proceeding with the extraction, following the sample procedure as described above for the samples.

2.4. Instrumentation

2.4.1. HPLC-FLD

Separation and quantification were performed on an Agilent Technologies 1200 Series consisted of a quaternary pump, a degassing device, an autosampler, a column thermostat system, and a fluorescence detector, controlled by the ChemStation for LC 3D systems software. Fluorescence detection was performed using 225 nm as excitation wavelength and 305 nm as emission wavelength.

2.4.2. LC-MS/MS

The UHPLC-MS/MS system comprised an Accela autosampler, an Accela 1250 pump, and a column thermostatting system coupled to a triple stage quadrupole mass spectrometer TSQ Quantum Access max (Thermo Fisher Scientific). The operating conditions are described in the previous work (Lestido Cardama et al., 2019).

2.4.3. Chromatographic conditions

Chromatographic separation of target analytes was performed on a Phenosphere ODS column (150*3.2 mm, 3 μm particle size) with an appropriate guard column from Phenomenex®. The mobile phase consisted of (A) ultrapure water and (B) a mixture of ACN:MeOH (50:50, v/v). The gradient elution conditions were: 45 % B in an isocratic mode for 2 min, followed by a gradient to 75 % B for 14 min, then a gradient to 100 % B for 7 min and finally an isocratic elution with 100 % organic phase during 5 min in order to elute rapidly the remaining compounds and clean the column. The delay time for recording the next chromatogram was 5 min. The flow rate was constant at 0.5 mL/min. The injection volume was 10 μL. The column oven temperature was kept at 30 °C.

2.5. Exposure estimation

Dietary exposure was estimated taking into account the obtained concentration of the selected analytes in each sample and the Spanish consumption data for this type of food (ENALIA 2). According GEMS/Food– EURO recommendations, to estimate dietary exposure, analytical results under the respective limit of detection (LOD) were considered to be equal to one-half of that limit (LOD/2) and values under the limit of quantification (LOQ) were considered to be equal to one-half of that limit (LOQ/2) (Sirot, Hommet, Tard, & Leblanc, 2012).

ENALIA 2 is a dietary survey conducted in Spain that includes the adult population between 18 and 74 years of age. It is an individual survey which allows to know the type of food and the quantities consumed (g/day) by this population and the frequency of food consumption. The methodology followed the EFSA guidance recommendations on the "General principles for the collection of national food consumption data in the view of a pan-European dietary survey". In our case, we focused on the adult population group from 18 until 74 years because it is the largest consumer group of this type of products.

An assessment of the risk associated with dietary exposure was evaluated comparing the obtained chemical intake values with the available TDI values established by EFSA, or other international institutions.

3. Results and discussion

3.1. Method optimization

In developing the chromatographic method, different C18 columns were tried to obtain the best resolution of the chromatographic peaks of the analytes, being Phenosphere ODS the one that best resolved and separated the compounds. This column is a reversed phase type C18 with an 11 % carbon load. The columns Biphenyl 100A (100*3 mm, 2.6 μm) and Kinetex C18 100A (100*2.1 mm, 2.6 μm) could not separate the two isomers of CdB. The columns Kromasil ODS C18 (150*3.2 mm, 5 μm), Luna C18(2)100A (150*3 mm, 2.6 μm), and ACE 3 C18-Hl (150*3 mm, 3 μm), could not separate the BPB peak from BADGE.H_2O peak. With the columns Evo C18 100A (150*3 mm, 5 μm) and Scharlau KromaPhase 100 (150*3 mm, 5 μm) good resolution was not obtained for the BPA peak. Several solvents were also tested in order to select the adequate mobile phase: ACN-water, MeOH-water, a mixture of ACN:MeOH (50:50, v/v)-water, ACN-ammonium acetate 10 mM, and MeOH-ammonium acetate 10 mM. The mobile phase organic modifier plays an important effect on the elution of diglycidylethers. The elution order of BADGE.H_2O and BADGE.H_2O.HCl changed when MeOH was used instead of ACN, which is probably due to the relative hydrophobicity of both solvents (Gallart-Ayala et al., 2010). Finally, the mixture of ACN:MeOH and water was selected as optimum in the separation of all compounds, including the two diastereomers of CdB. Different injection volumes (5, 10 and 20 μL) were tested and the best peak chromatographic resolution, without compromising the sensitivity, was with 10 μL.

With the aim to identify simultaneously bisphenols and BADGEs in the canned foods, a method based in LC–MS/MS was designed. For this, all the compounds were infused using electrospray ionization (ESI) and atmospheric pressure chemical ionisation (APCI) mode. Positive and negative APCI technique was selected because it turned out to be the best option for the detection of the majority of these compounds. Since when the mass instrumental conditions were optimized by direct infusion of individual standards, the APCI source showed better sensitivity for most compounds. Some authors proposed the use of ammonium buffer as a mobile phase additive to form ammonium adducts ions and improve the ionization efficiency of bisphenols diglycidyl ethers and their derivatives, but a negative effect was found in the ionization of some bisphenols where signals decreased. Increasing the ammonium buffer reduces the pH value of the mobile phase, which affects the dissociated state of some bisphenols and the ionization efficiency decreases accordingly (Cheng et al., 2017). The mixture of ACN:MeOH as mobile phase permitted to obtain higher responses for most of these compounds in APCI mode.

Several tests were done to achieve the best extraction procedure. It represents a challenging task due to the complex composition of the matrices and the trace levels of the target analytes present in the samples. High content of lipids can be difficult to remove through sample preparation, which can cause chromatographic disturbances and instrumental damage (Cunha, Oliveira, & Fernandes, 2017). Extraction with different solvents were tested based on the bibliography, such as ethyl acetate (Gallart-Ayala, Moyano, & Galceran, 2011; Tzatzarakis et al., 2017) and mixtures of polar and non-polar solvents (Sendón García et al., 2003). The mixture heptane-ACN 90 % was selected as the extraction solvent giving higher recoveries, while for the other mixtures, most of the analytes did not reach 70 % recovery. Acetonitrile has been found to provide considerably better extraction efficiencies for polar analytes, while heptane allowed the removal of the fat content. Other parameters were also optimized, namely the volume of heptane, the percentage of ACN in the extraction solvent and the conditions of the centrifugation step. Lower volumes of heptane gave more interferences in the chromatogram. When higher percentage of water was used in the extraction solvent, the reproducibility was poor. It was seen that the centrifugation at 249 × g gave more noise in the chromatogram. Concentration of the sample extract using a stream of nitrogen was discarded because a turbid solution was obtained.

3.2. Method validation

Validation parameters, such as linearity, sensitivity, repeatability and precision of the developed method were evaluated by HPLC-FLD.

Quantification was performed by external calibration curve prepared in solutions. For this, a series of standard solutions of known concentration were analysed during each working session. Calibration graphs were formed with the chromatographic peaks area against standard solution concentration. The quantification of CdB was carried out as the sum of the two isomers. Linearity parameters are shown in Table 2. From the resulting calibration curves with five calibration points, the calculated determination coefficients were in all cases $\geq$ 0.9994, showing a very good linearity of calibration function in this concentration range.

The limits of detection (defined as signal three times the height of the noise level) and the limits of quantification (defined as signal ten times the height of the noise level, corresponding to the lowest calibration level of the calibration curve) by HPLC-FLD were 0.005 mg/L and 0.0125 mg/L respectively for all the analytes included in the study. These limits achieved, allow the quantification of these compounds at the usual low concentrations that can be found in food samples, far below the migration limits when established.

In the case of the LC–MS/MS developed method, the LODs were in the range from 0.5 μg/L for CdB to 0.5 μg/mL for BADGE.2HCl and BADGE.H_2O.HCl (Lestido Cardama et al., 2019). This unsatisfactory sensitivity for these last two compounds is in line with the results obtained by Zhang, Xue, Zou, Dai, and Lin (2010) by APCI-MS, but a compromise had to be reached to be able to analyse all the analytes using the same technique.

Repeatability (HPLC-FLD), expressed by means of the percentage of relative standard deviation (RSD%) was determined by repetitive analysis (n = 8) of a standard solution of the mix at a concentration of 0.025 mg/L. The repeatability was lower than 10 % in all cases (Table 2).

Precision and recovery of the extraction method was determined by spiking experiments on food samples with the mixed standard solution at three concentrations (0.05, 0.1 and 0.2 μg/g), during three consecutive days (n = 6). The analyses were performed by duplicate. The sample of asparagus (ES) and the tuna's oil (AAL) were selected as representative examples of aqueous and fatty food, respectively. Since these

Table 2
- Method validation parameters of each compound by HPLC-FLD.

Compound	Retention time (min)	Range of linearity (mg/L)	Equation	R^2	LOD (mg/L)	LOQ (mg/L)	Repeatability (RSD%)	Tuna's oil (AAL)						Asparagus (ES)					
								Recovery (%)			Repeatability (RSD%)			Recovery (%)			Repeatability (RSD%)		
								0.05 μg/g	0.1 μg/g	0.2 μg/g	0.05 μg/g	0.1 μg/g	0.2 μg/g	0.05 μg/g	0.1 μg/g	0.2 μg/g	0.05 μg/g	0.1 μg/g	0.2 μg/g
BPF	4.71	0.0125–0.25	y = 51.5x+0.0238	0.9994	0.005	0.0125	6	102	114	103	8.35	1.98	2.87	76	78	74	4.30	1.87	1.51
BADGE.2H$_2$O	5.34	0.0125–0.25	y = 131.73x+0.1333	0.9998	0.005	0.0125	6	111	115	98	2.52	3.43	0.43	82	73	72	16.0	2.95	3.78
BPE	6.43	0.0125–0.25	y = 41.553x+0.0121	0.9998	0.005	0.0125	5	–	–	–	–	–	–	82	70	73	1.49	0.38	3.83
BPA	8.21	0.0125–0.25	y = 53.627x+0.0917	0.9998	0.005	0.0125	4	107	88	75	14.4	4.66	9.67	85	86	71	4.73	7.59	1.34
BPB	10.79	0.0125–0.25	y = 73.127x+0.1154	0.9999	0.005	0.0125	5	105	106	101	1.85	5.31	2.71	86	72	77	5.68	0.03	4.68
BADGE.H$_2$O	11.34	0.0125–0.25	y = 138.9x+0.0863	0.9999	0.005	0.0125	5	118	114	101	1.37	4.92	2.09	74	72	71	3.44	4.41	3.80
BADGE.H$_2$O.HCl	11.95	0.0125–0.25	y = 134.5x-0.0687	0.9999	0.005	0.0125	5	102	105	96	16.7	12.0	1.77	80	74	73	13.0	4.05	2.49
BPC	12.61	0.0125–0.25	y = 91.033x-0.0054	0.9998	0.005	0.0125	6	96	105	97	13.0	10.8	8.69	87	80	84	4.49	11.8	10.1
BADGE	16.51	0.0125–0.25	y = 163.1x+0.1088	0.9999	0.005	0.0125	2	90	87	86	3.54	1.93	2.55	76	71	74	9.15	5.17	2.34
BADGE.HCl	16.82	0.0125–0.25	y = 119.9x+0.0887	0.9998	0.005	0.0125	4	100	101	93	3.23	1.01	0.89	75	71	71	4.88	0.08	0.40
BADGE.2HCl	17.09	0.0125–0.25	y = 129.83x-0.0604	0.9999	0.005	0.0125	3	106	103	98	5.60	4.43	1.13	74	73	71	8.43	4.27	4.36
BPG	19.27	0.0125–0.25	y = 111.03x-0.0754	0.9999	0.005	0.0125	5	85	83	83	6.01	1.24	2.67	79	72	70	4.05	2.73	4.29
CdB	21.02–21.25	0.0125–0.25	y = 85.333x+0.6533	0.9997	0.005	0.0125	10	94	117	117	3.04	2.06	3.77	96	81	81	3.76	5.00	1.06

compounds tend to concentrate in fatty medium, the oil from the tuna can was used to perform the recovery assays. Chromatograms obtained for blank samples did not show any peaks near the retention times of the analytes, except for BPE in tuna's oil. The extraction of food samples was considered to be exhaustive after one extraction step, since a second extraction step resulted in recoveries values less than 10 % of those obtained in the first extraction. Recovery (%) and repeatability (RSD%) results are shown in Table 2. The results reported provide evidence that the optimized method achieves acceptable recoveries and average recoveries were in the range of 70–120 %. The uncertainty calculated according to the Guidelines for performance criteria and validation procedures of analytical methods used in controls of food contact materials (Bratinova, Raffael, & Simoneau, 2009) ranged between 0.01 and 6.80 %. Fig. 1.A shows a HPLC-FLD chromatogram obtained for the asparagus sample spiked at the level of 0.05 μg/g where all the analytes can be detected.

3.3. Analysis of food samples

The developed method was applied for the quantification of bisphenol related compounds in a total of twelve canned foodstuffs and four covering liquids (AAL, MAL, MEL SRL). The covering liquids were analysed when they were oily in nature, such as the olive oil in tuna (AAL), the olive oil in sardines (SRL), and the pickle in mussels (MEL). The syrup of the peaches (MAL) was also analysed since this is frequently consumed. Each sample spiked with all analytes at a concentration of 0.1 μg/g was also analysed, to verify that the mean recovery was comparable to the performance parameters of the validated method. Both, the extract of the sample and the extract of the spiked samples at a concentration of 0.1 μg/g, in duplicate, were quantified. Table 3 summarizes the concentration (μg/g) obtained for each sample.

The recoveries achieved were in the range between 70–124 %, though in some cases recovery data for some analytes could not be obtained due to possible interferences in the matrix at the same retention time of the analyte, or in some cases because the concentration of the analyte in the sample was higher than the spiked concentration. For this reason, the confirmation of the presence/absence of the compounds in the samples was evaluated by LC–MS/MS. Thus, the positive results could be verified; additionally in the case of CdB, with a better sensitivity by LC–MS/MS, the method allowed its detection in more samples (AA, MA, SR).

Among the target compounds, BPA, BADGE.2H$_2$O, BADGE.H$_2$O.HCL and CdB were detected, while no presence of BADGE, BADGE.H$_2$O, BADGE.HCl, BADGE.2HCl and other bisphenol analogues was detected in any of the analysed samples.

Regarding to the bisphenols, only BPA was detected in a concentration ranging from not detected to 202 μg/kg in the sample of mussels (ME). This result is comparable with the range of concentrations (<1.41 to 278.5 μg/kg) reported in canned food samples analysed by Choi et al. (2018). Cunha, Cunha, Ferreira, and Fernandes (2012) found values within the same range for canned seafood samples (1–99.9 μg/kg), but a mean higher value of 265.6 μg/kg for canned vegetables and fruits (Cunha & Fernandes, 2013). In addition to the mussels sample, other samples with the higher BPA values found were foods coming from aquatic environment, such as tuna and clams. The presence of BPA in this group of samples is related to the migration of this monomer from the can coating, rather than related to the aquatic environment contamination, as demonstrated in the study of Cunha et al. (2017).

BADGE was found in none of the samples analysed, which is in agreement with the results in canned tuna samples reported in the study of Lapviboonsuk and Leepipatpiboon (2014). It could be probably because the epoxy groups are easily hydrolysed during the food storage (Alabi et al., 2014; Gallart-Ayala et al., 2011), or because BADGE might have reacted with other food ingredients like sugars or proteins present in the matrix leading to the formation of new compounds. Although these reaction products are likely to be high molecular weight products

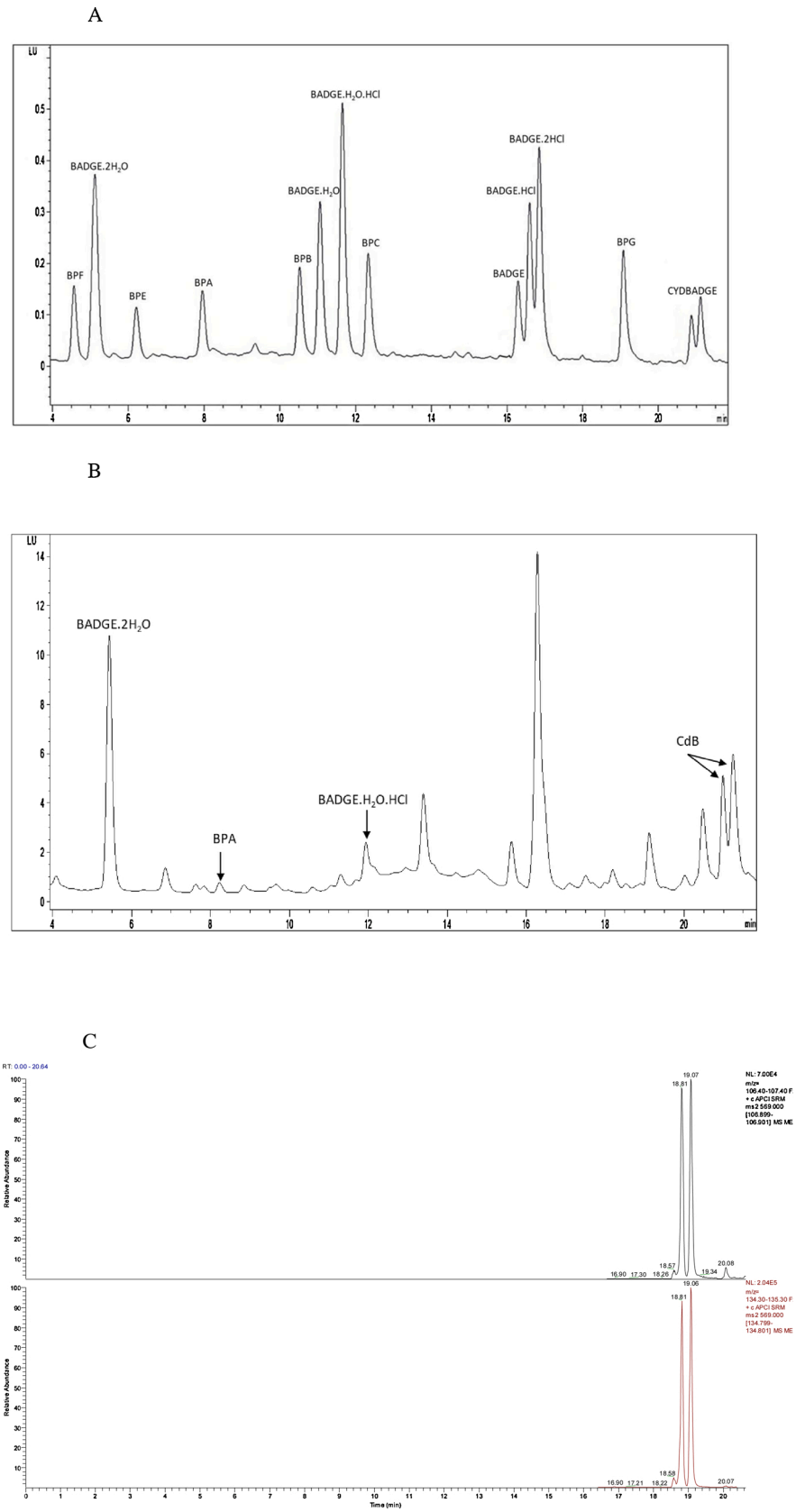

Fig. 1. HPLC-FLD chromatogram obtained for the spiked at the level of 0.05 μg/g in the sample of asparagus (A), after the extraction of the sample of mussels (B), and the LC–MS/MS chromatograms including the two transitions tuned for CdB in the same sample (C).

Table 3
Concentration of selected compounds in food samples.

Compound	Concentration (μg/g)													
	AAL*	AA	AH	AL	AN	AR	ES	MA	ME	MZ	SR	TO1	TO2	MAL*	MEL*	SRL*
BPF	<LOD	<LOD)	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
BADGE.2H$_2$O	<LOD	<LOD	<LOD	0.607	0.513	<LOD	<LOD	<LOD	0.724	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
BPE	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
BPA	<LOD	<LOD	<LOD	0.121	0.066	<LOD	<LOD	<LOD	0.202	<LOD	<LOD	<LOD	<LOD	<LOD	0.131	<LOD
BPB	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
BADGE.H$_2$O	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
BADGE.H$_2$O.HCl	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.189	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
BPC	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
BADGE	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
BADGE.HCl	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
BADGE.2HCl	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
BPG	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
CdB	<LOQ	<LOQ*	<LOD	0.578	0.342	<LOD	<LOQ	<LOQ*	1.43	<LOD	<LOQ*	<LOD	<LOD	<LOD	3.59	0.134

: covering liquid; LOD: limit of detection; LOQ: limit of quantification; LOQ: limit of quantification considering the signal by LC–MS/MS.

and therefore without or less toxicological relevance, their control is important since they may be broken down into smaller fragments and be absorbed from the gastrointestinal tract (Coulier et al., 2010). Fig. 1.B shows a HPLC-FLD chromatogram obtained of a sample of mussels, while Fig. 1.C shows a LC-MS/MS chromatogram with the two transitions tuned for CdB in the same food sample.

Within BADGE derivatives, BADGE.H$_2$O.HCl was detected in the samples of mussels (ME) with a concentration of 0.189 μg/g and BADGE.2H$_2$O was found in three samples with values in the range of < LOD – 0.724 μg/g. However, BADGE.HCl, BADGE.2HCl and BADGE.H$_2$O were not detected in any of the samples analyzed. The detected quantities were in compliance with European Union regulation, in all cases below the restriction levels (1 and 9 mg/kg).

CdB was other of the most detected compounds and the highest concentration was found in the sample of mussels, both as solid food (ME) and in the pickled sauce (MEL), at values of 1430 and 3590 μg/kg respectively. There are very few studies regarding this compound because the analytical standard is recently available. In a study developed in Switzerland, CdB was detected at higher levels in canned fish in oil (810 μg/kg), and in vegetables in water (75 μg/kg), while no CdB was detected in canned tomatoes or fruits in syrup, as in our study (Biedermann et al., 2013). In 2016, the German Federal Institute for Risk Assessment (BfR Opinion 022/2016) considered acceptable a migration level of 50 μg/kg food for CdB, which is exceeded in the samples analyzed in this study.

There was no significant relationship between the concentrations of contaminants and the type of food, the pH values or the content of fat. It is possible that the difference in the concentrations simply represent differences in the can production lines such as processing temperatures and times (Bhunia, Sablani, Tang, & Rasco, 2013), incorrect transport or storage conditions (Gallo et al., 2017) or the can size, since no corrections were made according to the packaging size (Noonan et al., 2011).

The results in this study allowed us to analyse the affinity of these analytes to the solid and/or liquid portion content of the can, in those samples where both parts were separately analysed. Noonan et al. (2011) found that the BPA concentration was higher, generally ≥10 fold, in the solid food over the liquid portion. Tzatzarakis et al. (2017) found higher levels of BPA in the solid phase of canned foods with high-fat content than in the liquid phase. Based on our results, it can be concluded that this fact depends on the nature of both parties and the solubility of the analytes, which generally present more affinity for the lipid-soluble phase than the water-soluble phase (Zhang et al., 2010). For example, in the case of the pickled mussels, the highest concentration of CdB was found in the liquid portion, and it was found that most of the CdB was within the fatty part of this.

Table 4 shows the results obtained for these analytes in canned samples in the latest studies carried out in Spain. As can be seen, they are in line with our results. In the study of Alabi et al. (2014), similar values of BPA were determined (not detected – 241 μg/kg), while González et al. (2020) quantified lower values in their samples (<0.17 – 88.66 μg/kg). BADGE was not found in none of the samples analysed, in agreement with the studies of Míguez et al. (2012) and Gallart-Ayala et al. (2011). However, Alabi et al. (2014), detected BADGE in one sample of mushroom at a concentration of 7.1 μg/kg. Regarding to BADGE derivatives, BADGE.2H$_2$O was the one with the highest concentration of 724 μg/kg, which is in line with the other studies, while BADGE.H$_2$O was not detected. BADGE.HCl and BADGE.2HCl were not detected in our samples as in the study of Míguez et al. (2012). With respect to BADGE.H$_2$O.HCl, our values are in the range of the results reported by the three studies (not detected – 533 μg/kg).

These results were compared with those obtained in the previous work of Lestido Cardama et al. (2019). In the aforementioned study the analytes of interest were identified in the polymeric can coatings of these samples. In the sample AL, 0.121 μg/g of BPA was quantified, but in its corresponding can extract, no levels of BPA had been detected. This could be because of all the released BPA had already migrated into the

Table 4
Comparison between our results with the latest studies carries out in Spain.

Reference	Instrument method	Sample analyzed	Analytes of interest	Results
Gallart-Ayala et al. (2011)	HPLC-MS-ESI (+)	Canned food simples of vegetables and fruits	BADGE	nd
			BADGE.H_2O	nd–53 μg/kg
			BADGE.2H_2O	2.8–675 μg/kg
			BADGE.HCl	nd–11 μg/kg
			BADGE.2HCl	nd–2.8 μg/kg
			BADGE.H_2O. HCl	nd–274 μg/kg
Míguez et al. (2012)	HPLC-MS-ESI (+)	Canned fish food samples including mussels. boquerons. sardines. mackerels and tuna	BADGE	nd
			BADGE.H_2O	nd–120 μg/kg
			BADGE.2H_2O	nd–625 μg/kg
			BADGE.HCl	nd
			BADGE.2HCl	nd
			BADGE.H_2O. HCl	nd–87 μg/kg
			BADGE.2H_2O	nd–959 μg/kg
Alabi et al. (2014)	HPLC-FLD	Canned foodstuffs including vegetables. legumes. fruits. fish and other seafood. meat products and grains	BPF	nd
			BPE	nd
			BPA	nd–241 μg/kg
			BADGE.H2O. HCl	nd–533 μg/kg
			BADGE.H_2O	nd–179 μg/kg
			BPB	nd–40 μg/kg
			BADGE.2HCl	nd–215 μg/kg
			BADGE.HCl	nd–21 μg/kg
González et al. (2020)	GC-MS	Canned food including pâté. mushrooms. chicken. fruit salad in syrup. asparagus. corn. squid. tuna. nuts. red beans. artichokes. peach in syrup. green beans. mackerel and olive oil	BADGE	nd–7.1 μg/kg
			BPA	<0.17–88.66 μg/kg
			BPB	<0.17–3.86 μg/kg
			BPE	<0.17–<0.83 μg/kg
			BPF	nd
			BPA	nd–202 μg/kg
			BPB	nd
			BPC	nd
			BPE	nd
			BPF	nd
			BPG	nd
Present study	FLD and APCI	Canned foodstuffs including fish. seafood. vegetables. grains and fruit	BADGE	nd
			BADGE.H_2O	nd
			BADGE.2H_2O	nd–724 μg/kg
			BADGE.HCl	nd
			BADGE.2HCl	nd
			BADGE.H_2O. HCl	nd – 189 μg/kg
			CdB	nd – 3590 μg/kg

nd: not detected.

food or the food was contaminated by another source, as it is a ubiquitous contaminant. Regarding to CdB, it was detected in the extraction of the internal side of the sardine can and in the corresponding cover liquid, although epoxy resins would not have been identified in the internal side. These results reinforce the theory that the migration into food might have been due to a possible set-off ; phenomena during the manufacturing process and storage of the packaging materials in the industry.

3.4. Estimation of the dietary exposure

Table 5 shows the estimated dietary exposure values (mean and 95th percentile) in Spanish adult population to those analytes that were found in the canned food samples analysed. For those samples where the covering liquid and the canned food had been analyzed separately, the calculated exposure data is the result of the whole. In general, low dietary exposure data to this type of compounds were obtained (0.003 to 0.985 μg/kg bw per day). It must be taken into account the uncertainties that are linked to exposure assessment such as in the sampling, the calculated uncertainty for the precision of the method described when calculating concentrations in samples, and the representativeness since the chemicals investigated could originated from other sources than packaging (Franz, 2005). For example, in our study one of the compounds analysed e.g., BPA is considered a ubiquitous contaminant. And indeed, the intrinsic uncertainty associated with food consumption data, among others.

The Scientific Committee of European Commission estimated dietary intake values of BPA at 110−370 ng/kg bw/day for adults, which are higher than our estimated dietary exposure in the 95th percentile, but the limited number of samples analysed in this study has to be taken into consideration.

Considering the food category, it can be concluded that the exposure to this group of bisphenol compounds is greater in seafood, while vegetables and grains were the categories that resulted in a lower level of exposure. From the public health standpoint, it is interesting to note that in all the samples analyzed, the BPA, BADGE and its hydrolysis products exposure turned out to be lower than their TDIs and t-TDI established by the EFSA, which demonstrate the safety of the studied coatings. Regarding to the other analogues of bisphenols and CdB, this comparison was not possible, because international organizations have not set regulations on their presence in food, migration limits or TDI values.

As the toxicity data available for CdB is limited, the threshold of

Table 5
Mean estimated dietary exposure (P95) in Spanish adult population (μg/kg bw per day).

MEAN (P95)	AA	AH	AL	AN	AR	ES	MA	ME	MZ	SR	TO1	TO2
BPF	0.005	0.005	0.005	0.007	0.005	0.005	0.035	0.004	0.003	0.009	0.003	0.003
	(0.01)	(0.01)	(-)	(0.01)	(0.01)	(0.01)	(-)	(-)	(0.01)	(0.02)	(0.01)	(0.01)
BADGE.2H_2O	0.005	0.005	0.313	0.359	0.005	0.005	0.035	0.199	0.003	0.009	0.003	0.003
	(0.01)	(0.01)	(-)	(0.68)	(0.01)	(0.01)	(-)	(-)	(0.01)	(0.02)	(0.01)	(0.01)
BPE	0.005	0.005	0.005	0.007	0.005	0.005	0.035	0.004	0.003	0.009	0.003	0.003
	(0.01)	(0.01)	(-)	(0.01)	(0.01)	(0.01)	(-)	(-)	(0.01)	(0.02)	(0.01)	(0.01)
BPA	0.005	0.005	0.062	0.046	0.005	0.005	0.035	0.077	0.003	0.009	0.003	0.003
	(0.01)	(0.01)	(-)	(0.09)	(0.01)	(0.01)	(-)	(-)	(0.01)	(0.02)	(0.01)	(0.01)
BPB	0.005	0.005	0.005	0.007	0.005	0.005	0.035	0.004	0.003	0.009	0.003	0.003
	(0.01)	(0.01)	(-)	(0.01)	(0.01)	(0.01)	(-)	(-)	(0.01)	(0.02)	(0.01)	(0.01)
BADGE.H_2O	0.005	0.005	0.005	0.007	0.005	0.005	0.035	0.004	0.003	0.009	0.003	0.003
	(0.01)	(0.01)	(-)	(0.01)	(0.01)	(0.01)	(-)	(-)	(0.01)	(0.02)	(0.01)	(0.01)
BADGE.H_2O.HCl	0.005	0.005	0.005	0.007	0.005	0.005	0.035	0.053	0.003	0.009	0.003	0.003
	(0.01)	(0.01)	(-)	(0.01)	(0.01)	(0.01)	(-)	(-)	(0.01)	(0.02)	(0.01)	(0.01)
BPC	0.005	0.005	0.005	0.007	0.005	0.005	0.035	0.004	0.003	0.009	0.003	0.003
	(0.01)	(0.01)	(-)	(0.01)	(0.01)	(0.01)	(-)	(-)	(0.01)	(0.02)	(0.01)	(0.01)
BADGE	0.005	0.005	0.005	0.007	0.005	0.005	0.035	0.004	0.003	0.009	0.003	0.003
	(0.01)	(0.01)	(-)	(0.01)	(0.01)	(0.01)	(-)	(-)	(0.01)	(0.02)	(0.01)	(0.01)
BADGE.HCl	0.005	0.005	0.005	0.007	0.005	0.005	0.035	0.004	0.003	0.009	0.003	0.003
	(0.01)	(0.01)	(-)	(0.01)	(0.01)	(0.01)	(-)	(-)	(0.01)	(0.02)	(0.01)	(0.01)
BADGE.2HCl	0.005	0.005	0.005	0.007	0.005	0.005	0.035	0.004	0.003	0.009	0.003	0.003
	(0.01)	(0.01)	(-)	(0.01)	(0.01)	(0.01)	(-)	(-)	(0.01)	(0.02)	(0.01)	(0.01)
BPG	0.005	0.005	0.005	0.007	0.005	0.005	0.035	0.004	0.003	0.009	0.003	0.003
	(0.01)	(0.01)	(-)	(0.01)	(0.01)	(0.01)	(-)	(-)	(0.01)	(0.02)	(0.01)	(0.01)
CdB	0.013	0.005	0.298	0.239	0.005	0.011	0.066	0.985	0.003	0.055	0.003	0.003
	(0.03)	(0.01)	(-)	(0.45)	(0.01)	(0.03)	(-)	(-)	(0.01)	(0.13)	(0.01)	(0.01)

toxicological concern (TTC) based Cramer structural class III value of 1.5 μg/kg bw/day is suggested to be a useful tool for their evaluation (Biedermann et al., 2013). Based on the Spanish consumption data and the highest concentration of CdB measured in the sample corresponding to pickled mussels, it can be concluded that our estimated dietary exposure is below this value (0.985 μg/kg bw per day).

In order to estimate real exposure, it is important to consider other exposure pathways in addition to diet such as dermal absorption and air inhalation (aggregate exposure) as well as the presence of traces of other endocrine disruptors in food (cumulative exposure), which could increase the total exposure and cause adverse effects, even at low levels. Moreover, biomonitoring studies of these compounds would be of value in order to explore their adsorption, distribution, metabolism and excretion, with the final objective to know the behaviour of these molecules within the body and make an assessment of their impact in the human health (González et al., 2020).

4. Conclusion

In brief, the analytical method developed and validated in this study allows a simultaneous quantification and identification of several bisphenol related compounds in a wide range of canned food samples using HPLC-FLD. The method can be used as a tool with the final objective to estimate the dietary exposure to these chemicals in canned foods. In addition, a LC–MS/MS method was proven to be an excellent analytical tool for confirmation purposes, in particular when interferences are present in the matrix. Although, it is also interesting to note that HPLC-FLD may be useful technique for control laboratories and routine analysis. The results obtained in the canned food samples, though limited in number, indicate that some of these compounds migrate to the food. Therefore, monitoring the concentration of these compounds in foods is essential for risk evaluation.

The exposure assessment of the adult population to these compounds transferred from the metal can coatings to the food was investigated. In this study seafood samples provided the highest contribution, reaching a mean exposure of 0.985 μg/kg bw per day for CdB in the pickled sauce of the mussels. Although the data are limited in number, they suggest a low dietary exposure to this type of compounds, and the reference TDIs were respected. Nevertheless, it is important to take into account other exposure pathways as well as the combined exposure to multiple endocrine disruptors for risk assessment determinations.

Author contributions

Conceptualization, R.S., J.B., P.P.L., and A.R.B.d.Q.; methodology, R.S., J.B., P.P.L., and A.R.B.d.Q.; investigation, A.L.C.; writing-original draft preparation, A.L.C.; writing-review and editing, R.S., J.B., M.I.S.; P.P.L., and A.R.B.d.Q.; supervision, R.S., P.P.L., and A.R.B.d.Q.; project administration, R.S., and A.R.B.d.Q.; funding acquisition, A.R.B.d.Q.

Funding

The study was financially supported by the Ministerio de Ciencia, Innovación y Universidades, by Fondo Europeo de Desarrollo Regional (FEDER), and by Agencia Estatal de Investigación Ref. No. PGC2018-094518-B-I00 “MIGRACOATING” (MICIU/FEDER, UE); and by the Ministerio de Economía y Competitividad, and by Fondo Europeo de Desarrollo Regional (FEDER), Ref. No. AGL2015-69609-P “MIGRAEXPO” (MINECO/FEDER, UE).

Acknowledgments

Antía Lestido is grateful for her grant “Programa de axudas á etapa predoutoral” da Xunta de Galicia (Consellería de Cultura, Educación e Ordenación Universitaria).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.fpsl.2021.100671.

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