Talanta 205 (2019) 120086

Contents lists available at ScienceDirect

Talanta

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

Direct analysis in real time accurate mass spectrometry determination of bisphenol A in thermal printing paper

G. Castro, I. Rodríguez*, M. Ramil, R. Cela

Department of Analytical Chemistry, Nutrition and Food Sciences. Institute for Research and Food Analysis (IIAA). Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain

ARTICLE INFO

Keywords:
Bisphenol A
Thermal printing paper
Ambient ionization
Direct analysis in real time
Mass spectrometry

ABSTRACT

Contact with thermal printing paper is a relevant source of dermal exposure to unbonded bisphenol A (BPA). In order to limit this exposure route, the European Union has introduced a drastic reduction in the maximum allowed concentration of BPA in thermal paper produced after beginning of year 2020. This study investigates the suitability of direct analysis in real time (DART), combined with accurate mass spectrometry, as a faster alternative to chromatography-based methods for the quantitative determination of BPA, and three analogues species, in receipts and tickets usually printed on thermal paper. The ionization efficiency of these compounds is evaluated under different conditions, and the effect of instrumental parameters of the DART source in the observed responses is discussed. The yield of the DART desorption-ionization process was greatly improved when compounds are previously converted into their acetyl derivatives; thereafter, the temperature of electronically excited helium atoms was the most relevant of the evaluated instrumental parameters. Under optimized conditions, the reported method provided recoveries in the range from 90 to 110%, a limit of quantification of 0.004% (w:w), well below the maximum concentration established after 2020 for BPA (0.02%, w:w), and permitted to perform duplicate determinations of each sample extract with a response time around 1 min. The accuracy of BPA levels found in non-spiked samples was confirmed using GC-EI-MS as reference technique. BPA was systematically noticed in the processed samples with concentrations ranging from 0.005% to more than 6%.

1. Introduction

Bisphenol A (BPA) is a high production volume chemical employed as monomer in the preparation of polymeric materials and epoxy resins. Moreover, as free compound, it is used in the elaboration of thermal printing paper. In this latter application, BPA, together with a thermochromic dye in presence of an organic solvent, is combined with a base layer of paper. In contact with a hot surface, and/or upon pressure, BPA reacts with the dye to develop an image on the paper surface [1]. This printing technology has a low cost, it does not require ink, and it is extensively employed in tickets, receipts and labels stuck on retail market products.

BPA is an endocrine disrupting chemical promoting a wide range of health outcomes in animals and humans [2,3]. Direct contact with thermal paper tickets is recognized as a relevant source of exposure to this compound [4]. In regards, increased urinary levels of BPA have been reported for operators of thermal paper manufacturing companies and female cashiers [5,6]. Moreover, dermal exposure has proved to turn in higher proportions of unconjugated BPA in the systemic circulation than dietary intake of the same species [7]. In order to reduce this exposure route, the EU has limited the concentration of BPA to a maximum of 0.02% (equivalent to 0.2 mg g^{-1}) for thermal printing paper commercialized after 2020 [8]. Simultaneously, alternative safer colour developers are under evaluation [9]. Despite these facts, recent surveys have revealed that BPA remains as the developer most often employed in thermal printing paper produced all over the world. Concentrations reported in these studies are up to 3 orders of magnitude higher than the limit established for year 2020 [10–12].

The determination of BPA in thermal printing paper is a two-step procedure. First, the compound is released from paper samples with polar organic solvents, such as methanol [10,13] or acetonitrile [11]. Thereafter, liquid chromatography (LC), followed by UV [12], fluorescence [14] or mass spectrometry (MS) detection [15], is employed as analytical technique. Alternatively, BPA can be also determined by gas chromatography (GC)-MS [16]. In this case, the detectability of the compound is greatly improved after derivatization, i.e. acetylation with acetic anhydride [17]. The above approaches provide LOQs low enough to satisfy the future regulation reducing the maximum concentration of

* Corresponding author.
E-mail address: isaac.rodriguez@usc.es (I. Rodríguez).

https://doi.org/10.1016/j.talanta.2019.06.086
Received 30 April 2019; Received in revised form 20 June 2019; Accepted 24 June 2019
Available online 26 June 2019
0039-9140/

BPA in thermal paper. However, the availability of faster determination procedures, not limited by the duration of the chromatographic separation step (from 10 to 30 min depending on the characteristics of the chromatographic column), is a matter of interest, particularly considering that control programs will involve the analysis of thousands of samples.

Ambient ionization sources followed by tandem (MS/MS), or high resolution (HR) mass spectrometry, have been proposed for the fast control of a limited number of analytes in different matrices, avoiding a chromatographic separation step. One of the most successful direct ionization sources is DART (used as the acronym of direct analysis in real time). DART can be classified as a kind of atmospheric pressure chemical ionization source. Thus, compounds are first volatilized and then ionized, mostly through charge transfer reactions with reactive ions and, in a minor extent, through *Penning* ionization. Reactive ions are produced by interaction of gases existing in the atmosphere of the laboratory (from permanent gases to water and solvent vapours) and electronically excited helium atoms generated in the DART source. Additionally to compounds ionization, formation of adducts, between neutral molecules of the analyte and ionized gases, such as ammonia, has been also reported [18–21].

Several applications of DART-MS have been developed in the areas of food, forensic and manufactured goods analysis [19,22,23]. From these studies, it can be concluded that DART ionization is particularly suitable for the ionization of low molecular weight and thermally stable molecules. To the best of our knowledge, previous applications of DART to BPA determination are limited. They have been focussed in the qualitative identification of BPA in epoxy coatings used in food packing [24], and in the evaluation of its relative ionization efficiency comparing DART with other ambient desorption ionization sources [25].

Herein, we investigate the suitability of DART-MS, based on a time-of-flight MS system, for the quantitative determination of BPA, and related bisphenol species, in the extracts obtained from thermal printing receipts and tickets. The ionization efficiency of selected species in the DART source, as free and acetylated compounds, is evaluated and the instrumental conditions affecting the performance of the overall procedure are discussed. The applicability of the method is assessed with analysis of thermal paper samples containing different concentrations of BPA, using GC with electron ionization (EI) MS detection as reference technique for accuracy assessment.

2. Material and methods

2.1. Standards and solvents

Standards of BPA (99%), bisphenol B (BPB), bisphenol E (BPE), bisphenol F (BPF) and bisphenol A diacetate 98% (BPADA) were supplied by Sigma-Aldrich (Milwakee, WI, USA). Deuterated BPA (BPA-d_6), deuterium atoms bonded to aliphatic carbons, was obtained from Toronto Research Chemicals (North York, ON, Canada). BPA-d_6 was used as internal surrogate (IS) during extraction of thermal printing paper samples, compounds acetylation and determination. Chemical structures and CAS numbers of bisphenol species are compiled in Table 1. Individual stock standards of the above compounds were prepared in methanol. Further dilutions and mixtures were made in the same solvent and stored at −20 °C.

Methanol (MeOH) (HPLC grade) was purchased by Merck (Darmstadt, Germany). Acetic anhydride, toluene and isooctane were obtained from Sigma-Aldrich.

2.2. Samples and sample preparation

Thermal printing paper samples (cash receipts and tickets) were collected during January and February of 2019 in different establishments from Spain and England. After reception, each sample was folded using aluminium paper, and stored individually, at room temperature, until analysis (c.a. 2–3 weeks). Before extraction, samples were cut in 4 mm diameter circled pieces with a stainless steel punch [13].

Extraction was carried out using 50 mg of circled pieces from each sample (ticket or receipt) spiked with the IS. MeOH (10 mL) was employed as extraction solvent. The process was carried out in closed glass vessels, for 10 min, under sonication [10,13]. After centrifugation, an aliquot of the obtained supernatant (0.1 mL unless otherwise stated) was acetylated as described elsewhere [26]. In brief, derivatization was carried out mixing the methanolic extract, or standard solution, with 8 mL of a $K_2HPO_3{\cdot}3H_2O$ 0.3 M (aqueous solution), using 50 µL of acetic anhydride as derivatization reagent, and 2 mL of isooctane to recover the acetylated derivatives. Tubes were capped, shaken manually for 5 min and centrifuged (2500 rpm for 5 min) to facilitate the separation between aqueous and organic phases. The fraction of isooctane was transferred into a 2 mL autosampler vial, ready to analysis either using DART-TOF-MS, or GC-EI-MS employed as reference technique.

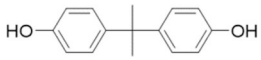
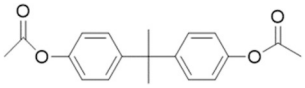
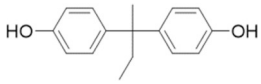
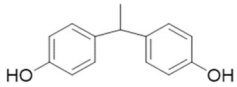
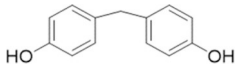
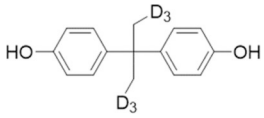
2.3. Equipment and determination conditions

2.3.1. DART-QTOF-MS

The DART-QTOF-MS system consisted of a DART-SVP ion source (IonSense Inc. Saugus, MA, USA, model number SVPS-200), equipped with a linear rail and *Quick Strip* transmission sample cards, with a 12-possition frame of stainless steel. The DART source was coupled to a QTOF-MS, Agilent 6520 model acquired from Agilent Technologies (Wilmington, DE, USA), through the commercial *Vapur* chamber, which reduces the entrance of helium and nitrogen in the high vacuum region of the MS instrument. A flow rate of helium, 2.5 L min^{-1}, was used during compounds desorption and ionization. In the standby mode, helium was replaced by nitrogen. During method development, DART was operated in positive and negative modes for native and acetylated bisphenol compounds ionization, applying a grid voltage of 400 V for positive and 350 V for negative mode. Under final conditions, compounds were determined as acetylated species using the positive-ion DART mode. The temperature of the source was set at 400 °C and the speed of the linear rail fixed at 0.2 mm s^{-1}. Standards and sample extracts (from 1 to 4 µL) were deposited in the stainless-steel mesh of cards using a 10 µL volume syringe. After solvent evaporation (c.a. 5 min), the card was loaded in the linear rail for analysis. The first position of each card was used to record the background spectrum corresponding to ambient ions generated in the DART source. This spectrum was subtracted to those obtained for standards and sample extracts. Samples were analysed in duplicate, leaving a non-spiked position in the card between different samples to prevent cross-contamination problems. Thus, 4 different samples can be processed in duplicate using the same card.

The QTOF instrument operated in high resolution (4 GHz) mode. Under final working conditions, analytes (as acetylated derivatives) were quantified in positive ionization mode applying a capillary voltage of 1000 V. The fragmentor voltage was set at 130 V. Accurate mass data were recorded in the range of *m/z* values from 50 to 1700, at a rate of 1 spectra s^{-1} (13700 scans are accumulated in each spectrum). The identity of acetylated compounds was confirmed with their MS/MS spectra recorded in the autoMS/MS mode. Selection of precursor ions was restricted to base peaks (ions) in the positive-ion DART spectra of acetylated compounds. Two product ion spectra were recorded by precursor, when detected in the accurate MS function. After 0.5 min, selection of precursor ions was re-activated in order to record product ion spectra from compounds in the following spot. Collision energies for MS/MS determination were 15 eV (BPA and BPB) and 10 eV (BPE and BPF). Recalibration of the *m/z* axis in the TOF MS analyser was performed using background ions with *m/z* values of: 135.1016, 152.1281 and 391.2860. The first two values correspond to the $[M+H]^+$ and $[M + NH_4]^+$ ions associated to diethylene glycol monoethyl ether (DEGMEE) [27]; the latter one corresponds to the $[M+H]^+$ ion of bis (ethylhexyl) phthalate. Both species are recognized as ubiquitous in

Table 1
Names, abbreviations, structures and CAS numbers of bisphenol compounds studied in this work.

Compound	Abbreviated name	Structure	Formula	Monoisotopic mass	CAS
Bisphenol A	BPA		$C_{15}H_{16}O_2$	228.1150	80-05-7
Bisphenol A diacetate	BPADA		$C_{19}H_{20}O_4$	312.1362	10192-62-8
Bisphenol B	BPB		$C_{16}H_{18}O_2$	242.1307	77-40-7
Bisphenol E	BPE		$C_{14}H_{14}O_2$	214.0994	2081-08-5
Bisphenol F	BPF		$C_{13}H_{12}O_2$	200.0837	620-92-8
Bisphenol A dimethyl-d6	BPA-d6		$C_{15}D_6H_{10}O_2$	234.1527	86588-58-1

indoor environments and provided signals with enough intensity for continuous re-calibration of the TOF MS analyser. According to the design of the card holder mounted in the linear rail module (see Fig. S1), the ionization flow of excited helium atoms is blocked between consecutive samples (spots); thus, recalibration of the TOF instrument is only possible during ionization of spots, but not when the linear rail is moving from spot to spot.

2.3.2. GC-EI-MS

GC-EI-MS was used as reference technique. The employed system was an Agilent 7890A gas chromatograph, equipped with an autosampler (Agilent 7693 model) and connected to a quadrupole mass spectrometer (Agilent MS 5975 C model). The MS analyser was operated in the single ion monitoring mode (SIM), selecting two characteristic ions per compound. Separations were carried out in a HP-5MS capillary column (30 m × 250 µm x 0.25 µm) acquired from Agilent and operated at a constant carrier gas flow of 1.2 mL min^{-1} (He, 99.999%). The temperature of the GC oven was as follows: 70 °C (1 min) rate at 10 °C min^{-1} to 280 °C (5 min). The electron impact source (EI) and the quadrupole mass analyser were set at 230 °C and 150 °C, respectively. Standards and sample extracts (2 µL volume), as acetylated species, were injected in splitless mode with the injector temperature at 280 °C. The transfer line between the GC and the MS was also set at 280 °C. Retention times and *m/z* ratios corresponding to quantification and qualification ions of each bisphenol are given as supplementary information, Table S1.

2.4. Recoveries assessment and samples quantification

The yield of the sample preparation procedure was investigated with samples of thermal printing paper, containing low levels of BPA, spiked with target compounds at two different levels: 0.02 and 0.2%. Concentrations in thermal paper extracts were determined by comparison with a set of calibration standards, acetylated under same conditions as sample extracts, and containing the equivalent concentration of BPA-d_6. Responses for calibration standards and extracts for spiked and non-spiked samples were obtained by DART-TOF-MS, using a mass window of 25 ppm around the *m/z* values for the [M + NH_4^+] species in the positive-ion DART spectra of acetylated compounds. Confirmation of target compounds in non-spiked samples required mass errors below 20 ppm for at least one of the two product ions observed in the MS/MS spectra recorded using the autoMS/MS function.

Concentrations in non-spiked samples were also calculated by comparison with responses obtained for acetylated standards. Quite often, the concentrations of BPA existing in thermal printing paper samples overpassed the linear response range of the DART-TOF-MS system, and also that for the GC-EI-MS. In that case, the primary methanolic extract obtained from thermal paper samples was diluted before acetylation.

Using GC-EI-MS determination, the concentrations in sample extracts were also established by comparison with calibration curves obtained for acetylated species, using BPA-d_6 as internal standard.

3. Results and discussion

3.1. DART-MS spectra of bisphenol compounds

For a given compound, the yield of DART ionization depends on a balance among mass and/or charge transfer process, formation of adducts with reactive ions generated from ambient species, and thermal stability during volatilization from the stainless steel mesh in the *Quick Strip* cards.

Preliminary ionization experiments were performed using BPA as model compound. A drop (1 µL) of the non-acetylated compound (10 µg mL^{-1}) was deposited on the mesh of the transmission card. In these experiments, the speed of the linear rail was set at 0.5 mm s^{-1}, the temperature of helium in the DART source maintained at 350 °C and spectra recorded in positive and negative modes. Regarding the TOF instrument, capillary and fragmentor voltages were set at 1000 and 130 V, respectively. In negative mode, the base peak in the DART-TOF mass spectrum of BPA appeared at *m/z* 227 (nominal value) suggesting the formation of $[M-H]^-$ species, as previously reported in the literature [24], Fig. 1A. The base peak in the spectrum obtained under positive ionization corresponded to a fragment ion at *m/z* 135 (assigned to the empirical formula $C_9H_{11}O$), whilst the molecular ion remained undetected, Fig. 1B. So, under investigated conditions, it is evident that free BPA is partially degraded during the DART desorption-ionization process.

As regards the commercial di-acetylated compound (BPADA), no response was observed in negative-ion DART (10 µg mL^{-1} standard). The spectrum obtained in positive-ion DART reflected an adduct between BPADA and NH_4^+. The experimental *m/z* measured for this ion was 330.1704 in good agreement with the theoretical value (330.1705)

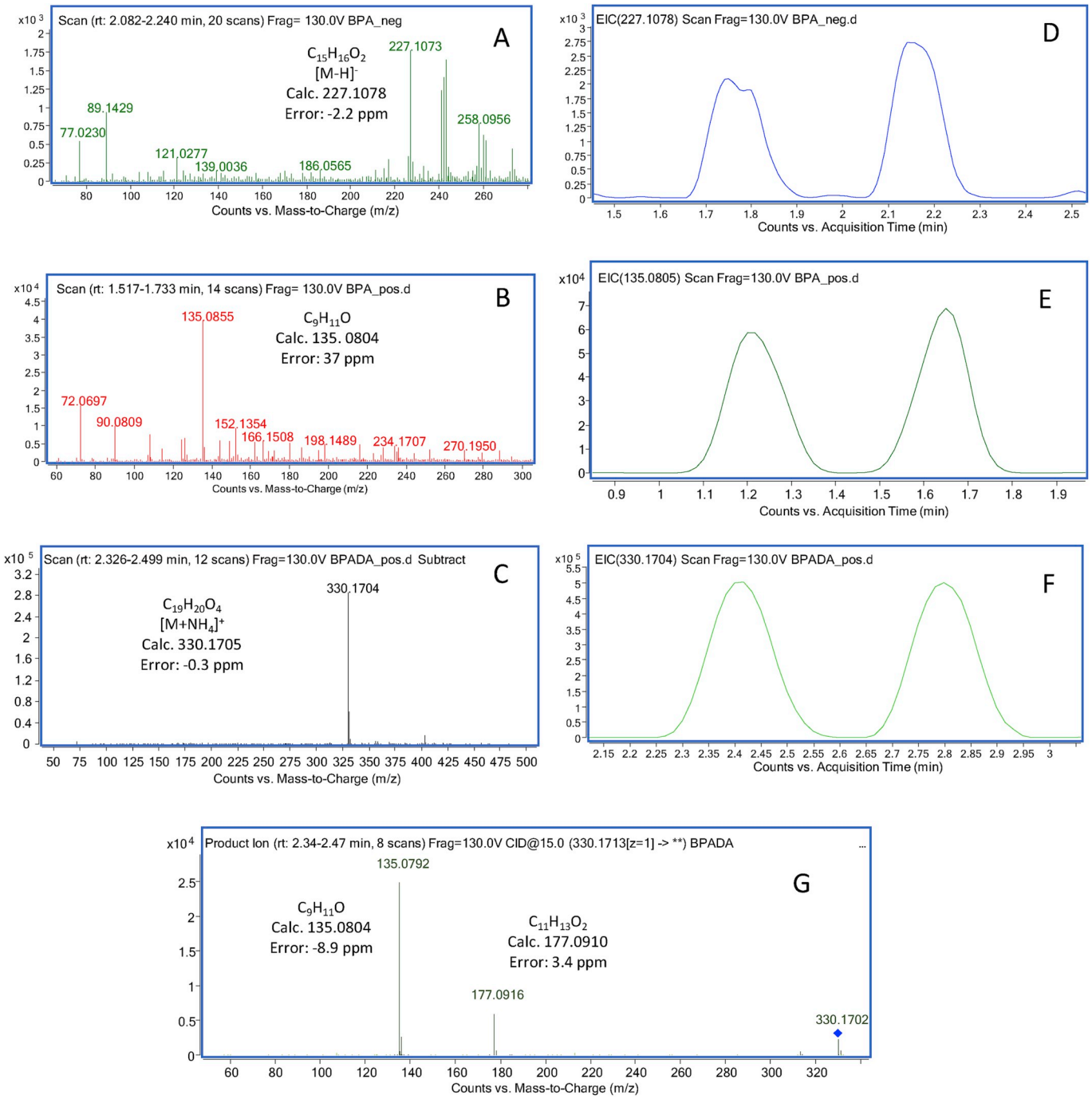


Fig. 1. DART-MS spectra of BPA under positive (A) and negative (B) ionization modes. C, positive-ion DART spectra of BPADA. D, E and F chronograms for the base peak in above MS spectra corresponding to a 10 μg m L^{-1} standard. G, product ion scan spectrum of BPADA.

for the above adduct (mass error −0.3 ppm), Fig. 1C. Acetylation of BPA lead to the same spectrum to that corresponding to the commercial standard of BPADA (figure not shown). The EIC chronograms (duplicated drops of each species were deposited in the *Quick Strip* card) obtained for the base ion in the spectrum of BPA as free compound using negative-ion DART, positive-ion DART, and for BPADA under the latter ionization mode are shown in Fig. 1D and F. Responses increased two orders of magnitude from the negative DART chronogram for BPA, to that recorded for BPADA using positive-ion DART. The product ion scan spectrum of BPADA contained two major signals corresponding to the phenolic ring bonded to the tertiary carbon (nominal *m/z* 135) and same fragment with the acetyl group introduced in the derivatization reaction (nominal *m/z* 177), Fig. 1G. Mass errors for product ions in the above spectra remained below 9 ppm.

The behaviour of the rest of bisphenol compounds involved in this research was similar to that of BPA: low ionization yield in negative mode rendering the $[M - H]^-$ ion, and fragmentation during positive DART ionization, figure not shown. After acetylation, their positive-ion DART spectra showed a single cluster of ions reflecting formation of adducts between the acetylated derivatives and ammonium ions, Fig. 2A and C. Product ion scan spectra (Fig. 2D and F) confirm the fragmentation pattern observed for the acetylated form of BPA. Mass errors in MS and MS/MS modes remained below 14 ppm.

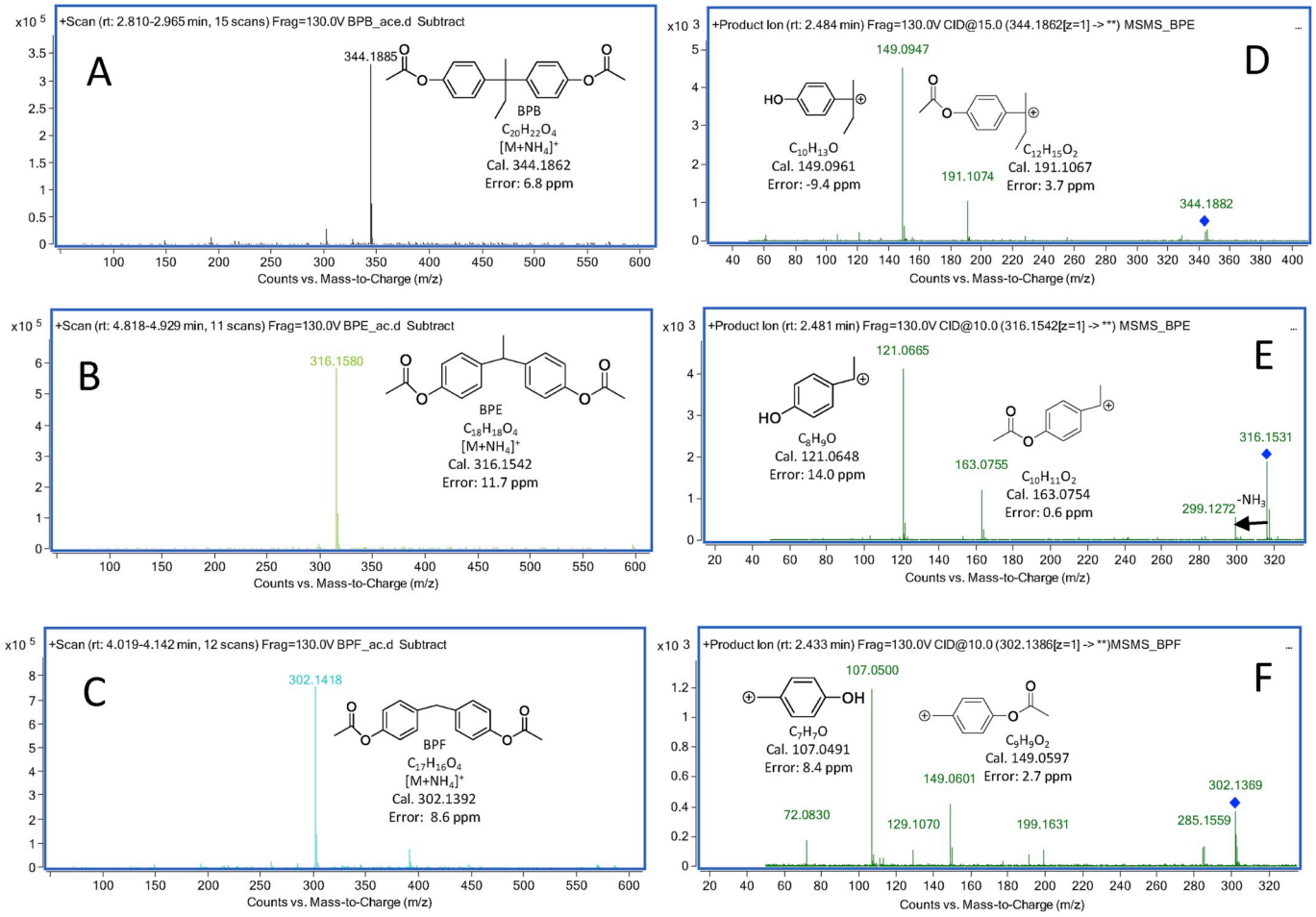


Fig. 2. Positive-ion DART spectra (A to C) and product ion scan spectra (D to F) of BPB, BPE and BPF.

3.2. Instrumental parameters of the DART source

Previous studies revealed that the efficiency of DART ionization is affected by several instrumental parameters, such as the temperature of the desorption-ionization gas (helium), the speed of the linear rail, the distance between the ceramic cap in the DART and the sample, the vacuum level in the *Vapur* interface, and the volume of the drop deposited on the stainless steel mesh of the *Quick Strip* sample cards.

In this study, the vacuum level was adjusted by turning the needle valve in the diffusion pump to maximize the signal corresponding to background ions (nominal *m/z* values 135, 152 and 391). The distance between the ceramic cap in the DART and the sample card, was set to 6 mm, equivalent to that existing between the sample card and the ceramic tube inserted in the *Vapur* interface.

Sensitivity of TOF-MS detection is correlated with the number of scans accumulated per MS spectrum [28]. In this research, MS spectra were recorded at 1 Hz, the lowest possible acquisition frequency in the QTOF instrument, to accumulate the maximum of scans (13700) in each stored spectrum. So, the movement of the linear rail was maintained at the lowest value 0.2 mm s^{-1} to record as many spectra as possible per spot in the sample card. In practice, combining MS and autoMS/MS modes, with a maximum of 4 precursor ions per cycle, around 20 spectra were recorded per spot.

The effect of temperature was investigated in the range from 250 °C until 400 °C, with increments of 50 °C, using a mixture of acetylated derivatives of the investigated compounds (1 µg mL^{-1}). Fig. 3A shows the results obtained for duplicate measurements at the four investigated temperatures. Peak areas in the EIC MS chronograms for the $[M + NH_4]^+$ ion of each compound increased with temperature. In further experiments, a value of 400 °C was employed.

The effect of the volume deposited in the mesh of the sample card is shown in Fig. 3B. Between 1 and 4 µL, responses of acetylated bisphenol species increased significantly. This behaviour is in agreement with a higher mass of compound per spot. On the other hand, increasing the volume of solvent deposited on the mesh of cards led to wider spots, with a low concentration of compound per unit of surface and longer evaporation times. This fact might be responsible for the decrease of responses observed, in some cases, for 4 µL drops. The surface and shape of spots on the sample card mesh, is not only affected by the solvent volume, but also by the properties of the solvent. Using the commercial standard of BPADA, it was observed that isooctane led to smaller surface spots than other solvents, such as toluene and particularly methanol. In the latter case, a higher spread of the drop was noticed before solvent evaporation. Such behaviour translated into non reproducible responses. So, isooctane was chosen as solvent for extraction of acetylated compounds, from aqueous reaction media in presence of acetic anhydride, and the volume deposited in the sample card limited to 3 µL.

3.3. Performance of DART-TOF-MS detection for bisphenol compounds

The performance of DART-TOF-MS was investigated in terms of repeatability, linearity and limits of quantification (LOQs). Repeatability was checked with responses obtained for a mixture of acetylated compounds at 100 ng mL^{-1}. Drops (3 µL) corresponding to the same acetylated mixture were deposited in consecutive positions of the *Quick Strip* card, n = 5. The relative standard deviation values (RSDs) for the area of $[M + NH_4]^+$ ions of each species ranged from 8

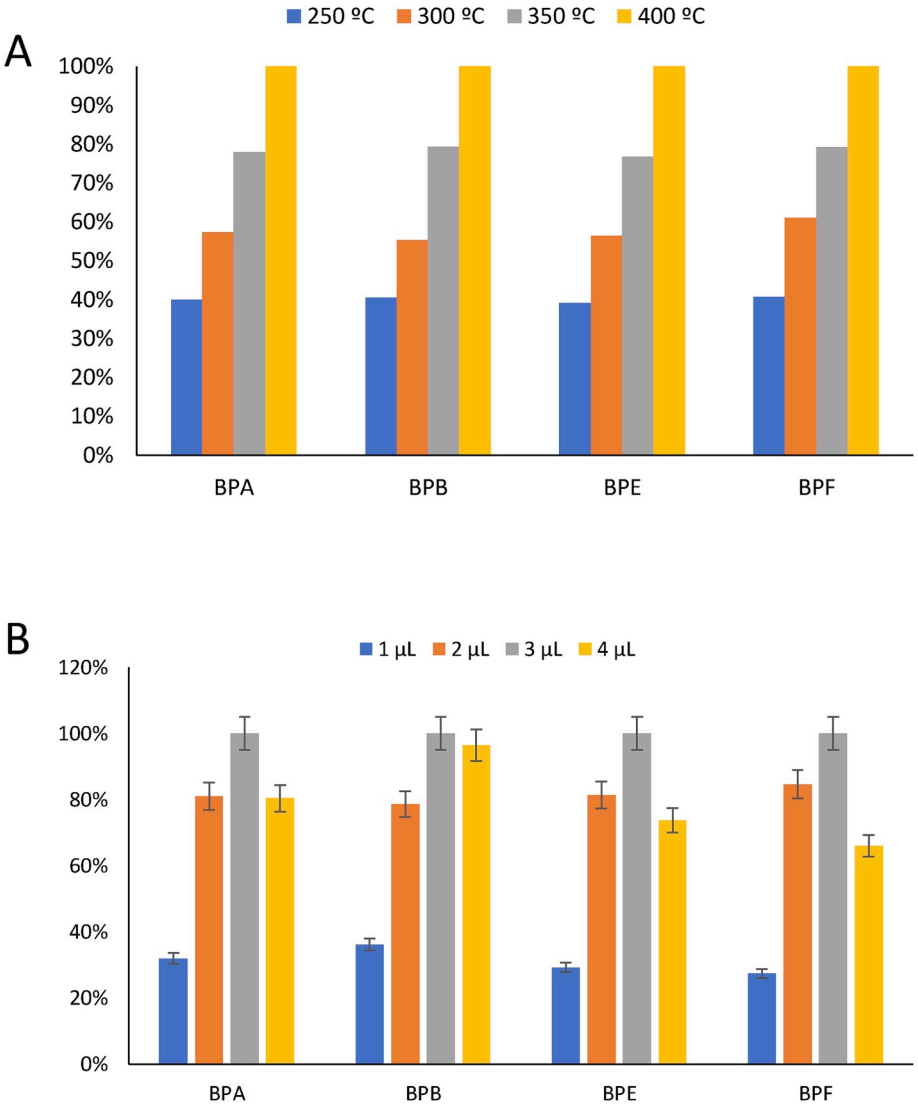


Fig. 3. A, effect of DART helium gas temperature in the normalized responses for $[M + NH_4]^+$ ions of analytes, n = 2. B, responses as function of the volume of solution deposited in the *Quick Strip* card, normalized values (n = 3) to those obtained for 3 µL.

Table 2
Performance of the DART-TOF-MS system (without considering sample preparation) for acetylated bisphenol compounds determination.

Compound	$[M + NH_4]^+$	Linearity (10–2000 ng mL^{-1}, n = 8 levels)		Repeatability (RSDs %; n = 5)	Reproducibility (RSDs %; n = 3)	LOQs (ng mL^{-1})
		R^2 (no IS correction)	R^2 (after IS correction)			
BPA	330.1705	0.9702	0.9990	8%	5%	8
BPB	344.1862	0.9726	0.9981	11%	5%	5
BPE	316.1549	0.9905	0.9977	11%	4%	8
BPF	302.1392	0.9746	0.9988	10%	5%	6
BPA-d_6	336.2082	–	–	–	–	–

to 11%. After IS correction, the obtained RSDs varied between 5 and 11%, Table 2. The linearity in the response of the system was also evaluated using MS detection. Acetylated standards were prepared in the concentration range from 10 to 2000 ng mL^{-1} (n = 8 levels), with the IS maintained at 50 ng mL^{-1}. The plots of responses versus concentration fitted a linear model. The determination coefficients (R^2) of the obtained calibration curves varied from 0.97 to 0.99, without IS correction. After response normalization to those obtained for BPA-d_6, R^2 values above 0.99 were achieved for all compounds, Table 2. The chronograms corresponding to the $[M + NH_4]^+$ ions of target compounds in the series of calibration standards are provided as supplementary information, Fig. S2. Mass errors for the $[M + NH_4]^+$ ions of acetylated compounds in the series of calibration standards are given as supplementary information, Table S2. Except in case of BPE and BPF at

Table 3
Summary of recoveries (%), with RSDs, for spiked samples of a thermal printing paper sample, n = 4 replicate extractions and determinations.

Compound	Addition level 0.02%		Addition level 0.2%	
	DART-TOF-MS	GC-EI-MS	DART-TOF-MS	GC-EI-MS
BPA	107 ± 5	106 ± 10	96 ± 6	97 ± 4
BPB	96 ± 4	117 ± 10	96 ± 6	112 ± 3
BPE	105 ± 6	108 ± 13	98 ± 9	99 ± 1
BPF	107 ± 8	102 ± 12	103 ± 8	105 ± 7

the lower concentration levels (10 and 25 ng mL^{-1}), errors remained below 10 ppm, with a maximum value of 12 ppm for BPE in the 10 ng mL^{-1} standard.

The reproducibility (intraday variability) in the slopes of calibration curves, obtained after IS correction, was in the range from 4 to 5% for calibration graphs obtained in three different days, Table 2. Instrumental LOQs were estimated from responses obtained for the lowest level calibration standard, considering also the stability of the EIC signal in the chronogram for an acetylation blank, containing only the IS. Estimated values varied from 6 to 8 ng mL^{-1}.

The features of GC-EI-MS for acetylated compounds are provided in the supplementary section (Table S1). Linearity was evaluated using the same series of acetylated standards employed in the DART-TOF-MS system. After IS correction, similar R^2 values were obtained. Before IS correction (data not shown), the repeatability of GC-EI-MS response and linearity were slightly better than those observed for DART-TOF-MS. LOQs were twice lower for the GC-EI-MS instrument (Table S1), although in the same order of magnitude as those compiled in Table 2 for DART-TOF-MS.

Accuracy of the proposed method, accounting for compounds extraction, acetylation and determination was investigated through recoveries achieved for a thermal paper sample (the one containing the lowest concentrations of investigated species, sample code 17, Table 4) spiked at two different concentration levels: 0.02 and 0.2%. The first level corresponds to the limit of concentration permitted in thermal paper by the regulation of the European Commission after 2020 [8] for BPA, and the second level was chosen as a 10 times higher value, which is still in the range of values currently reported in thermal printing paper for BPA. The IS was added to samples at 0.02%, equivalent to 50 ng mL^{-1} in the acetylated extract, before extraction. Recoveries (R %) were calculated using DART-TOF-MS and GC-EI-MS. In both cases, the following equation was used: $R\ (\%) = [(C_s - C_b)/C_t] \times 100$, where C_s and C_b are the concentrations measured in the extracts from spiked and non-spiked fractions of each thermal paper (n = 3 replicates) and C_t is the concentration added. Obtained recoveries varied between 96 and 107% with RSD below 9% in case of DART-MS, and from 97 to 117% with a maximum RSD of 13% for GC-MS, Table 3. In summary, equivalent recoveries were obtained with both techniques. Fig. 4 shows the EIC chronograms corresponding to duplicate determinations of the non-spiked thermal paper sample and same matrix spiked at 0.02% using the $[M + NH_4]^+$ ion of BPA. The autoMS/MS spectrum recorded from this ion in one of the spiked samples is also included in the figure.

Table 4
Concentrations (%) of BPA in receipts and tickets. Average values for duplicate determinations.

Code	Type	Concentration (%)
1	Supermarket	4.4
2	Supermarket	1.7
3	Supermarket[a]	6.3
4	Fruit shop	1.9
5	Food[a]	0.014
6	Sport shop	0.005
7	Fashion shop	4.0
8	Fashion shop	0.016
9	Fashion shop	2.3
10	Fashion shop	0.014
11	Pound shop	3.0
12	Toy shop	2.3
13	Library	3.2
14	Pharmacy	1.9
15	Cinema ticket	2.4
16	Train ticket	0.007
17	Train ticket[a]	0.006

[a] Samples from United Kingdom.

The LOQs of the reported procedure (DART-TOF-MS) were calculated taking into account the dilutions employed during sample preparation: extraction of 50 mg samples with 10 mL of MeOH and further acetylation of 0.1 mL of the methanolic extract, followed by back extraction of derivatives with 2 mL of isooctane. Considering the lowest point in the calibration graph (10 ng mL^{-1}), the estimated LOQ of the method for BPA was 0.04 mg g^{-1} (equivalent to 0.004%), five times lower than the future MRL fixed for BPA in thermal printing paper. This procedural LOQ can be extended to the rest of compounds since it leads to acetylated extracts with a concentration of 10 ng mL^{-1}, corresponding to the lowest level in calibration curves. The upper limit for the linear response range of the procedure was 0.8%; thus, quantification of samples exceeding this percentage of BPA requires dilution of the primary methanolic extract before acetylation. The upper range of DART-TOF-MS was equivalent to that obtained by GC-EI-MS, since both procedures provided linear responses until 2000 ng mL^{-1} for acetylated standards of the investigated compounds.

3.4. Analysis of thermal printing samples

The optimized methodology was applied to investigate the levels of target compounds in thermal paper printed receipts and tickets. Samples were processed as described in material and methods and final extracts quantified using DART-TOF-MS and GC-EI-MS. BPA was the only compound noticed above LOQs reported in section 3.4. Concentrations obtained by DART-TOF-MS varied from 0.005% up to a maximum of 6.30%, Table 4. Levels found in this study were in the same range of values as those reported by other authors in recent publications [9]. On the other side, only 6 of the processed samples fulfil the future legislation regarding maximum BPA levels in thermal printing paper.

Accuracy of BPA levels obtained for the analysed samples thermal printing paper was verified using GC-EI-MS as reference technique. Fig. 5 shows the correlation plot of DART-TOF-MS concentrations (X-axis) versus those provided by GC-EI-MS (Y-axis). Data are expressed as percentage of BPA in the thermal paper. Values fit a linear model with a determination coefficient (R^2) higher than 0.98 and a slope of 1.05 ± 0.04. In addition to this representation, the student test was used to compare differences between pairs of values measured for each sample with both determination techniques. At the 95% confidence level, DART-TOF-MS and GC-EI-MS provided equivalent values for BPA in the processed samples.

4. Conclusions

For the first time, DART QTOF-MS is proposed for the quantitative determination of four bisphenol-type compounds in samples of thermal printing paper. Acetylation of target compounds turned a key parameter to improve the efficiency of the desorption-ionization process at the DART source. Combination with QTOF-MS guarantees the selectivity of compounds determination, whereas product ion scan spectra permitted to verify the identity of responses in the chronograms

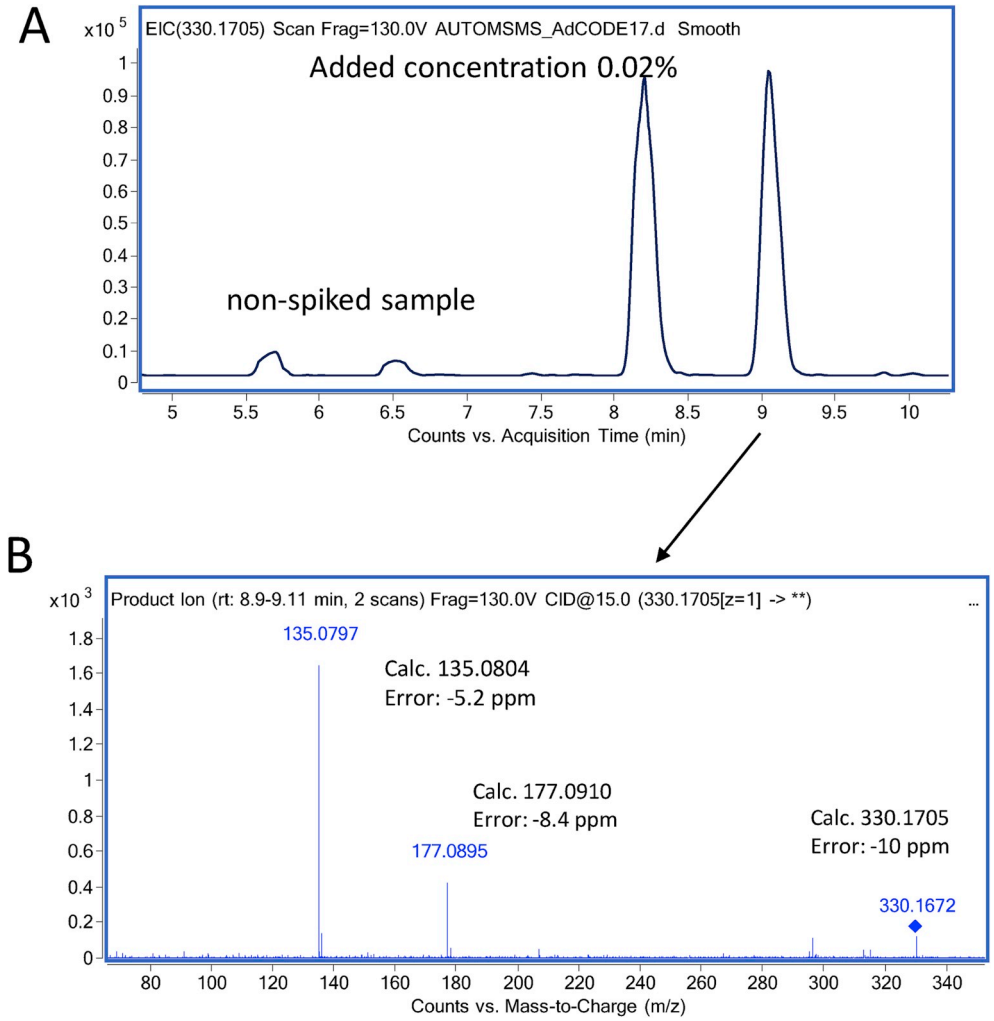


Fig. 4. A, DART-MS chronogram obtained under final working conditions for BPA in non-spiked and spiked (addition level 0.02%) pieces obtained from the same receipt. Duplicate determinations. B, product ion scan spectrum of BPA in the spiked sample.

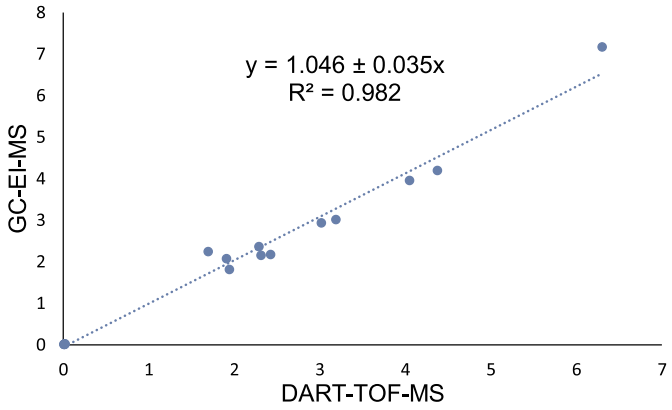


Fig. 5. Correlation plot between concentrations measured by GC-EI-MS and DART-MS for BPA in receipts and tickets. Values as percentage.

corresponding to non-spiked samples. Under final working conditions, DART-MS achieved LOQs in the low ng per mL level, with a linear response range covering more than two-orders of magnitude. Four samples, with the corresponding blank positions, can be processed in duplicate with the same *Quick Strip* card within an analysis time of a few minutes. Recoveries obtained for spiked samples and concentrations measured in non-spiked samples of receipts and tickets were in agreement with those obtained by GC-MS. BPA was ubiquitous in the processed samples. In most cases, the concentrations of this compound are well above the maximum permitted levels by the EU regulation to be implemented in year 2020.

Conflict of interest

None.

Acknowledgements

This study was supported by Xunta de Galicia, Spanish Government and EU FEDER program (grant numbers GRC-ED431C 2017/36 and CTQ2015-68660-P).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.talanta.2019.06.086.

References

[1] H. Mielke, F. Partosch, U. Gundert-Remy, The contribution of dermal exposure to the internal exposure of bisphenol A in man, Toxicol. Lett. 204 (2011) 190–198, https://doi.org/10.1016/j.toxlet.2011.04.032.
[2] J.A. García, C. Gallego, F.G., Toxicidad del Bisfenol A: revisión, Rev. Toxicol. 32

(2015) 144–160 http://rev.aetox.es/wp/wp-content/uploads/hemeroteca/vol32-2/vol 32-2-144-160.pdf.
[3] K.A. Thayer, K.W. Taylor, S. Garantziotis, S.H. Schurman, G.E. Kissling, D. Hunt, B. Herbert, R. Church, R. Jankowich, M.I. Churchwell, R.C. Scheri, L.S. Birnbaum, J.R. Bucher, Bisphenol A, bisphenol S, and 4-hydroxyphenyl 4-isoprooxyphenyl sulfone (BPSIP) in urine and blood of cashiers, Environ. Health Perspect. 124 (2016) 437–444, https://doi.org/10.1289/ehp.1409427.
[4] S.P. Porras, M. Heinälä, T. Santonen, Bisphenol A exposure via thermal paper receipts, Toxicol. Lett. 230 (2014) 413–420, https://doi.org/10.1016/j.toxlet.2014.08.020.
[5] M. Heinälä, K. Ylinen, T. Tuomi, T. Santonen, S.P. Porras, Assessment of occupational exposure to bisphenol a in five different production companies in Finland, Ann. Work Expo. Heal. 61 (2017) 44–55, https://doi.org/10.1093/annweh/wxw006.
[6] R.S. Hehn, NHANES data support link between handling of thermal paper receipts and increased urinary bisphenol a excretion, Environ. Sci. Technol. 50 (2016) 397–404, https://doi.org/10.1021/acs.est.5b04059.
[7] J. Liu, J.W. Martin, Prolonged exposure to bisphenol a from single dermal contact events, Environ. Sci. Technol. 51 (2017) 9940–9949, https://doi.org/10.1021/acs.est.7b03093.
[8] European Comission, Commission regulation (EU) 2016/2235 of 12 december 2016 amending annex XVII to regulation (EC) No 1907/2006 of the european parliament and of the council concerning the registration, evaluation, authorisation and restriction of chemicals (REACH) as regar, off, J. Eur. Union. 2001 (2016) 20–30 http://eur-lex.europa.eu/pri/en/oj/dat/2003/l_285/l_28520031101en00330037.pdf.
[9] M.K. Björnsdotter, J. de Boer, A. Ballesteros-Gómez, Bisphenol A and replacements in thermal paper: a review, Chemosphere 182 (2017) 691–706, https://doi.org/10.1016/j.chemosphere.2017.05.070.
[10] P. Vervliet, C. Gys, N. Caballero Casero, A. Covaci, Current-use of developers in thermal paper from 14 countries using liquid chromatography coupled to quadrupole time-of-flight mass spectrometry, Toxicology 416 (2019) 54–61, https://doi.org/10.1016/j.tox.2019.02.003.
[11] J.M. Molina-Molina, I. Jiménez-Díaz, M.F. Fernández, A. Rodriguez-Carrillo, F.M. Peinado, V. Mustieles, R. Barouki, C. Piccoli, N. Olea, C. Freire, Determination of bisphenol A and bisphenol S concentrations and assessment of estrogen- and anti-androgen-like activities in thermal paper receipts from Brazil, France, and Spain, Environ. Res. 170 (2019) 406–415, https://doi.org/10.1016/j.envres.2018.12.046.
[12] M. Eckardt, T.J. Simat, Bisphenol A and alternatives in thermal paper receipts - a German market analysis from 2015 to 2017, Chemosphere 186 (2017) 1016–1025, https://doi.org/10.1016/j.chemosphere.2017.08.037.
[13] Y. Yang, Y. Yang, J. Zhang, B. Shao, J. Yin, Assessment of bisphenol A alternatives in paper products from the Chinese market and their dermal exposure in the general population, Environ. Pollut. 244 (2019) 238–246, https://doi.org/10.1016/j.envpol.2018.10.049.
[14] G. Russo, F. Barbato, L. Grumetto, Monitoring of bisphenol A and bisphenol S in thermal paper receipts from the Italian market and estimated transdermal human intake: a pilot study, Sci. Total Environ. 599–600 (2017) 68–75, https://doi.org/10.1016/j.scitotenv.2017.04.192.
[15] H.J. Eichman, B.J. Eck, A.F. Lagalante, A comparison of electrospray ionization, atmospheric pressure chemical ionization, and atmospheric pressure photoionization for the liquid chromatography/tandem mass spectrometric analysis of bisphenols. Application to bisphenols in thermal paper receipts, Rapid Commun. Mass Spectrom. 31 (2017) 1773–1778, https://doi.org/10.1002/rcm.7950.
[16] J. Zhang, C.Y. Wen, Q. Li, B.E. Meteku, R. Zhao, B. Cui, X. Li, J. Zeng, Electro-enhanced solid-phase microextraction of bisphenol A from thermal papers using a three-dimensional graphene coated fiber, J. Chromatogr., A 1585 (2019) 27–33, https://doi.org/10.1016/j.chroma.2018.11.063.
[17] P. Viñas, I. López-García, N. Campillo, R.E. Rivas, M. Hernández-Córdoba, Ultrasound-assisted emulsification microextraction coupled with gas chromatography-mass spectrometry using the Taguchi design method for bisphenol migration studies from thermal printer paper, toys and baby utensils, Anal. Bioanal. Chem. 404 (2012) 671–678, https://doi.org/10.1007/s00216-012-5957-z.
[18] J.H. Gross, Direct analysis in real time - a critical review on DART-MS, Anal. Bioanal. Chem. 406 (2014) 63–80, https://doi.org/10.1007/s00216-013-7316-0.
[19] T. Guo, W. Yong, Y. Jin, L. Zhang, J. Liu, S. Wang, Q. Chen, Y. Dong, H. Su, T. Tan, Application of DART-MS for food quality and safety assurance in food supply chain, Mass Spectrom. Rev. 36 (2017) 161–187, https://doi.org/10.1002/mas.21466.
[20] X. Li, X. Wang, L. Li, Y. Bai, H. Liu, Direct analysis in real time mass spectrometry: a powerful tool for fast analysis, Mass Spectrom. Lett. 6 (2015) 1–6, https://doi.org/10.5478/MSL.2015.6.1.1.
[21] J. Hajslova, T. Cajka, L. Vaclavik, Challenging applications offered by direct analysis in real time (DART) in food-quality and safety analysis, TrAC Trends Anal. Chem. (Reference Ed.) 30 (2011) 204–218, https://doi.org/10.1016/j.trac.2010.11.001.
[22] A.D. Lesiak, J. Shepard, Recent advances in forensic drug analysis by DART-MS, Bioanalysis 6 (2014) 819–842, https://doi.org/10.4155/bio.14.31.
[23] B. Antal, Á. Kuki, L. Nagy, T. Nagy, M. Zsuga, Rapid detection of hazardous chemicals in textiles by direct analysis in real-time mass spectrometry (DART-MS), Anal. Bioanal. Chem. 408 (2016) 5189–5198, https://doi.org/10.1007/s00216-016-9603-z.
[24] R. Paseiro-Cerrato, J. Devries, T.H. Begley, Evaluation of short-term and long-term migration testing from can coatings into food simulants: epoxy and acrylic-phenolic coatings, J. Agric. Food Chem. 65 (2017) 2594–2602, https://doi.org/10.1021/acs.jafc.7b00081.
[25] R.M. Räsänen, P. Dwivedi, F.M. Fernández, T.J. Kauppila, Desorption atmospheric pressure photoionization and direct analysis in real time coupled with travelling wave ion mobility mass spectrometry, Rapid Commun. Mass Spectrom. 28 (2014) 2325–2336, https://doi.org/10.1002/rcm.7028.
[26] T. Rodríguez-Cabo, I. Rodríguez, M. Ramil, A. Silva, R. Cela, Multiclass semi-volatile compounds determination in wine by gas chromatography accurate time-of-flight mass spectrometry, J. Chromatogr., A 1442 (2016) 107–117, https://doi.org/10.1016/j.chroma.2016.03.005.
[27] S.R. Kumbhani, L.M. Wingen, V. Perraud, B.J. Finlayson-Pitts, A cautionary note on the effects of laboratory air contaminants on ambient ionization mass spectrometry measurements, Rapid Commun. Mass Spectrom. 31 (2017) 1659–1668, https://doi.org/10.1002/rcm.7951.
[28] A.R. Fontana, I. Rodríguez, M. Ramil, J.C. Altamirano, R. Cela, Solid-phase extraction followed by liquid chromatography quadrupole time-of-flight tandem mass spectrometry for the selective determination of fungicides in wine samples, J. Chromatogr., A 1218 (2011) 2165–2175, https://doi.org/10.1016/j.chroma.2011.02.025.