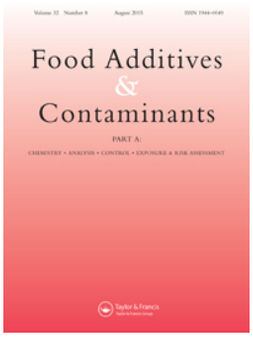

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Comparing different gas chromatographic methods for the quantification of bisphenol A (BPA) trace levels in paper and cardboard products from the market

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Bisphenol A (BPA; 4,4′-(propane-2,2-diyl)diphenol), a suspected endocrine disruptor with weak estrogenic activity, is used in a variety of consumer products, including paper and cardboard products used as food contact materials. The present study compared four different gas chromatographic methods for the analysis of BPA in paper and cardboard food packages. Eighteen different food packages were extracted and BPA was determined using two different derivatisation reactions – trimethylsilylation with N,O-*bis*(trimethylsilyl) trifluoroacetamide (BSTFA) and halide alkylation with pentafluorobenzoyl chloride (PFBOCl) – and four different separation and detection techniques. The BSTFA derivatives were quantified with (1) GC-MS in single-ion monitoring (SIM) mode with electron ionisation (EI-GC-MS) and (2) GC-MS/MS in multiple reaction monitoring (MRM) mode using electron ionisation (EI-GC-MS/MS); while the PFBOCl derivatives were quantified with (3) GC-MS using electron ionisation (EI-GC-MS) as well as (4) GC-MS with negative chemical ionisation (NCI-GC-MS). All developed methods showed good linearity ($R^2 > 0.9938$), precision (CV < 4.5% for reproducibility; CV < 2.2% for repeatability) and sensitivity, with limits of detection (LODs) between 0.02 µg kg^{-1} for the pentafluorobenzoyl derivatives measured with the NCI-GC-MS method and 6 µg kg^{-1} for the pentafluorobenzoyl derivatives determined with EI-GC-MS. Levels of BPA in the samples were in agreement for all methods, ranging from values below the limit of quantitation (LOQ) to 11.9 mg kg^{-1} paper. In a last step, the maximum potential migration into food products was calculated for all tested paper and cardboard samples, assuming a 'worst case' scenario of 100% migration.

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

Introduction

Bisphenol A (4,4′-(propane-2,2-diyl)diphenol – BPA), a suspected endocrine disruptor with weak estrogenic activity, has been associated with a wide range of adverse health effects in humans (Liao & Kannan 2011). It is primarily used as a monomer in the production of the polymer polycarbonate, and as starting material for the production of epoxy resins for cans, toys, microwave containers and water pipes (Fasano et al. 2012). Furthermore, BPA is used in a variety of consumer products, including paper and cardboard used as food contact materials. In these products, the sources for BPA are printing inks, adhesives, lacquers, varnishes and coatings, for which BPA is used as an antioxidant and softening agent (Vinggaard et al. 2000). Especially, epoxy-based inks, used for offset printing, contain notable amounts of BPA, whereas the concentration of BPA in water-based inks, used for flexo-printing, is considerably lower. Another source of BPA in paper and cardboard products are thermal papers entering the recycling stream (Biedermann et al. 2010; Mendum et al. 2011). Thermal papers like tickets, bills, luggage tags and faxes contain BPA as a colour developer in the thermal sensitive layer (Liao & Kannan 2011). According to the European Commission (EC), approximately 30% of all thermal papers enter the paper recycling stream (European Commission 2002). It is believed that most of the BPA found in paper products arises from recycling, as higher levels of BPA concentration have been found in products made from recycled fibres than in virgin paper products (Vinggaard et al. 2000). Recycled paper is used in the production of a wide variety of different paper products, from toilet and copy paper, newspapers, and cardboard boxes to corrugated cardboard used as food contact material (Vinggaard et al. 2000; Gehring et al. 2004; Ozaki et al. 2004; Lopez-Espinosa et al. 2007; Suciu et al. 2013). Clearly, the use of recycled paper and cardboard products used as food packaging materials pose a potential risk, as BPA migrates from the packaging to the packed good (Aurela et al. 2001; Castle 2004; Zülch & Piringer 2010; Suciu et al. 2013). In particular the probability of an increased migration rate is higher for fat-containing and moist food products. As a consequence, recycled paper and cardboard are mainly used as direct packaging materials for dry foods like flour, grain, sugar, salt, rice and pasta (Binderup et al. 2002; Suciu et al. 2013).

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Due to a variety of adverse health effects, determined in a variety of studies investigating the exposure of consumers to BPA (Haighton et al. 2002; Völkel et al. 2002; Dekant & Völkel 2008; van Goetz et al. 2010), EFSA decreased the previously TDI for BPA from 0.05 mg kg^{-1} body weight (bw) (EFSA 2006) to 0.005 mg kg^{-1} bw (EFSA 2014). As a result of the ubiquitous occurrence, BPA has been detected in serum, urine, plasma and tissue (Inoue et al. 2001; Geens et al. 2009; Jiménez-Díaz et al. 2010; Chen et al. 2012; Kosarac et al. 2012). Due to a full re-evaluation of the exposure and toxicity of BPA performed by the EFSA in 2015, this temporary TDI was recently lowered to 0.004 mg kg^{-1} bw (EFSA 2015a). EFSA concludes that BPA poses no health risk for any age group because current exposure to BPA from dietary and non-dietary sources is too low to cause harm (EFSA 2015b). Nevertheless, the TDI is determined as a temporary TDI (t-TDI) and depends on the outcome of an ongoing long-term study in rats, which should help to reduce remaining uncertainties about potential health risks (EFSA 2015b).

Concerning BPA in paper products, the main risk for the consumer is due to the migration of BPA from the packaging material into the packaged food. Besides the TDI levels proposed by the EFSA, a specific migration limit (SML) of 0.6 mg kg^{-1} food was proposed by the Council of Europe (2009), dependent on Commission Directive No. 2002/72/EC of 6 August 2002 relating to plastic materials and articles intended to come in contact with food (European Commission 2002). This corresponds to a maximum permitted quantity (QM) of 0.1 mg dm^{-2} paper (Council of Europe 2009), because 1 kg food is defined to be in direct contact with 6 dm^2 packaging material. The maximum permitted concentration of BPA per kg paper is therefore dependent on the grammage (weight per m^2) of the paper.

Analytically, low levels of BPA, down to the range of ng kg^{-1}, can be measured with either HPLC or GC, with either GC-MS or GC-MS/MS, and LC-MS; LC-MS/MS being the most commonly used techniques. LC has also been used in combination with fluorescence detection (FLD) (Yi et al. 2010; Santillana et al. 2011) and diode array detection (DAD) (Rezaee et al. 2009). However, these methods are characterised by poor selectivity and sensitivity, resulting in high LODs and LOQs. Therefore, the coupling of chromatography with MS is the method of choice.

In comparison with single MS, tandem MS is a more sensitive and selective analytical method as it generally achieves improved detection limits in complex matrices (Kelly 2000; Jeannot et al. 2002; Quintana et al. 2004; Stanford & Weinberg 2007).

Despite the advantage that both LC-MS and LC-MS/MS can analyse BPA directly, as these methods are applied in compliance analysis for plastics, for the analysis of complex samples, such as extracts of paper and cardboard, a reduced response is often observed due to ion suppression reactions, especially when electrospray ionisation is used (Gómez et al. 2007). GC analysis instead requires a derivatisation step prior to analysis, but is characterised by increased selectivity, separation and sensitivity. The derivatisation step produces more volatile compounds, improving the selectivity and sensitivity of the analysis. Hence, for the determination of BPA at trace and ultra-trace concentrations in complex matrices, as is expected for paper extracts, GC-MS and CG-MS/MS are preferable, sensitive and selective methods of measurement.

Due to the broad range of derivatisation reagents for GC-MS and GC-MS/MS, different ionisation modes have been used, including negative chemical ionisation (NCI) (Kuch & Ballschmiter 2001; Tsukioka et al. 2003; Möder et al. 2007; Geens et al. 2009; Zhao et al. 2009; Li et al. 2010) and electron impact ionisation (EI) (Hernando et al. 2004; Hibberd et al. 2009; Fenlon et al. 2010; Albero et al. 2012; Kosarac et al. 2012; Lu et al. 2013). The quantification at trace levels is usually performed in SIM for GC-MS and in MRM for GC-MS/MS. Concerning the derivatisation, different reagents have been used to derivatise BPA for GC analysis. Silylation is commonly used for GC-MS with EI, whereas samples analysed by GC-MS using NCI are predominantly derivatised with polyhalogenated reagents. Most common silylation reagents are *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; Kosarac et al. 2012; Lu et al. 2013), N-methyl-N-(trimethylsilyl)trifluoroacetamide (MSTFA) (Yu et al. 2007) and N-*tert*-butyldimethylsilyl-N-methyltrifluoroacetimide (MTBSTFA) (Kosjek et al. 2007). Possible issues with silylation reagents in EI mode result from the fragment ions caused by EI, which could decrease the response of the quantification ions, leading to a decreased sensitivity of the target ions (Zhao et al. 2009).

An alternative method is the derivatisation with polyhalogenated reagents like pentafluorobenzylbromide (PFBBr) (Kuklenyik et al. 2003; Tsukioka et al. 2003; Möder et al. 2007; Zhao et al. 2009) or pentafluorobenzoylchloride (PFBOCl) (Kuch & Ballschmiter 2001; Boitsov et al. 2004; Geens et al. 2009; Li et al. 2010) using NCI. Analyses using NCI make use of an electron capture reaction, achieving high selectivity and sensitivity for chemicals having a high electron affinity like polyhalogenated compounds.

The aim of the present study was the development and comparison of different GC methods which are sensitive and selective for the quantification of BPA in paper and cardboard samples used as food packaging materials. Therefore different derivatisation techniques for different

matrices were adapted and optimised for the determination of BPA in paper and board samples, as this is the first work dealing with the derivatisation of BPA in paper extracts. In this study, BPA was determined with EI-GC-MS in SIM mode, and EI-GC-MS/MS in MRM after trimethylsilylation with BSTFA, as well as EI-GC-MS and NCI-GC-MS after derivatisation with PFBOCl. All developed methods were validated and used to determine the BPA levels in 18 food packaging samples made of paper and cardboard.

The determination of BPA was performed using a screening approach, analysing extracts of paper samples, instead of a migration test using food simulant E for dry foods (verification of compliance test according to the Council of Europe 2009). Hence, the main focus of the work is on the methodical comparison of different GC methods.

Material and methods

Samples

Eighteen different paper and paperboard packages, including primary, secondary and tertiary packages, were analysed. Primary packages are the first layer of the packaging, in direct contact with the product. Secondary packages are used to group primary packages together. Tertiary packages are used for storage and transport. All products were packages for dry food samples, collected between 2012 and 2013. Primary and secondary samples were collected from different supermarkets in Austria. Tertiary samples were provided by an international paper and cardboard manufacture. All samples were immediately wrapped in aluminium foil after sampling and stored at RT, and sample work-up was exclusively done with gloves and BPA-free laboratory ware. The properties of the samples and their packaging type are given in Table 1.

Table 1. Packaging type and properties of the samples.

Sample number	Product	Packaging type	Type of paper
1	Pasta box 1	Primary	Virgin fibre
2	Pasta box 2	Primary	Recycled
3	Couscous box	Primary	Virgin fibre
4	Chocolate box	Primary	Virgin fibre
5	Rice box	Secondary	Recycled
6	Sugar box	Secondary	Recycled
7	Cereals box	Secondary	Recycled
8	Transport box sanitary products	Tertiary	Recycled
9	Transport box sweets 1	Tertiary	Recycled
10	Transport box milk 1	Tertiary	Recycled
11	Transport box pastry	Tertiary	Recycled
12	Transport box cereals	Tertiary	Recycled
13	Transport box sweets 2	Tertiary	Recycled
14	Transport box cookies	Tertiary	Recycled
15	Transport box sparkling wine	Tertiary	Recycled
16	Transport box milk 2	Tertiary	Recycled
17	Transport box chocolate	Tertiary	Recycled
18	Transport box sweets 3	Tertiary	Recycled

Chemicals and reagents

All solvents, standards and reagents were of analytical grade. Methanol and ethyl acetate were from Promochem (LCG Standards, Wesel, Germany), while *n*-hexane was from J.T. Baker (Deventer, the Netherlands). Pyridine, N,O-*bis*(trimethylsilyl) trifluoroacetamide (99%)–trimethylchlorsilane (1%) (BSTFA-TMCS), bisphenol A (BPA) and potassium hydroxide were purchased from Sigma-Aldrich (Steinheim, Germany). Pentafluorobenzoylchloride (PFBOCl) was from Alfa Aesar (Karlsruhe, Germany). The internal standard bisphenol A-d16 (BPA-d16) was from Dr. Ehrenstorfer GmbH (Augsburg, Germany).

Preparation of calibration standards

Standard and internal standard solutions were prepared in methanol. Stock solutions were prepared at a concentration of 1 g l^{-1} and stored at −18°C. Working solutions for calibration were prepared 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.

Four- and five-point calibration curves at different concentration levels were prepared and analysed in triplicate. Concentration of the standard solutions in µg kg^{-1} paper are based on 2 g paper taken for extraction (see the extraction of paper and board samples). For EI-GC-MS of the pentafluorobenzoyl derivatives, the calibration points were 25, 50, 250, 500 and 2500 µg kg^{-1} paper. For NCI-GC-MS the lower calibration range was 0.05–1 (0.05, 0.1, 0.5 and 1) µg kg^{-1} and the higher calibration range was from 0.5 to 50 (0.5, 5, 25 and 50) µg kg^{-1} paper. For GC-MS analysis of the BSTFA derivatives, calibration curves at two different calibration levels were prepared. The levels of the lower calibration level were 5, 20, 35 and 50 µg kg^{-1}, those of the higher level 50, 200, 350 and 500 µg kg^{-1} paper. The calibration of the GC-MS/MS analysis was performed for the same calibration ranges with an additional lower level at 0.5, 2, 3.5 and 5 µg kg^{-1} paper.

Extraction of paper and board samples

A total of 2 g of manually cut paperboard (approximately 0.5 × 0.5 cm) was weighed into a 40 ml glass vial with a PTFE-lined screw cap. A sample weight of 2 g was taken to ensure the samples were representative. After adding

10 µl internal standard solution (BPA-d16 in methanol) and 20 ml methanol, the samples were extracted for 30 min in an ultrasonic bath. The extracts were then decanted and concentrated to a volume of 1 ml in a Concentration Evaporator (Biotage TurboVap® 500, Biotage, Uppsala, Sweden) at ventilator speed B and a water bath temperature of 35°C. Concentrated extracts were filtered through a 0.2 µm PTFE syringe filter to remove residual paper components. Extracts were collected in 2 ml vials with a screw cap and stored at −18°C until derivatisation (typically within 1 week).

Derivatisation of paper and board samples

Derivatisation of paper and board samples: derivatisation with PFBOCL

Derivatisation was carried out by modifying a method used by Kuch and Ballschmiter (2001). All extracts and standard solutions were evaporated to dryness under a gentle stream of nitrogen and re-dissolved in 1 ml bidistilled water. Then, 50 µl of KOH 2 M and 20 µl of the PFBOCl solution (10% in toluene) were added. The derivatives were extracted with 2 × 2 ml *n*-hexane by shaking manually for 2 min at RT. The organic phase was transferred to a new vial and the combined organic phases were evaporated to a volume of 1 ml with the Concentration Evaporator at ventilator speed B and a water bath temperature of 35°C. The total sample preparation time was approximately 25 min per extract. Derivatives were stored at −18°C and were stable for about 8 weeks. Due to the high sensitivity of some methods, further dilution steps were necessary. Therefore, derivatised extracts were diluted with ethylacetate. Dilutions are shown in Table 2.

Derivatisation with BSTFA

After the extracts and standard solutions were evaporated to dryness under a gentle stream of nitrogen, all samples were derivatised by adding 50 µl of N,O-*bis*(trimethylsilyl)trifluoroacetamide (BSTFA) (99%)–trimethylchlorisilane (TMCS) (1%) and 50 µl pyridine. After gently shaking the samples, they were allowed to react for 15 min at RT before being 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 sensitivity of some methods, further dilution steps were necessary. Therefore, derivatised extracts were diluted with ethyl acetate. Dilutions are shown in Table 2.

Gas chromatographic analysis

Analysis of the pentafluorobenzoyl derivatives was carried out by GC-MS in SIM mode operated either in EI or NCI mode. BSTFA derivatives were exclusively analysed in EI mode by GC-MS in SIM mode and GC-MS/MS in MRM mode.

Table 2. Dilution of the derivatised extracts.

	Dilution			
Sample number	EI-GC-MS (PFBOCl derivative)	NCI-GC-MS (PFBOCl derivative)	GC-MS (BSTFA derivative)	GC-MS/MS (BSTFA derivative)
1	Undiluted	1:10	Undiluted	Undiluted
2	Undiluted	1:100	n.a.	n.a.
3	Undiluted	1:10	Undiluted	Undiluted
4	Undiluted	1:10	Undiluted	Undiluted
5	Undiluted	1:1000	1:10	1:100
6	1:10	1:5000	n.a.	n.a.
7	Undiluted	1:1000	n.a.	n.a.
8	1:10	1:10 000	n.a.	n.a.
9	1:10	1:10 000	1:1000	1:2000
10	1:10	1:10 000	1:1000	1:2000
11	1:10	1:10 000	n.a.	n.a.
12	1:10	1:10 000	1:1000	1:2000
13	1:10	1:10 000	1:1000	1:2000
14	1:10	1:10 000	1:1000	1:2000
15	1:10	1:10 000	1:1000	1:2000
16	1:10	1:10 000	n.a.	n.a.
17	1:10	1:10 000	n.a.	n.a.
18	1:10	1:10 000	n.a.	n.a.

Analysis of PFBOCL derivatives

GC-MS analysis of the pentafluorobenzoyl derivatives was performed using a Shimadzu GC-MS QP 2010 plus mass spectrometer system (Kyoto, Japan) operated in either EI or NCI mode. The instrument was equipped with an AOC 5000 autosampler (Shimadzu, Kyoto, Japan) and a Phenomenex ZB5-MS capillary column (30 m × 0.25 mm I.D.; 0.25 µm film thickness; vendor location). Injections (1 µl) were carried out in splitless mode at an inlet temperature of 240°C. Helium was used as carrier gas with a constant flow rate of 0.8 ml min^{-1} with a linear velocity of 40 cm s^{-1}. The GC oven programme was maintained at 90°C for 1 min and then increased to 320°C at 10°C min^{-1}, with a final hold of 5 min. The MS interface temperature was set to 300°C and the ion source temperature was at 200°C. For the MS operating in EI mode the electronic impact was 70 eV. For operating in NCI mode, isobutane, purity 99.95% (Linde) was used as the ionisation gas at a pressure of 0.3 bar. For quantification the MS was operated in SIM mode; the used target ions are listed in Table 2. The selection of the relevant ions was done by carefully inspecting the full-scan mass spectra of the analytes (mass range *m*/*z* 50–700, scan speed: 3.3 cycles per s).

Table 3. Mass spectrometric parameters for the different GC-MS methods.

GC-MS analysis	Compound	Molecular mass (g mol^{-1})	Quantifier ion (*m/z*)	Qualifier ions (*m/z*)
EI-GC-MS	BPA	616	601	195
(PFBOCl)	BPA-d16	630	612	195
NCI-GC-MS	BPA	616	616	617
(PFBOCl)	BPA-d16	630	630	631
EI-GC-MS	BPA	372	357	358, 372
(BSTFA)	BPA-d16	386	368	386

Analysis of BSTFA derivatives

GC-MS analysis of the BSTFA derivatives was performed using the same Shimadzu GC-MS system and settings as for the PFBOCl analyses, except for a lower MS interface temperature (280°C), and a different mass range for the full-scan spectra (50–450 amu, scan speed 3.3 cycles per s). For quantification the MS was operated in SIM; the selected the target ions are given in Table 3.

GC-MS/MS analysis of the BSTFA derivatives was carried out on a Shimadzu GC-MS TQ 8030 system equipped with an EI ion source, an AOC 5000 autosampler (all Shimadzu) and a Phenomenex ZB5-MS capillary column (30 m × 0.25 mm I.D.; 0.25 µm film thickness). Injections (1 µl) were carried out in splitless mode at 240°C. Helium was used as carrier gas with a constant flow rate of 0.8 ml min^{-1} with a linear velocity of 40 cm s^{-1}. The oven programme was maintained at 90°C for 1 min, raised at a rate of 10°C min^{-1} to 260°C and subsequently raised at a rate of 20°C min^{-1} to 310°C, remaining at this level for 3 min. The MS interface temperature was 280°C; the ion source temperature was 200°C. For quantification the MS was operated in MRM mode, with argon, purity 99.999% (Linde), used as the collision gas. The used mass transitions and their corresponding collision induced dissociation energies (CID) are summarised in Table 4.

Table 4. Mass spectrometric parameters for the GC-MS/MS analysis.

Compound	Molecular mass (g mol^{-1})	Precursor ion (*m/z*)	Product ion (*m/z*)	Collision energy (V)
BPA	372	357.2	191.2	20
		358.2	192.2	20
		372.2	357.2	10
BPA-d16	386	368.3	197.3	20
		369.3	198.3	20
		386.3	368.3	10

Method validation

All statistical analyses were performed using ValiData Version 3.02.48 statistical software.

Calculation of the potential migration into food

The maximum potential migration of BPA into a dry food matrix was calculated depending on the BPA concentration and grammage of the samples. A 100% migration rate was assumed, which represents the 'worst case' scenario.

The calculation was based on the conventional surface-to-volume ratio of 1 kg food to 6 dm^2 packaging material. This value derives from the assumption that 1 kg food is packed cubically, which leads to a surface area of 6 dm^2 packaging material per kg food. In the case of conditions where the ratio of the mass of food to the contact area differs from the conventional ratio, the real surface-to-volume ratio has to be taken. For the calculation of the potential migration into food of the analysed samples, the simplification of the conventional ratio was used. Calculations per kg food concerning LOD and LOQ were performed for 100% migration and a heavy weight paper of 400 g m^{-2}, as the migration rate for heavy weight papers is higher than for low-weight papers. Furthermore, most food packaging materials consist of heavy weight carton and corrugated board with a grammage between 200 and 500 g m^{-2}.

Results and discussion

Assessment of the two different derivatisation reagents

GC-MS analysis of underivatised BPA showed a poor peak shape and sensitivity because of the polarity of the hydroxyl groups. Therefore, all methods applied are based on a derivatisation step prior to injection in order to transform BPA into a less polar and more volatile compound. Thereby, the derivatisation improves the selectivity and sensibility of the chromatographic analysis.

Derivatisation with PFBOCL

The derivatisation with PFBOCl, transforming BPA into a highly electrophilic compound through the introduction of 10 fluorine atoms, was based on a previously described method (Kuch & Ballschmiter 2001). The reported method was modified and optimised by a step-by-step optimisation of the volume of the potassium hydroxide solution (KOH) added, the volume and concentration of PFBOCl added, the extraction temperature and the extraction time. Optimised parameters are described in the experimental section. During the extractive derivatisation, polar substances remained in the aqueous phase, thus providing also a purification by the derivatisation reaction

(Geens et al. 2009). Derivatised extracts were analysed by EI-GC-MS and NCI-GC-MS both in SIM mode, which improved the selectivity and sensitivity compared with normal scan mode.

Both EI-GC-MS and NCI-GC-MS chromatograms of a standard mixture of BPA and BPA-d16 derivatives at a concentration of 50 µg kg^{-1}, as well as their corresponding mass spectra, are shown in Figures 1a, 1b and 2a, 2b respectively. Because of the introduction of the fluorine atoms, BPA is transformed into a highly electrophilic compound. As NCI is a highly selective and sensitive method for the detection of halogenated compounds, it is the preferred ionisation technique for the pentafluorobenzoyl derivatives, compared with EI. Furthermore, NCI is characterised by a 'softer' ionisation, yielding a dominant molecular ion and less fragmentation than EI. This can be seen in the spectra shown for EI and NCI mode in Figures 2a and 2b. Using EI-GC-MS, the pentafluorobenzoyl derivatives give a fragmentation pattern with the molecular ion *m/z* 601 and the base ion *m/z* 195 of the pentafluorobenzoyl group, while the NCI spectrum gives only the molecular ion at *m/z* 616 of the molecular mass and the protonated molecular ion at *m/z* 617.

Both ionisation modes were suitable for analysing the pentafluorobenzoyl derivatives of BPA; however, the sensitivity of NCI-GC-MS was approximately 100 times higher than EI-GC-MS, as further outlined in the method validation section.

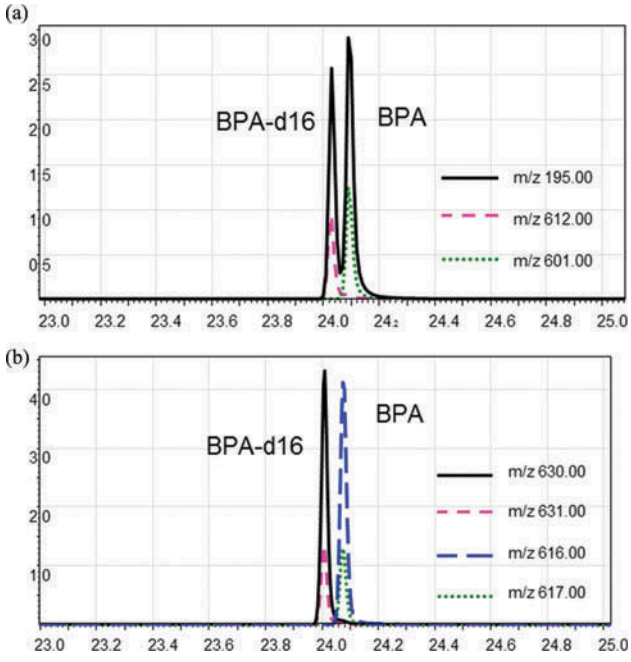

Figure 1. (colour online) (a) EI-GC-MS chromatogram of BPA and BPA-d16 derivatised with PFBOCl (50 µg kg^{-1}); and (b) NCI-GC-MS chromatogram of BPA and BPA-d16 derivatised with PFBOCl (50 µg kg^{-1}).

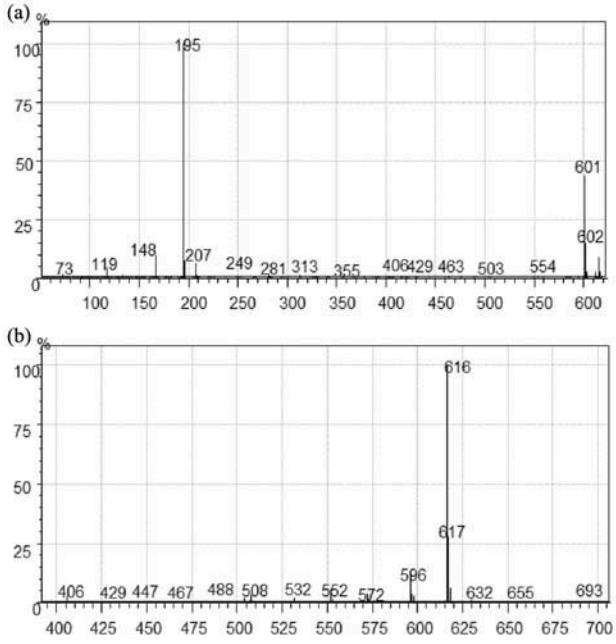

Figure 2. (a) EI spectrum of BPA derivatised with PFBOCl; and (b) NCI spectrum of BPA derivatised with PFBOCl.

Derivatisation with BSTFA

Silylation is one of the derivatisation procedures widely used 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-TCMS is characterised by simplicity, low solvent consumption and a fast reaction of the hydroxyl groups. However, silylated derivatives can only be analysed with EI because of their low electrophilicity for NCI. For the BSTFA derivatives, GC-MS analysis was performed in SIM mode, leading to improved selectivity and sensitivity in comparison with the scan mode. In addition, BSTFA derivatives were also analysed with GC-MS/MS using MRM. For MRM, the most abundant ions were chosen as precursor and product ions for quantification and confirmation. A total of three transitions were selected: one for quantifying and two for qualifying purposes. Compared with EI-GC-MS in SIM mode, tandem MS showed enhanced selectivity and sensitivity, which was highlighted by lower background noise and a higher signal. The GC-MS/MS method also reduced all spectral interferences present in complex samples through ion selection for both precursor and product ions, considerably reducing the matrix effects. The GC-MS/MS method showed a 10 times higher sensitivity than the GC-MS method. A GC-MS and a GC-MS/MS chromatogram of a standard mixture of BPA and BPA-d16 derivatives at a concentration of 50 µg kg^{-1} and their corresponding mass spectra are presented in Figures 3a, 3b and 3c.

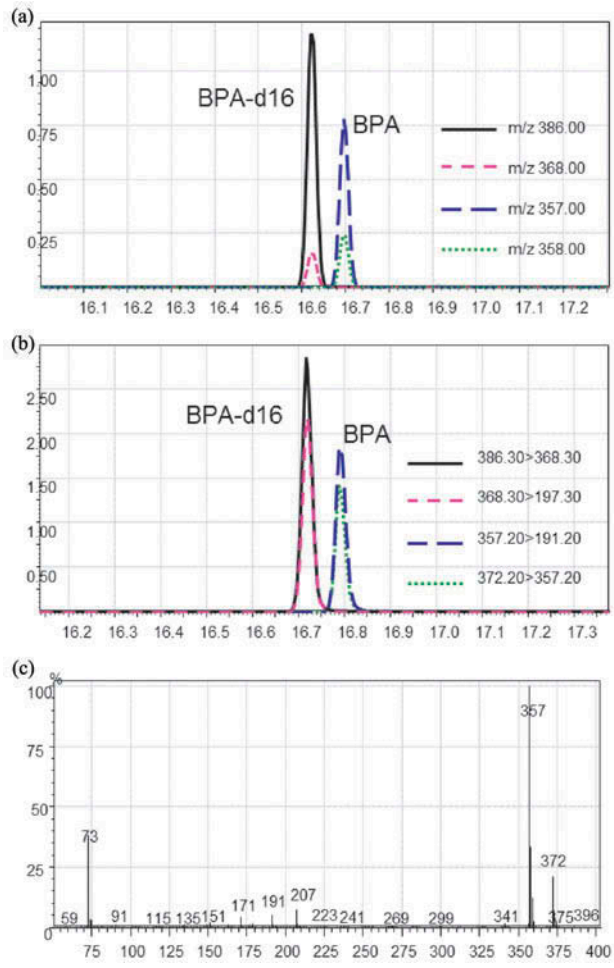

Figure 3. (colour online) (a) EI-GC-MS chromatogram of BPA and BPA-d16 derivatised with BSTFA (50 µg kg^{-1}); (b) EI-GC-MS/MS chromatogram of BPA and BPA-d16 derivatised with BSTFA (50 µg kg^{-1}); and (c) EI spectrum of BPA derivatised with BSTFA.

Method validation

The analytical methods were evaluated to prove their applicability to the analysis of BPA in paper and paperboard products. Recovery, linearity range, precision and sensitivity were calculated and compared. Method validation was done for all methods at the lowest calibration level. Validation results are presented in Table 5.

Recovery

Recovery experiments were performed in triplicate by spiking paper samples at a concentration level of 50 µg kg^{-1} before extraction. Satisfactory recovery was obtained for all proposed methods, with recoveries of 74% for the EI-GC-MS of the pentafluorobenzoyl derivatives, 88% for the NCI-GC-MS of the pentafluorobenzoyl derivatives, 96% for the GC-MS of the silylated derivatives, and 93% for the GC-MS/MS analysis of the silylated derivatives. No significant differences for the recoveries were obtained between the replicates, with residual SDs < 4% for all methods. The better recovery rates obtained for the silylated derivatives seem to be a result of the derivatisation procedure. The extractive derivatisation of the pentafluorobenzoyl derivatives is more complex and elaborate than the silylation reaction, most likely leading to the main losses of the analytes during the extraction and concentration step of the derivatisation with PFBOCl.

Linearity

Linearity was evaluated by injecting three replicates of the standard solutions at the concentration levels shown in Table 5. All standards contained the deuterated internal standard at a concentration of 50 µg kg^{-1} paper. Good linearity was obtained for all methods with correlation coefficients > 0.9938 in all cases. Linearity was assumed when the regression coefficient > 0.99 with RSD < 15%.

Sensitivity

LOD and LOQ were determined by analysing the derivatised standard solutions at the lowest calibration range for the different methods. Values are shown in Table 6, ranging from 0.02 to 6 µg kg^{-1} paper for LOD and from 0.08 to 22 µg kg^{-1} paper for LOQ. The lowest LOQ was achieved with PFBOCl derivatisation and NCI-GC-MS analysis. The LOD and LOQ values for the GC-MS of the silylated samples are lower than those reported in the literature; however, these studies used GC-MS without derivatisation. In Suciu et al. (2013), an LOD of 0.015 mg l^{-1} and an LOQ of 0.064 mg l^{-1} were determined with GC-MS without derivatisation. Because the study reported the LOD and LOQ in mg l^{-1}, for

Table 5. Validation parameters obtained with the different GC-MS methods.

Method	Recovery (%)	Linearity		Repeatability (RSD %)	Reproducibility (RSD %)
		Range (µg kg^{-1})	R^2		
EI-GC-MS (PFBOCl derivative)	74	25–2500	1.000	0.20	0.78
NCI-GC-MS (PFBOCl derivative)	78	0.05–1	0.9982	0.27	2.15
GC-MS (BSTFA derivative)	96	5–50	0.9938	1.45	4.84
GC-MS/MS (BSTFA derivative)	93	0.5–5	0.9988	2.18	2.49

Table 6. LOD and LOQ in paper and food for the different methods.

Method	LOD paper (μg kg^{-1})	LOQ paper (μg kg^{-1})	LOD food (μg kg^{-1})	LOQ food (μg kg^{-1})
EI-GC-MS (PFBOCl derivative)	6	22	0.2	0.6
NCI-GC-MS (PFBOCl derivative)	0.02	0.08	0.0006	0.002
GC-MS (BSTFA derivative)	2	8	0.05	0.2
GC-MS/MS (BSTFA derivative)	0.2	0.7	0.005	0.02

comparison the values obtained in this study were converted to mg l^{-1}. The LOD of 0.05 μg kg^{-1} and the LOQ of 2 μg kg^{-1} determined in this study correspond to an LOD and an LOQ of 0.0001 and 0.004 mg l^{-1}, respectively. Comparing these values, a significant increase in sensitivity is apparent, which is achieved through derivatisation of BPA. For all other methods no previous reports were found. The low LOD and LOQ achieved with NCI-GC-MS for the analysis of the pentafluorobenzoyl derivatives demonstrates the high selectivity and sensitivity of the NCI for compounds having a high electron affinity.

In addition to the quantification of the LOD and LOQ of BPA per kg paper, the LOD and LOQ were calculated in 1 kg food for the assumption of 100% migration and the conventional surface-to-volume ratio of 1 kg food per 6 dm^2 packaging material. The calculation was performed for a heavy weight paper, having a grammage of 400 g m^{-2}, taking into account that the concentration in the food for heavy weight papers like carton and board is higher than for low-weight papers like copy paper. Calculated values ranged from 0.0006 to 0.2 μg kg^{-1} food for LOD and from 0.002 to 0.6 mg kg^{-1} food for LOQ (Table 6).

Precision

For an evaluation of the precision of the proposed methods, repeatability and reproducibility were determined, expressed as per cent relative standard deviation (RSD %). Reproducibility and repeatability were determined by intra- and inter-day experiments. Repeatability was determined by analysing a spiked sample at a concentration of 50 μg kg^{-1} in triplicate. For reproducibility the same sample was analysed in triplicate on different days. Repeatability and reproducibility, calculated for all methods, are summarised in Table 5. Intra- and inter-day experiments showed good precision for all methods. Repeatability determined was < 2.2% and reproducibility was < 4.8%.

Concentration of BPA in paper and cardboard used for food packaging

The developed and validated methods were applied to quantify BPA in 18 different paper and paperboard samples used for food packaging. The analysed packages included four primary, three secondary and 11 tertiary packages. All primary packages were food boxes for dry foodstuffs like rice, pasta, polenta or couscous. According to the printing on the packages, of these, three packages were produced of virgin fibres and one was made of recycled fibres. All secondary and tertiary products were produced of recycled fibres with no information concerning the recycling content. BPA was detected in all analysed samples, but not all methods were sensitive and selective enough to detect BPA in all samples (Table 7). The EI-GC-MS method applied to the pentafluorobenzoyl derivatives was not sensitive enough to detect BPA in primary samples produced of virgin fibres (Table 7). The concentrations of BPA in the selected paper and paperboard samples analysed with the different methods are shown in Table 7.

As the measurements were internally standardised, the concentrations are inherently corrected for recovery losses. Concentrations of primary samples ranged from 0.01 to 0.41 mg kg^{-1} paper, with the highest concentration for the primary sample produced of recycled fibres. In primary samples produced of virgin fibres the concentration of BPA in the pentafluorobenzoyl derivatives was lower than the LOQ of the EI-GC-MS method for these derivatives. For all other proposed methods BPA could be detected in virgin fibre primary samples; however, detected levels were relatively low, with concentrations between 0.01 and 0.02 mg kg^{-1} paper. In general, larger amounts of BPA were found in recycled paper and cardboard products than in virgin products: generally, the concentration of the primary sample produced of recycled fibres is 40 times higher than those of the samples produced of virgin fibres.

Concentrations in secondary samples ranged from 0.10 to 6.35 mg kg^{-1}. The lowest concentration of 0.10 mg kg^{-1} is equivalent to the values obtained for the primary packaging material produced of recycled fibres, whereas the highest concentration of 6.35 mg kg^{-1} corresponds to the values obtained for tertiary samples. Significantly higher BPA concentrations were found in tertiary packages with values between 4.43 and 13 mg kg^{-1}, invariably derived from recycled corrugated cardboard.

Concerning printing, no significant differences could be observed between flexo-printed and offset-imprinted samples. It can be concluded that the type of paper, if

Table 7. Concentration of BPA in the samples, analysed with the different methods.

Sample number	Concentration (mg kg^{-1}) (RSD%)				
	EI-GC-MS (PFBOCl derivative)	NCI-GC-MS (PFBOCl derivative)	GC-MS (BSTFA derivative)	GC-MS/MS (BSTFA derivative)	Mean all methods + (RSD%)
1	< LOQ[a]	0.01 ± 0.0004 (4.5)	0.01 ± 0.001 (9.9)	0.01 ± 0.001 (6.4)	0.01 ± 0.003 (19.8)
2	0.43 ± 0.02 (3.8)	0.40 ± 0.01 (1.6)	n.a.	n.a.	0.41 ± 0.02 (5.1)
3	< LOQ[a]	0.01 ± 0.0001 (0.8)	0.01 ± 0.0004 (3.9)	0.01 ± 0.001 (5.3)	0.01 ± 0.003 (23.8)
4	< LOQ[a]	0.02 ± 0.0007 (3.7)	0.02 ± 0.003 (6.5)	0.02 ± 0.001 (6.1)	0.02 ± 0.002 (10.8)
5	0.7 ± 0.13 (19.2)	0.69 ± 0.01 (1.3)	0.66 ± 0.02 (2.4)	0.72 ± 0.04 (5.5)	0.68 ± 0.03 (4.3)
6	6.69 ± 0.08 (1.2)	6.3 ± 0.36 (5.7)	n.a.	6.1 ± 0.10 (1.7)	6.4 ± 0.31 (4.9)
7	0.12 ± 0.001 (9.4)	0.11 ± 0.01 (4.6)	n.a.	0.10 ± 0.009 (8.7)	0.10 ± 0.01 (6.4)
8	9.7 ± 0.14 (1.5)	12.5 ± 0.24 (1.9)	n.a.	n.a.	11.1 ± 2.0 (18.2)
9	10.0 ± 0.2 (2.3)	11.9 ± 0.39 (3.3)	10.1 ± 0.14 (1.4)	10.6 ± 0.24 (2.3)	10.7 ± 0.8 (8.0)
10	10.0 ± 0.19 (1.9)	11.1 ± 0.10 (0.8)	10.3 ± 0.10 (0.9)	10.8 ± 0.14 (1.3)	10.5 ± 0.5 (4.8)
11	4.8 ± 0.18 (3.7)	5.0 ± 0.15 (3.0)	n.a.	n.a.	4.9 ± 0.19 (4.0)
12	4.3 ± 0.22 (5.2)	4.4 ± 0.41 (9.3)	4.32 ± 0.02 (0.5)	4.64 ± 0.07 (1.6)	4.4 ± 0.14 (3.1)
13	9.89 ± 0.03 (0.3)	10.5 ± 0.26 (2.5)	8.8 ± 0.16 (1.8)	9.1 ± 0.23 (2.5)	9.6 ± 0.77 (8.0)
14	11.8 ± 0.37 (3.1)	13.7 ± 0.40 (2.9)	13.9 ± 0.08 (0.6)	13.3 ± 0.28 (2.1)	13.0 ± 0.8 (6.3)
15	7.71 ± 0.04 (0.5)	7.92 ± 0.08 (1.0)	8.2 ± 0.13 (1.2)	8.4 ± 0.10 (1.2)	8.1 ± 0.30 (3.7)
16	4.70 ± 0.01 (0.2)	5.4 ± 0.33 (6.1)	n.a.	n.a.	5.0 ± 0.47 (9.4)
17	10.2 ± 0.19 (1.8)	10.8 ± 0.18 (1.7)	n.a.	n.a.	10.5 ± 0.4 (3.7)
18	5.6 ± 0.12 (2.1)	6.1 ± 0.20 (3.3)	n.a.	n.a.	5.8 ± 0.35 (5.9)

Notes: [a]LOQ = 0.022 mg kg^{-1}.
n.a., Not analysed.

recycled or virgin, and the recycling content have a considerably higher impact on the BPA concentration than the type of printing.

As the concentration range of secondary and tertiary samples exceeded the concentration range of the proposed methods, the derivatised extracts were diluted to perform an adequate quantification (see the methods section – gas chromatographic analysis). Due to the high selectivity of the methods, a reduction of the initial sample weight of 2 g would be possible. However, the lower the sample weight, the less representative the sample. Thus, to ensure representative samples, a sample weight of 2 g was taken. In general, the values obtained are in agreement with previously reported values for paper and cardboard food packaging products (Ozaki et al. 2004; Mendum et al. 2011; Suciu et al. 2013).

Estimating the concentration of BPA in the food through migration from the packaging material

The concentration of BPA in the food matrix was calculated for the assumption of 100% migration. Dependent on the grammage and the conventional surface-to-volume ratio of 1 kg dry food in direct contact with 6 dm^2 packaging material, the maximum possible migration for all samples was calculated. The calculation for 100% migration should demonstrate the 'worst case' scenario. However, our calculations cannot substitute any migration tests for the testing for compliance with the SML restrictions using the conventional European Union test simulants of foodstuffs. For the migration from paper and board into dry food, simulant E (modified polyphenylene oxide) has to be proved as the most suitable food simulant (Aurela et al. 2001; Summerfield & Cooper 2001; Triantafyllou et al. 2007; Zülch & Piringer 2010).

Our results show the applicability of all methods for the analysis of BPA in paper extracts, as all methods are sensitive enough to determine if the migration concentration of BPA is below the SML of 0.6 mg kg^{-1}, even for the worst-case scenario of 100% migration under the assumption of the conventional surface-to-volume ratio. Thus, all the methods can be seen as a controlling tool for the maintenance of the SML of 0.6 mg kg^{-1} by the paper producers. However, the found concentrations of virgin fibre primary samples tend to be lower than the LOQ of the EI-GC-MS method with pentafluorobenzoyl derivatisation. Therefore, we recommend the analysis of pentafluorobenzoyl derivatives with NCI-GC-MS, taking advantage of the high sensitivity and selectivity of NCI for highly electrophilic polyhalogenated substances. For the analysis with EI-GC-MS, trimethylsilylation is the preferred derivatisation technique as it is less time consuming and less prone to analyte loss during the extraction and evaporation steps.

Calculated maximum migration values for all samples analysed with the different methods, as well as the mean values of all methods for the respective samples, are

Table 8. Calculated migrations into food for all different methods.

Sample number	Concentration (µg kg^{-1}) (RSD%)				
	EI-GC-MS (PFBOCl derivative)	NCI-GC-MS (PFBOCl derivative)	GC-MS (BSTFA derivative)	GC-MS/MS (BSTFA derivative)	Mean all methods + (RSD%)
1	< LOQ[a]	0.14 ± 0.01 (4.5)	0.12 ± 0.01 (9.9)	0.17 ± 0.01 (6.4)	0.14 ± 0.03 (19.8)
2	7.8 ± 0.3 (3.8)	7.3 ± 0.1 (1.6)	n.a.	n.a.	7.6 ± 0.4 (5.1)
3	< LOQ[a]	0.15 ± 0.01 (0.8)	0.15 ± 0.01 (3.9)	0.23 ± 0.01 (5.3)	0.18 ± 0.04 (23.8)
4	< LOQ[a]	0.60 ± 0.02 (3.7)	0.75 ± 0.05 (6.5)	0.67 ± 0.04 (6.1)	0.67 ± 0.07 (10.8)
5	18 ± 3 (19.2)	19 ± 3 (1.3)	18 ± 0.4 (2.4)	20 ± 1 (5.5)	19 ± 1 (4.3)
6	153 ± 2 (1.2)	143 ± 8 (5.7)	n.a.	139 ± 2 (1.7)	145 ± 7 (4.9)
7	2.9 ± 0.3 (9.4)	2.8 ± 0.1 (4.6)	n.a.	2.5 ± 0.2 (8.7)	2.7 ± 0.2 (6.4)
8	290 ± 4 (1.5)	375 ± 7 (1.9)	n.a.	n.a.	333 ± 61 (18.2)
9	308 ± 7 (2.3)	364 ± 12 (3.3)	311 ± 4 (1.4)	325 ± 7 (2.3)	327 ± 26 (8.0)
10	223 ± 4 (1.9)	248 ± 2 (0.8)	230 ± 2 (0.9)	243 ± 3 (1.3)	236 ± 11 (4.8)
11	150 ± 6 (3.7)	158 ± 5 (3.0)	n.a.	n.a.	154 ± 6 (4.0)
12	128 ± 7 (5.2)	131 ± 12 (9.3)	127 ± 0.6 (0.5)	136 ± 2 (1.6)	131 ± 4 (3.1)
13	240 ± 1 (0.3)	255 ± 6 (2.5)	214 ± 4 (1.8)	221 ± 5 (2.5)	232 ± 19 (8.0)
14	242 ± 8 (3.1)	281 ± 8 (2.9)	269 ± 2 (0.6)	273 ± 6 (2.1)	266 ± 17 (6.3)
15	185 ± 1 (0.5)	191 ± 2 (1.0)	197 ± 2 (1.2)	202 ± 2 (1.2)	194 ± 7 (3.7)
16	117 ± 0.2 (0.2)	134 ± 8 (6.1)	n.a.	n.a.	126 ± 12 (9.4)
17	261 ± 5 (1.8)	275 ± 5 (1.7)	n.a.	n.a.	268 ± 10 (3.7)
18	135 ± 3 (2.1)	147 ± 5 (3.3)	n.a.	n.a.	141 ± 8 (5.9)

Notes: [a]LOQ = 0.6 µg kg^{-1}.
n.a., Not analysed.

shown in Table 8. The values obtained for the maximum potential migration are between < LOQ for some primary samples derivatised with PFBOCl and analysed with EI-GC-MS and 375 µg kg^{-1} food for a tertiary sample of a pentafluorobenzoyl derivate analysed with NCI-GC-MS. Considering the mean values obtained with the different methods, the calculated concentrations per kg food are between 0.14 and 333 µg kg^{-1}. In compliance with the concentrations obtained in the paper samples, the lowest migration values are calculated for primary samples produced of virgin fibres, whereas the highest values are obtained for tertiary packages produced of recycled corrugated board. The calculated migrations are between 4000 and two times below the SML of 0.6 mg kg^{-1} (600 µg kg^{-1}). Thus, under the assumption that the total amount of BPA in the samples is extracted, analysed samples are assumed to be safe according to the Council of Europe (2009).

On the basis of the SML and the data obtained in this study, food packaging material produced from paper and paperboard can be considered safe even for the worst case of 100% migration, which is, however, very unlikely to occur. Previous BPA migration studies into salt, sugar and food simulant E – modified polyphenylene oxide (MPPO) – were always lower than 1% (Suciu et al. 2013). Several studies also observed that the migration from paper and board depends on the structure of the paper as well as the period of and temperature during storage (Triantafyllou et al. 2007; Zülch & Piringer 2010).

Conclusions

The applicability of the methods was demonstrated by monitoring BPA in paper and board samples from the market. BPA was determined in different food paper packages (primary, secondary and tertiary) after extraction of the samples in methanol and derivatisation with either PFBOCl or BSTFA. PFBOCl derivatives were analysed with EI-GC-MS and NCI-GC-MS, whereas BSTFA derivatives were analysed with GC-MS and GC-MS/MS. The concentrations of BPA determined with the different methods were compared, as well as the calculated migration concentration into food. Furthermore, all methods were validated in terms of recovery, linearity range, precision and sensitivity to prove their applicability to the analysis BPA in paper and paperboard products.

The results show that BPA is a ubiquitous contaminant, present in all analysed samples. Furthermore, it was shown that the use of recycled fibres in paper production has a strong impact on the BPA content in the end-product. For example, the highest values of BPA were found in tertiary packages produced of recycled corrugated board, whereas the lowest BPA concentrations were detected in primary packages produced from virgin fibres.

All methods were validated and are adequate to analyse primary, secondary and tertiary samples, with the exception of the EI-GC-MS method of the pentafluorobenzoyl derivatives, which is not sensitive and selective enough to detect BPA in the primary paper samples.

Concerning the SML, all methods show an LOQ lower than the SML of 0.6 mg kg^{-1} food, thus they are suitable

for the detection of BPA in samples undergoing a migration study. Furthermore, none of the samples exceeded the concentration of the SML, assuming 100% migration of BPA from the paper packaging into the packaged food and a surface-to-volume ratio of 1 kg food per 6 dm^2 paper. On the basis of the calculated results, the analysed samples can be considered safe for their purpose of contact with dry foodstuffs.

In the case of the derivatisation procedure, derivatisation with BSTFA is the preferable method, as it is less susceptible to analytes as no extraction and concentration step is necessary. Thus, EI-GC-MS will be the more frequently used GC technique as BSTFA derivates are limited to detection with EI-GC-MS.

Disclosure statement

No potential conflict of interest was reported by the authors.

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