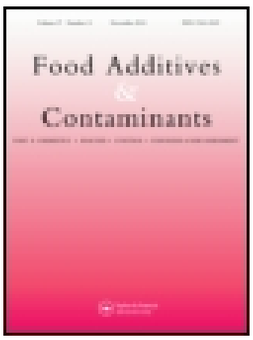

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Analytical determination of bisphenol A (BPA) and bisphenol analogues in paper products by GC-MS/MS

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ABSTRACT

Bisphenol A (BPA; 4-[2-(4-hydroxyphenyl)propan-2-yl]phenol), a suspected endocrine disruptor with a weak estrogenic activity, is used in a variety of consumer products, including food-contact materials made of paper and cardboard products. Due to restrictions on the use of BPA because of its potential health risks, BPA is gradually being replaced by other bisphenols because no limitations exist for these substances. This study presents a method for the simultaneous analysis of BPA, bisphenol AF (BPAF), bisphenol B (BPB), bisphenol E (BPE), bisphenol F (BPF) and bisphenol S (BPS) in paper and board products using gas chromatography-tandem mass spectrometry (GC-MS/MS). Paper samples were extracted by liquid extraction, as well as by Folch extraction, derivatised with *N,O-bis*(trimethylsilyl)trifluoroacetamide (BSTFA) and the results compared. The developed method showed good linearity ($R^2 > 0.9965$) and precision, yielding relative standard deviations (RSDs) of less than 16.6% for reproducibility and 19.8% for repeatability. The limits of detection and limits of quantification for the different bisphenols ranged from 0.23 to 2.70 µg kg^{-1} paper and from 0.78 to 9.10 µg kg^{-1} paper, respectively. Analysis of different paper products (recycled, virgin fibre) showed that all the analysed bisphenols were present in the samples, except for BPAF and BPB. A calculation of the 'worst-case' scenario assuming a maximum potential migration of 100% of the analytes into food showed that the analysed products can be assumed to be safe regarding the migration of bisphenols.

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Bisphenol A (BPA); bisphenol analogues; paper and cardboard; food packaging; derivatisation; gas chromatography-tandem mass spectrometry (GC-MS/MS)

Introduction

Bisphenols are a group of compounds containing two hydroxyphenyl functionalities. This group of compounds includes several analogues, joined together by a differently substituted bridging atom, mainly a carbon atom, except for bisphenol M (BPM), bisphenol P (BPP) and bisphenol S (BPS). Among the bisphenols, bisphenol A (BPA) is the best known and most frequently studied.

BPA is primarily used as a monomer in the production of polycarbonate and as starting material for the production of epoxy resins. It is via these routes that BPA is present in a variety of consumer products including paper and board used as food containers. As BPA is a suspected endocrine disrupter with a weak estrogenic activity, it has been associated with a wide range of adverse health effects (Haighton et al. 2002; Völkel et al. 2002; Dekant & Völkel 2008; von Goetz et al. 2010; Liao & Kannan 2011). As a result, in 2015 the EFSA lowered the TDI for BPA to 0.004 mg kg^{-1} bw (EFSA 2015a). However, this TDI is determined as a temporary TDI (t-TDI) and depends on the outcome of an ongoing long-term study that should help to reduce remaining uncertainties about potential health risks (EFSA 2015b). Furthermore, an SML of 0.6 mg kg^{-1} food was proposed by the Council of Europe (2009), corresponding to a maximum permitted quantity (QM) of 0.1 mg dm^{-2} paper.

These limitations regarding the use of BPA led to a gradually replacement of BPA by other bisphenols in many industrial applications (Liao et al. 2012b, 2012c; Yang et al. 2014a), as no limits have been established for these compounds (Gallart-Ayala et al. 2011). An exception is BPS, which is authorised for use as a monomer in plastic food-contact materials with an SML of 0.05 mg kg^{-1} food under European Regulation (EC) 10/2011 (European Commission 2011). However, as the SCF in 2000 proposed that no TDI could be

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established for BPS (SCF 2000), the SML was assigned on the basis of BPS's low migration rates (Geuke 2014). However, no regulation exists regarding the occurrence of BPS in non-plastic food-contact material. Furthermore, BPS is not listed in a report compiling non-plastic food-contact material by EFSA's Scientific Cooperation Working Group in 2012 (EFSA 2012).

With regard to the replacement of BPA by bisphenol analogues, bisphenol F (BPF) and bisphenol B (BPB) are used as alternatives in the production of epoxy resins and polycarbonate for food-contact materials (Liao et al. 2012b; Liao & Kannan 2013, 2014; Yang et al. 2014a, 2014b). Furthermore, BPB and bisphenol AF (BPAF) are used for the manufacturing of phenolic resins (Cunha & Fernandes 2010; Liao & Kannan 2014; Yang et al. 2014a). Moreover, BPAF is mainly used as a cross-linker in the synthesis of fluoroelastomers (Liao & Kannan 2014; Yang et al. 2014b). In addition to its use in the production of epoxy resins, BPS is used as an anticorrosive agent in epoxy glues, as a monomer in the synthesis of polythersulfosane and, increasingly, as an additive in thermal papers, substituting BPA as a colour developer (Becerra & Odermatt 2012; Liao et al. 2012c; Gallart-Ayala et al. 2013). As the production and consumption of bisphenol analogues, especially those of BPF and BPS, have increased recently (Danzl et al. 2009), it is feasible that these substances will become ubiquitous food contaminants and environmental pollutants in future.

It is of significant concern that these bisphenol analogues do not seem to be safer than BPA, as several studies demonstrate. BPF, BPE, BPB and BPS possess a moderate to slight acute toxicity and genotoxicity (Liao et al. 2012b), and show an estrogenic activity similar to that of BPA (Chen et al. 2002; Gallart-Ayala et al. 2011; Jiao et al. 2012; Gallart-Ayala 2013; Yang et al. 2014b). BPS even exhibits a higher estrogenic activity probably due to its polarity and the presence of a sulfur in the structure (Rivas et al. 2002). Additionally, BPAF can cause testosterone reduction in male rats (Feng et al. 2012), and BPAF and BPB can activate the human pregnan X receptor (Sui et al. 2012).

For legislative and toxicological reasons, sensitive and selective analytical methods are required to detect low concentrations of bisphenols down to the ng kg^{-1} range. Analytical methods either based on GC or LC are typically combined with MS due to high sensitivity, selectivity and precision (Dekant & Völkel 2008). In comparison with single MS, tandem MS is more sensitive and selective as it minimises or even removes matrix interferences by selecting adequate precursor and product ions (Sánchez-Avila et al. 2011). Especially in complex matrices, MS/MS achieves improved LODs (Kelly 2000; Jeannot et al. 2002; Quintana et al. 2004; Stanford & Weinberg 2007), as methods based on MS/MS are reported to be approximately 10 times more sensitive than MS detection (Jeannot et al. 2002). Although GC analysis requires a derivatisation step prior to analysis, it provides increased selectivity and sensitivity compared with LC analysis. Derivatisation enhances the volatility and thermal stability of the target analytes, hence improving the selectivity and sensitivity of the analysis (Jeannot et al. 2002; Gómez et al. 2007). This is of special importance as electrospray ionisation (EI) has been shown to be prone to a reduced response due to ion-suppression reactions (Gómez et al. 2007; Albero et al. 2012). Most common derivatisation reagents used in combination with EI are silylation reagents, such as *bis*(trimethylsilyl)trifluoroacetamide (BSTFA), with or without trimethylchlorsilane (TMCS) as a catalyst (Hernando et al. 2004; Hibberd et al. 2009; Fenlon et al. 2010; Albero et al. 2012; Lu et al. 2013; Kosarac et al. 2012), *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA) (Yu et al. 2007), and *N-tert*-butyldimethylsilyl-*N*-methyltrifluoroacetimide (MTBSTFA) (Kosjek et al. 2007).

The aim of the present study was to develop and validate a sensitive and selective method for the simultaneous determination of six selected bisphenols (BPA, BPAF, BPB, BPE, BPF and BPS) in paper samples using a GC-MS/MS method after derivatisation with BSFTA-TMCS. The chemical structures of the selected bisphenols are illustrated in Figure 1. Sample preparation in terms of extraction and derivatisation as well as chromatographic analysis were optimised to achieve low LOQs. Feasibility of the method was assessed by measurement of different paper samples used in the production of food packages. Finally, the maximum migration into food was calculated assuming the 'worst case' of 100% migration, instead of performing a migration test.

Materials and methods

Samples

Six different cellulose, paper and board samples used for the production of packages including food and

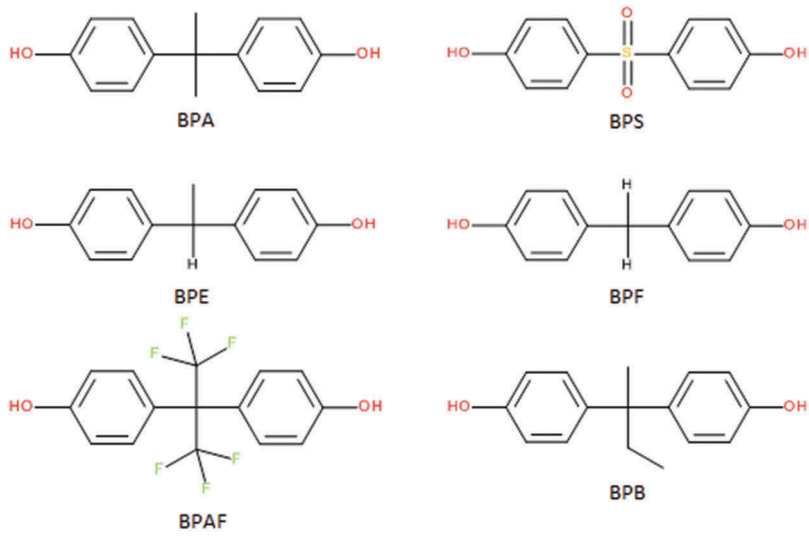

Figure 1. Structures of the analysed bisphenols.

hygiene packages were analysed. Analysed samples are basic raw materials used for the production of packages with no direct contact to food or any other sensitive material at the time of analysis. The samples consisted of three fresh fibre and three recycled samples of unknown recycling content. All products were from different European paper and board manufacturers, produced in 2015. For method validation, a virgin fibre unbleached cellulose paper from an Austrian paper manufacturer was used. The grammage of the paper used for method validation was 80 g m^{-2}. All samples were immediately wrapped in aluminium foil after sampling and stored at RT. Sample work-up and preparation were exclusively done with gloves and BPA-free laboratory ware. The properties of the samples are given in Table 1.

Chemicals and reagents

Solvents, standards and reagents used were of analytical grade. Methanol and dichloromethane were from Carl Roth GmbH (Karlsruhe, Germany). *N*,*O*-*bis*(trimethylsilyl)trifluoroacetamide (99%)–trimethylchlorsilane (1%) (BSTFA-TMCS), pyridine, bisphenol A (BPA), bisphenol E (BPE), and bisphenol S (BPS) were purchased from Sigma-Aldrich (Steinheim, Germany). Bisphenol AF (BPAF) and bisphenol F (BPF) were from Alfa Aesar (Karlsruhe, Germany). Bisphenol B (BPB) and the internal standard bisphenol A-d_{16} (BPA-d_{16}) were from Dr. Ehrenstorfer GmbH (Augsburg, Germany).

Table 1. Packaging type and properties of the samples.

Sample	Product	Packaging type	Grammage (g m^{-2})
1	Coated board	Fresh fibre	240
2	Cellulose rolled	Fresh fibre	300
3	Board primary bleached	Fresh fibre	230
4	Testliner white	Recycled	135
5	Coated recycled	Recycled	180
6	Recycled bleached	Tertiary	100

Preparation of calibration standards

Stock solutions of standard and internal standard were prepared at a concentration of 1 g l^{-1} in methanol and stored at −18°C until use. Working solutions for calibration were prepared as a standard mix by dilution of the stock solutions with methanol, and stored at −18°C for a maximum of 3 weeks. The internal standard was diluted to give a final concentration of the internal standard of 50 µg kg^{-1} paper.

For calibration, four-point calibration curves at different concentration levels and different calibration ranges (low, middle and high) were prepared and analysed in triplicate. The calibration points at the lower level were 0.5, 2, 3.5 and 5 µg kg^{-1} paper. The middle calibration range was from 5 to 50 (5, 20, 35 and 50) µg kg^{-1} and the high calibration range was from 50 to 500 (50, 200, 350 and 500) µg kg^{-1} paper. The internal standard was added to all calibration points at a concentration of 50 µg kg^{-1} paper.

For the standard addition, solutions for calibration were prepared to give the same concentration

points as the solvent calibration by adding 10 µl of the addition solution to the paper.

Extraction of paper samples

Extraction of paper samples was performed as solvent extraction and Folch extraction (Folch et al. 1957).

Solvent extraction

For method validation, the cellulose was cut manually (approximately 0.5 × 0.5 cm), 1 g was weighed into a 40 ml glass vial with a PTFE-lined screw cap and 10 µl of the respective addition solution containing the internal standard were added. After addition of 20 ml methanol, the samples were extracted for 30 min in an ultrasonic bath, the solvent decanted and concentrated to a volume of 0.5 ml under nitrogen in a Concentration Evaporator (Biotage TurboVap® II, Biotage, Uppsala, Sweden) at a water bath temperature of 40°C. Finally, concentrated extracts were filtered through a 0.2 µm PTFE syringe filter to remove residual paper components, collected in 2 ml vials with a screw cap and stored at −18°C until derivatisation (typically within 1 week).

For paper samples the extraction procedure was the same, except that instead of the addition solution only the internal standard solution was added.

Folch extraction

For method validation cellulose paper was cut manually (approximately 0.5 × 0.5 cm), 1 g was weighed into a 40 ml glass vial with a PTFE-lined screw cap and 10 µl of the respective addition solution containing the internal standard were added. Samples were slurried in 10 ml water acidified with phosphoric acid and homogenised with a disperser (Ultra-Turrax®, IKA, Staufen, Germany). After addition of 20 ml Folch solution (dichloromethane plus methanol 2 + 1), the samples were again homogenised for 1 min, the tubes filled with 10 ml dichloromethane and centrifuged for 10 min at 3500 rpm. The organic phase was concentrated to a volume of 0.5 ml under nitrogen in a Concentration Evaporator at a water bath temperature of 40°C. Finally, concentrated extracts were filtered through a 0.2 µm PTFE syringe filter to remove residual paper components, collected in 2 ml vials with a screw cap and stored at −18°C until derivatisation (typically within 1 week).

For paper samples the extraction procedure was the same, except that instead of the addition solution only the internal standard solution was added.

Derivatisation of standards and paper samples

Derivatisation was carried out by a trimethylsilylation with BSTFA– TMCS (1%) and pyridine as catalyst.

Extracts and standard solutions were evaporated to dryness under a gentle stream of nitrogen, 50 µl of BSTFA and pyridine were added and the samples were gently shaken. After a reaction time of 15 min at RT, they were filled with ethyl acetate to a defined volume of 500 µl. Derivatives were stored at −18°C, and were stable for about 3 weeks. Due to the high content of BPA in recycled samples, further dilution was necessary, as the concentration of BPA exceeded the concentration range of the proposed method. These extracts were diluted before derivatisation with ethyl acetate by a factor of 100. Therefore, the corresponding samples as well as the dilution factor were determined in pre-experiments and the amount of internal standard adapted to the dilution factor to give a concentration of 50 µg kg^{-1} paper in the derivatised extract.

Gas chromatographic analysis

Gas chromatographic analysis was carried out by GC-MS/MS in MRM mode. GC-MS/MS analysis of the BSTFA derivatives was carried out on a Shimadzu GC-MS TQ 8040 system equipped with an EI source, an AOC 5000 autosampler (all Shimadzu, Kyoto Japan), and a Phenomenex ZB5-MS capillary column (30 m × 0.25 mm I.D.; 0.25 µm film thickness). A total of 1 µl was injected in splitless mode at an injector temperature of 250°C. Carrier gas was helium at 82.8 kPa with a linear velocity of 40 cm s^{-1}. The oven temperature programme was set at 90°C for 1 min, raised at a rate of 10°C min^{-1} to 300°C, remaining at this level for 1 min. The temperatures of the MS interface and the ion source were 280 and 200°C respectively. For quantification the MS was operated in MRM using argon as collision gas at 200 kPa pressure (Linde;

purity 99.999%). Transitions and collision energies were optimised by inspecting the mass spectra of the compounds and monitoring the transitions by scanning a collision energy range from 10 to 30 in steps of two. The used mass transitions for quantification and qualification and their corresponding collision induced dissociation energies (CID) are summarised in Table 2. Data were acquired in three different observation windows. Window 1 (14–15.9 min) was used to monitor BPAF; window 2 (16–18.5 min) was used to monitor BPF, BPE, BPA-d_{16}, BPA and BPB; and window 3 (20–22 min) was used for the analysis of BPS.

Method validation

Method validation was performed in terms of recovery, linearity, sensitivity and precision (repeatability and reproducibility) using ValiData Version 3.02.48 statistical software – Excel-Macro for method validation (W. Wegscheider, C. Rohrer, R. Neuböck, MU Leoben, Austria).

Calculation of the migration

For compliance with the regulations concerning the migration limits, the maximum potential migration, assuming a 100% migration, was calculated. Migration was calculated for all analysed bisphenols for migration into a dry food matrix or food simulant, depending on the bisphenol concentration analysed and the grammage of the paper samples. Assumption of 100% migration was chosen to represent the 'worst-case' scenario. The calculation was based on the definition of the European Commission of 1 kg dry food being in direct contact with 6 dm^2 packaging material. (European Commission 2011).

Results and discussion

Method development

Method development was performed in terms of extraction, derivatisation and validation.

Extraction

Extraction was performed as solvent extraction with different solvents, as well as a Folch extraction. A simple solvent extraction with methanol, as performed in a prior work for the analysis of BPA (Jurek & Leitner 2015), was, as in the case of the other bisphenols, not successful due to very low recovery rates for all bisphenols (< 40%) including BPA (< 60%). It seems that recovery rates are strongly matrix dependent, as in the prior work recovery rates of 74–93% for BPA were achieved with methanolic solvent extraction in copy paper (Jurek & Leitner 2015) instead of the cellulose used in this work. Thereupon several methods for the extraction of bisphenols from paper samples were tested and modified for efficiency prior to sample analysis.

Testing five different extraction solvents (methanol, methanol/acetone 1:1, methanol/acetone 3:7, methanol/acetone 7:3, methanol/ethyl acetate 1:1) also showed no improvement of the recovery rates. We presumed that the bisphenols were deprotonated by the solvent media, being present as phenolates, inhibiting a quantitative derivatisation. However, a solely aqueous extraction was not possible, as the derivatisation has to be performed under exclusion of water. To overcome this problem we decided to perform a Folch extraction (Folch et al. 1957), extracting the bisphenols out of an aqueous extract by a Folch solution (methanol/dichloromethane 2 + 1). Acidification of the water used for

Table 2. Mass spectrometric parameters for the GC-MS/MS analysis.

Compound	MW (g mol^{-1})	RT (min)	Quantifying transition *m/z* (V)	Qualifying transition 1 *m/z* (V)	Qualifying transition 2 *m/z* (V)
BPAF	480	15.43	411.0 > 73.0 (CE15)	480.0 > 411.0 (CE15)	480.0 > 73.0 (CE27)
BPF	344	16.72	179.0 > 73.0 (CE15)	344.0 > 73.0 (CE25)	344.0 > 179.0 (CE21)
BPE	358	16.99	343.2 > 73.0 (CE27)	344.2 > 73.0 (CE27)	344.2 > 191.2 (CE18)
BPA-d_{16}	386	17.23	386.3 > 368.3 (CE10)	368.3 > 197.3 (CE20)	369.3 > 198.3 (CE20)
BPA	372	17.31	357.2 > 191.2 (CE20)	358.2 > 192.2 (CE20)	372.2 > 357.2 (CE10)
BPB	386	18.01	357.3 > 73.1 (CE27)	358.3 > 73.1 (CE27)	358.3 > 191.2 (CE18)
BPS	394	21.01	394.0 > 379.0 (CE12)	379.0 > 73.0 (CE27)	394.0 > 73.0 (CE27)

CE: collission energy.

homogenisation of the paper and further Folch extraction showed reliable results, verifying the assumption of the deprotonation of the bisphenols to phenolates.

As a methanolic solvent extraction is a frequently performed extraction method for the extraction of bisphenols out of different matrices (Kuo & Ding 2004; Biedermann et al. 2010; Geens et al. 2012; Liao & Kannan 2013; Goldinger et al. 2015) sample analysis was performed not only for Folch extraction but also for a methanolic solvent extraction. However, in most cases methanolic solvent extraction is performed prior to HPLC and LC, and not GC analysis (Biedermann et al. 2010; Liao et al. 2012c; Goldinger et al. 2015).

Solvent extraction versus Folch extraction

Solvent extraction is a fast and simple extraction method with very less operational effort, whereas Folch extraction is more complex and elaborate, as in a first step prior to the proper extraction the paper has to be suspended in an acidic aqueous medium. This is necessary as the Folch solution (dichloromethane/methanol 2 + 1) is not strong enough to extract analytes quantitatively from the paper matrix.

Nevertheless, Folch extraction is characterised by a better recovery than solvent extraction, especially for the extraction of highly complex recycled board samples. The reason for the low recovery rates applying a solvent extraction seemed to be (1) a deprotonation of the analytes in the methanolic medium, as well as (2) a clarification of the matrix applying a Folch extraction by extracting the bisphenols out of the aqueous slurry into dichloromethane (see 'Method validation – recovery').

Derivatisation with BSTFA

Most often GC-MS and GC-MS/MS analysis of underivatised BPA shows a poor peak shape and sensitivity because of the polarity of the hydroxyl groups. A derivatisation step prior to GC analysis transforms BPA into a less polar and more volatile compound and improves the selectivity and sensitivity of the chromatographic analysis. However, using a brand new GC column, the peak shape of underivatised BPA can be perfectly sharp and symmetrical. Nevertheless, depending on the coating thickness of the column, peaks start tailing with an increasing number of injections. On this account derivatisation bisphenols prior to GC analysis is advisable.

Silylation is one of the most widely used derivatisation reactions to improve GC behaviour of polar compounds containing phenolic groups, such as bisphenols (Albero et al. 2012). Thereby the hydroxyl groups are replaced by trimethylsilyl groups, leading to more volatile and stable derivatives. Derivatisation with BSTFA is characterised by simplicity, low solvent consumption and a fast reaction of the hydroxyl groups. The only drawback is that no aqueous samples can be derivatised, as water inhibits the derivatisation reaction.

In terms of method development, different amounts of derivatisation reagent were used (50 and 100 µl) with the aim to improve the recovery rates performing a solvent extraction. However, as the results obtained by doubling the derivatisation reagent provided no improvement of the results we concluded that the efficiency reducing step is the extraction.

Method validation

The analytical method for both extraction techniques – solvent extraction and Folch extraction – were evaluated for their applicability to the analysis of bisphenols in paper and paperboard products. Due to the bad recoveries of the solvent extraction, range of linearity, precision and sensitivity were only determined for the Folch extraction. Method validation was done for all terms of validation at the lowest calibration range of 0.5–5 µg kg^{-1} paper, except for BPS, where the middle calibration range with calibration levels of 5–50 µg kg^{-1} paper was applied, as the lower calibration levels of BPS were below the LOD. In addition, the range of linearity was verified over all three calibration ranges from 0.5 to 500 µg kg^{-1} paper, respectively from 5 to 500 µg kg^{-1} paper for BPS. A chromatogram of a standard mix at a concentration of 100 µg kg^{-1} is represented in Figure 2.

Recovery

Recovery experiments were performed for both extraction techniques in triplicate by spiking paper

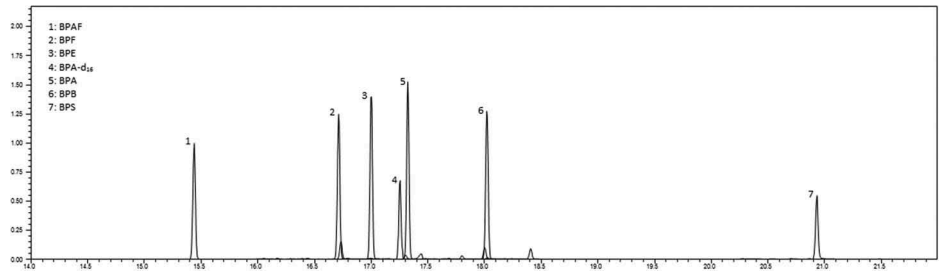

Figure 2. GC-MS/MS chromatogram of a standard mix (BPA, BPAF, BPB, BPE, BPF and BPS: 100 µg kg^{-1}; and BPA-d$_{16}$: 50 µg kg^{-1}).

samples at all concentration levels of the lowest calibration range before extraction. Satisfactory recoveries were obtained for all analytes using the Folch extraction, with recoveries ranging as follows: 70–116% for BPA, 72–116% for BPB, 70–115% for BPE, 80–117% for BPF, 70–115% for BPAF and 78–107% for BPS. In contrast, recovery for the solvent extraction method was poor, with the best values obtained for BPA with 34–60%, whereas recoveries of the other bisphenols were below 40%. It seems that recovery rates are strongly matrix dependent, as in prior work recovery rates of 74–93% for BPA were achieved with methanolic solvent extraction in copy paper (Jurek & Leitner 2015) instead of the cellulose used in this work.

The poor recoveries obtained by the solvent extraction could be explained in two ways. The bisphenols seemed to deprotonate in the alkaline medium of the solvent extraction, leading to a hindrance of the derivatisation reaction as part of the analytes are only available as phenolates. In contrast, this deprotonation is inhibited in Folch extraction, where the slurrying of the paper samples in acidic medium takes place. Secondly, in Folch extraction a clarifying process seems to take place, separating the analytes in the dichloromethane layer from matrix substances hindering the derivatisation, as indicated by matrix-dependent recovery rates. Especially for complex matrixes like recycled board samples, recovery rates obtained by the solvent extraction are very low, with the lowest values obtained for the samples with the highest recycling content. For the Folch extraction method no such matrix effects were observed. Despite this obvious advantages of Folch extraction compared with solvent extraction, it is a more complex sample preparation method, thus more susceptible to analyte loss during the extraction process.

Linearity

Analytes were evaluated for linearity by spiking paper samples at all calibration levels. Linearity was verified for the respective lowest calibration range (5–50 µg kg^{-1} paper for BPS and 0.5–5 µg kg^{-1} paper for all other bisphenols), as well as for the whole calibration range (5–500 µg kg^{-1} paper for BPS and 0.5–500 µg kg^{-1} paper for all other bisphenols). Linearity was evaluated by injecting three replicates of the standard solutions at each concentration level. All spiked samples contained the deuterated internal standard at a concentration of 50 µg kg^{-1} paper. All compounds showed a good linearity with correlation coefficients obtained all higher than 0.9965. Linearity was assumed when the regression coefficient was higher than 0.99 with a RSD of less than 15% (Table 3).

Sensitivity

Sensitivity was determined by the LOD and LOQ. Derivatised spiked blank samples at the respective lowest calibration range were analysed for the different analytes. The determination of the LODs and LOQs were performed by ValiData version 3.02.48 statistical software, using the internal standard calibration procedure at two different calibration ranges. LODs ranged from 0.23 to 2.7 µg kg^{-1} paper, and LOQs were between 0.78 and 9.1 µg kg^{-1} paper (Table 4). LOD and LOQ for all

Table 3. Linearity of the analytes.

	Linearity lowest range		Linearity all range	
Analyte	Range (µg kg^{-1})	R^2	Range (µg kg^{-1})	R^2
BPAF	0.5–5	1.0000	0.5–500	0.9992
BPF	0.5–5	0.9992	0.5–500	0.9974
BPE	0.5–5	0.9991	0.5–500	0.9995
BPA	0.5–5	0.9991	0.5–500	0.9992
BPB	0.5–5	0.9965	0.5–500	0.9980
BPS	5–50	0.9999	5–500	0.9996

Table 4. Repeatability and reproducibility.

	Repeatability		Reproducibility	
Analyte	Range (µg kg^{-1})	% RSD	Range (µg kg^{-1})	% RSD
BPAF	0.5–5	2.33–7.19	0.5–500	2.41–9.88
BPF	0.5–5	1.58–8.91	0.5–500	1.22–12.04
BPE	0.5–5	0.26–14.31	0.5–500	2.85–15.68
BPA	0.5–5	0.39–19.83	0.5–500	1.73–16.58
BPB	0.5–5	2.54–10.62	0.5–500	3.06–11.53
BPS	5–50	3.07–10.15	5–500	2.98–9.76

bisphenols except BPS were in the same range, with the lowest LOD and LOQ found for BPAF. The LODs of BPA and BPF are far lower than those reported in the literature. In a recent study of different bisphenol analogues, LODs for source-segregated paper from household waste and paper from non-sorted household waste were two orders of magnitude higher (Pivnenko et al. 2015). However, these data were obtained using an LC-MS/MS method and different sample pretreatment procedures. For GC-MS/MS of derivatised bisphenols, no comparable data could be found. LODs of 0.33 mg kg^{-1} for BPA and 0.16 mg kg^{-1} were reported for BPF, however a LC-MS method was used (Pérez-Palacios et al. 2012).

Similar to the higher calibration range in comparison with the other bisphenols, the LODs and LOQs of BPS were also an order of magnitude higher than those of the other bisphenols. We also observed a higher activity of BPS in the GC system. Despite the derivatisation of the phenolic group there is a much more pronounced tailing in comparison with the other bisphenols in our investigations. We also see a slight decrease in the sensitivity of BPS over time, so this should be taken into account when measuring large numbers of matrix-loaded samples. This may be based on the general difficulties arising with the GC analysis of sulfur compounds. It is well known that these compounds have absorptive, adsorptive, photo-oxidative and metal catalytic features that can lead to irreversible adsorption, reaction with each other, catalytic reaction, rearrangements catalysed by different materials, and reaction with substances with which they came in contact (Wardencki 1998). As no other methods were found in the literature about the GC analysis of BPS after derivatisation with BSTFA, no data for comparison exist. A pyrolysis GC-MS method, however, reported an LOD for BPS of 0.41–0.97 mg kg^{-1} for different paper products (Becerra & Odermatt 2012). To further enhance selectivity and sensitivity of the analysis of BPS, the use of selective and specific detectors (pulsed flame photometric detector or sulfur chemiluminescence) could be worth investigating.

Precision

Precision was determined in terms of repeatability and reproducibility and expressed as RSD (%). Repeatability was determined by intra-day experiments analysing a spiked sample at all concentration levels in triplicate. Reproducibility was determined by inter-day experiments of the spiked samples at 3 different days. Intra- and inter-day experiments showed good precision for all methods. Repeatability determined was < 19.8% and reproducibility was < 16.6% (Table 5).

Concentration of bisphenols in paper and board samples

The validated method was used to quantify the concentrations of bisphenol analogues in six different paper and board products, including three virgin fibre and three recycled samples. Quantification was performed for solvent extracts and Folch extracts. A deuterated internal standard (BPA-d_{16}) was added to the samples to compensate for matrix effects and loss of analytes during sample work-up and analysis. Therefore, low recovery rates of the solvent extraction method are inherently corrected for recovery loss, enabling a comparison with the samples extracted with Folch extraction.

Peak identification was based on the following criteria: retention time; transition of the target ion; and a comparison of the ratio of the target transition and two selected qualifier transitions (±30% of the transition ratios).

The concentrations of the bisphenols in the selected paper and paperboard samples analysed with the different methods are shown in Table 6. All six samples contained quantifiable levels of BPA and BPF, while BPAF and BPB were not detected in any samples. BPS was detected in all samples, but

Table 5. LOD and LOQ.

	BPAF	BPF	BPE	BPA	BPB	BPS
LOD paper (µg kg^{-1})	0.23	0.33	0.35	0.32	0.35	2.70
LOQ paper (µg kg^{-1})	0.78	1.08	1.14	1.06	1.16	9.10

Table 6. Concentration of bisphenols in paper and board samples.

	Concentration (μg kg^{-1}) (RSD%)					
Sample	BPAF	BPF	BPE	BPA	BPB	BPS
1	< LOQ	83 ± 8.4	< LOQ	40 ± 0.2	< LOQ	< LOQ
2	< LOQ	56 ± 9.1	6.0 ± 0.9	3179 ± 80	< LOQ	11 ± 0.9
3	< LOQ	21 ± 6.0	< LOQ	112 ± 4	< LOQ	< LOQ
4	< LOQ	83 ± 5.2	6.1 ± 0.6	6021 ± 194	< LOQ	59 ± 1.2
5	< LOQ	50 ± 6.2	< LOQ	9641 ± 296	< LOQ	106 ± 5
6	< LOQ	83 ± 10	6.8 ± 0.3	733 ± 21	< LOQ	49 ± 3.0

levels were below the LOQ in two virgin fibre samples. One virgin fibre and two recycled fibre samples contained BPE. In general, larger amounts of BPA and BPS were found in recycled paper and cardboard products compared with virgin products, with recycled fibre products containing two to 200 times higher concentrations than fresh fibre samples. For BPE and BPF no such trend could be observed (Table 6).

Concerning the concentrations of BPA, the concentration of sample 2 – a non-bleached virgin fibre cellulose sample – is equivalent to the values obtained for the recycled samples. Furthermore, sample 2 is also the only sample produced of virgin fibres where BPS was found. A possible reason for this may be the lamination that covers the sample.

The BPA concentrations in all recycled samples and one fresh fibre sample (sample 2) exceeded the concentration range of our method, therefore the sample extracts were diluted by the factor 100 to allow for an adequate quantification of BPA. Concentrations of BPA ranged from 40 to 9641 μg kg^{-1} paper, with the highest concentration for the coated recycled sample (sample 5). Overall, higher concentrations of BPA were detected in recycled samples (samples 4–6) than in virgin fibre samples (samples 1–3). These results are in agreement with Liao et al. (2012c) who also reported higher concentrations of BPA in recycled samples.

The unusual high concentration of BPA of 3179 μg kg^{-1} found in virgin fibre sample 2 may arise from a thin lamination film applied on one side of the product.

In general, concentrations of BPA found in these samples are in agreement with values reported in literature, ranging from 10 to 30,000 μg kg^{-1} (Vinggaard et al. 2000; Gehring et al. 2004; Ozaki et al. 2004; Mendum et al. 2011; Liao et al. 2012c; Pérez-Palacios et al. 2012; Suciu et al. 2013; Goldinger et al. 2015; Pivnenko et al. 2015, 2016). Values higher than 1000 mg kg^{-1} were reported for thermal papers containing BPA as a colour developer; on average, the concentration of BPA in thermal papers was one magnitude higher than in non-thermal papers (Mendum et al. 2011; Liao et al. 2012a; Goldinger et al. 2015).

In comparison with the literature, concentrations of BPA found in the samples are in the lower range. This could indicate that the analysed products are designated for the production of sensitive products, such as food and hygiene products and their corresponding packages.

Beside BPA, BPF was the only compound quantified in all samples, in the range of 21–83 μg kg^{-1} paper. Compared with reported concentrations of BPF in waste paper products (Pivnenko et al. 2015), our samples contained slightly lower concentrations of BPF, ranging from 24 to 85 μg kg^{-1}.

BPS was present in all recycled samples and in one virgin fibre sample (sample 2), and concentrations ranged from 11 to 106 μg kg^{-1}, with the lowest concentration found in the virgin fibre sample. As sample 2 is the only virgin paper containing BPS, it is suspected that BPS derives from the coating, presumably accountable for the high BPA concentration in the same sample. Reported concentrations of BPS are on average higher than determined in this work, as most data on BPS refer to the analysis of thermal paper (Liao et al. 2012a; Goldinger et al. 2015; Pivnenko et al. 2015). Concentrations covering non-thermal paper products are in the same range as published in this work (Liao et al. 2012a; Goldinger et al. 2015).

Studies showed that BPA is increasingly replaced by bisphenol analogues, as those samples having low concentrations of BPA are typically characterised by high concentrations of bisphenol analogues (Pivnenko et al. 2015, 2016). In particular, the use of BPS as a colour developing substance in thermal paper is rising (Liao et al. 2012a), suggesting that the detectable BPS content in other paper products than thermal paper is introduced via the recycling process of thermal paper high in BPS.

BPE was detected in one virgin fibre sample and two recycled samples at concentrations below 7 μg kg^{-1} paper. Comparable results in the literature vary from less than the LOD to 600 μg kg^{-1} (Pivnenko et al. 2015). All other bisphenol analogues analysed (BPAF and

BPB) were not detected or were below the LOQ, indicating that these substances at the moment are not used as BPA replacements, similar to work by Pivnenko et al. (2015).

As already mentioned, quantification of bisphenols was performed for Folch extracts as well as for solvent extracts. Both methods provided corresponding results, as results were inherently corrected for recovery loss by the internal standard. However, recovery of the internal standard of the solvent extracts was about two to four times lower than in the Folch extracts. Recovery rates obtained with the Folch method were between 76% and 92% (average of 86%), whereas the recoveries provided by the solvent extraction were between 21% and 47% (average of 35%). Based on these results, the more elaborate Folch method is recommended for quantitative analysis. Solvent extraction is a suitable method for estimating concentrations of bisphenols in the samples to be analysed, e.g., for the determination of the calibration range, as bisphenol concentrations in paper products vary from ng kg^{-1} to mg kg^{-1} paper.

Estimation of the concentration of bisphenols in food and food-contact materials: migration from the packaging material

The concentration of BPA in the food matrix was calculated for the assumption of 100% migration, demonstrating the 'worst-case' scenario. Depending on the grammage and based on the definition of 1 kg dry food being in direct contact with 6 dm^2 packaging material, the maximum possible migration for all samples was calculated. In reality, this is a simplified estimation, as migration of different contaminants from paper was reported to be much lower than 100% (Aurela et al. 1999, 2001; Summerfield & Cooper 2001; Anderson & Castle 2003; Jickells et al. 2005; Fiselier et al. 2010; Jung et al. 2010; Suciu et al. 2013). To determine the effectively occurring migration, migration tests following defined procedures have to be carried out. Such migration experiments are predominantly carried out using defined food simulants for different food matrices. The migration of constituents out of paper and board into dry food is frequently tested by migration into Tenax®, as Tenax has to be proved as the most suitable food simulant for dry foodstuffs (Aurela et al. 2001; Summerfield & Cooper 2001; Triantafyllou et al. 2007; Zülch & Prininger 2010). Studies also showed that the migration from paper and board depends on the structure of the paper, as well as the period of storage and temperature during storage (Triantafyllou et al. 2007; Zülch & Prininger 2010).

Calculated concentrations of the maximum migration of all samples analysed are shown in Table 7. Values obtained for the 'worst-case' migration are between < LOQ and 104 μg kg^{-1} food. Therefore, the calculated values demonstrate the influence of the grammage of the paper on the concentration of the migrants. The heavier the paper, the higher concentration of the migrants in 1 kg food or food-contact material, on the basis of the same initial concentration of the migrant per kg paper. A total of 6 dm^2 of a heavy weight paper are heavier than the same area of a low weight paper, resulting in more mass of packaging material protecting 1 kg of food product. Due to this connection between paper grammage and analyte concentration, the sample with the highest concentration does not automatically also present the sample with the highest migration concentration. This phenomenon can be seen by comparison of samples 2 and 4 with grammages of 300 and 135 g m^{-2}, respectively. The concentration of BPA in sample 4 is nearly twice as high as in sample 2, i.e., 6012 compared with 3179 μg kg^{-1} in the paper products; however, the migration concentration of BPA in sample 2 is slightly higher than in sample 4 (57 compared with 49 μg kg^{-1}).

Table 7. Calculated migration of bisphenols – assumption of 100% migration.

	Concentration (μg kg^{-1}) (RSD%)					
Sample	BPAF	BPF	BPE	BPA	BPB	BPS
1	< LOQ	1.2 ± 0.1	< LOQ	0.58 ± 0.003	< LOQ	< LOQ
2	< LOQ	1.0 ± 0.1	0.11 ± 0.02	57 ± 1.4	< LOQ	0.20 ± 0.02
3	< LOQ	0.29 ± 0.08	< LOQ	1.5 ± 0.05	< LOQ	< LOQ
4	< LOQ	0.67 ± 0.04	0.05 ± 0.005	49 ± 1.6	< LOQ	0.48 ± 0.01
5	< LOQ	0.54 ± 0.07	< LOQ	104 ± 3	< LOQ	1.1 ± 0.06
6	< LOQ	0.50 ± 0.1	0.04 ± 0.002	4.4 ± 0.2	< LOQ	0.29 ± 0.02

The same applies to samples 3 and 6. In this case the migration concentration of sample 6 is 2.9 times higher compared with sample 3, whereas in the paper products the concentration of sample 6 is 6.5 times higher.

The calculated migration concentrations for BPS were between 1000 and six times below the SML of 0.6 mg kg^{-1} (600 µg kg^{-1}). Although the SML of 0.05 mg kg^{-1} (50 µg kg^{-1}) food for BPS was established for plastic food-contact materials (European Commission 2011), the calculated migration of BPS in all paper samples was between 45 and 250 times lower than these SML. Therefore, the analysed products can be assumed to be safe regarding the migration of BPA and BPS. For all other bisphenols analysed the migration concentrations is between 1250 and 40 times lower than the SML of BPS; however, no SMLs exist for these compounds.

In a second step the BPA uptake was calculated using the assumption of the European Commission that an average person with a bodyweight of 60 kg consumes 1 kg of food per day packed in this package of concern (Council of Europe 2009). On basis of the t-TDI of 4 µg kg^{-1} bw the maximum uptake for BPA results in a concentration of 240 µg for a 60-kg person. Due to the lack of TDI for the other bisphenols, no further calculations could be made. The calculated values showed that none of the samples exceeded the t-TDI (Table 7). Even for sample 5, with the highest migration concentration of 104 µg kg^{-1} resulting in a concentration of 1.7 µg kg^{-1} bw, is 2.3 times below the t-TDO of 4 µg kg^{-1} bw.

A 100% migration is a very unrealistic scenario, as previous studies showed a migration of less than 1% for BPA into salt, sugar and the food simulant Tenax (Suciu et al. 2013). Furthermore, the daily intake of food is more diverse; therefore, the analysed paper products can be considered safe even for use as food-contact materials. However, to determine effectively the migration of bisphenols from paper products, migration tests in food and food simulant materials should be carried out.

Conclusions

A complete analysis procedure, including extraction, derivatisation and GC-MS/MS analysis, was developed for the determination of BPA, BPAF, BPB, BPE, BPF and BPS in paper and board samples. The applicability of the method was demonstrated by analysing different paper and board products of virgin and recycled fibres.

Paper samples were extracted with a methanolic solvent or a Folch extraction with methanol and dichloromethane, derivatised with BSTFA and analysed with GC-MS/MS. The method was validated in terms of recovery, linearity range, precision and sensitivity to prove their applicability.

The proposed method shows satisfactory recoveries for the Folch extracts, good linearity and precision, as well as satisfactory low LODs and LOQs. For the solvent extraction low recovery rates due to strong matrix dependency were found.

Bisphenols were quantified in the different paper products and migration concentrations of the bisphenols were calculated per kg food assuming 100% migration.

Beside BPA, BPE, BPF and BPS were detected in the samples, indicating that there is a beginning process of the substitution of BPA by other bisphenols. BPA was found the dominant bisphenol, being a ubiquitous contaminant, as the concentrations of BPA in the samples are considerably higher than those of the other bisphenols.

Concerning the migration of bisphenols into food and food simulants, the analysed samples showed levels much lower than the specific migration limits (BPA and BPS), assuming 100% migration. Thus, the samples can be considered safe for the use as food-contact materials.

Disclosure statement

No potential conflict of interest was reported by the authors.

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