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Rapid Analysis of Bisphenol A and Its Analogues in Food Packaging Products by Paper Spray Ionization Mass Spectrometry

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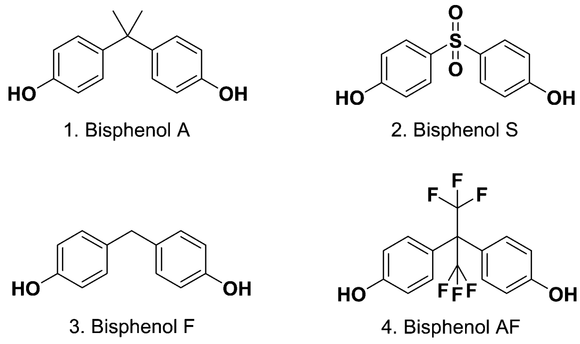
Supporting Information

ABSTRACT: In this study, a paper spray ionization mass spectrometric (PS-MS) method was developed for the rapid in situ screening and simultaneous quantitative analysis of bisphenol A and its analogues, i.e., bisphenol S, bisphenol F, and bisphenol AF, in food packaging products. At the optimal PS-MS conditions, the calibration curves of bisphenols in the range of 1−100 μg/mL were linear. The correlation coefficients were higher than 0.998, and the LODs of the target compounds were 0.1−0.3 μg/mL. After a simple treatment by dichloromethane on the surface, the samples were analyzed by PS-MS in situ for rapid screening without a traditional sample pretreatment procedure, such as powdering, extraction, and enrichment steps. The analytical time of the PS-MS method was less than 1 min. In comparison with conventional HPLC-MS/MS, it was demonstrated that PS-MS was a more effective high-throughput screening and quantitative analysis method.

KEYWORDS: *bisphenol A, bisphenol S, bisphenol F, bisphenol AF, paper spray ionization mass spectrometry, food packaging products*

INTRODUCTION

Bisphenol A (Figure 1) is widely employed to produce polycarbonate plastics and epoxy resins, which are used in many plastic food packaging products, including baby bottles, drinking containers, and snack packaging.[1−6] However, there are a number of studies that confirm the considerable damage of bisphenol A on human health, including neural disorders, behavioral dysfunction, reproductive damage, etc.[7−13] In 2015, a document on risk assessment was published in the Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) Panel's "Scientific opinion on the risks to public health related to the presence of bisphenol A in foodstuff". The CEF Panel established a temporary tolerable daily intake (t-TDI) of 4 μg/kg bw/d by aplying a total uncertainty factor of 150.[14]



1. Bisphenol A
2. Bisphenol S
3. Bisphenol F
4. Bisphenol AF

Figure 1. Chemical structures of bisphenol A and analogues (M_1 = 228.29, M_2 = 250.27, M_3 = 200.24, M_4 = 336.23).

In addition, bisphenol A analogues, such as bisphenol S, bisphenol F, and bisphenol AF (Figure 1), have similar physicochemical properties to **1**. Therefore, the analogues are rendered as candidates for replacement of **1** in industrial applications.[9] Unfortunately, this similarity is also expected to result in harmful toxicological profiles. Kitamura et al.[15] demonstrated that **1** and **2** were potent anti-androgen compounds. Castro et al.[16] found potential adverse effects of **3** and **2** in the developing brain of mammals. Kinch et al.[17] demonstrated that **1** and **2** induce precocious hypothalamic neurogenesis at low-dose exposures. Additional harmful effects have been proven, including genotoxicity, DNA damage,[18] oxidative stress, etc.[19] In 2016, Chen et al.[20] reviewed the environmental occurrence, human exposure, and toxicity of bisphenol analogues other than **1**. They showed that **2**, **3**, and **4** may drive a new global contamination trend as **1** replacements.

Because of their high sensitivity and selectivity, LC-MS and GC-MS are usually used to identify **1** and its analogues.[21−23] However, sample pretreatment methods, such as liquid−liquid extraction,[22] solid-phase extraction,[23] or solid-phase microextraction,[24] for complex samples, e.g., urine, require considerable time and labor, and the analytical throughput of

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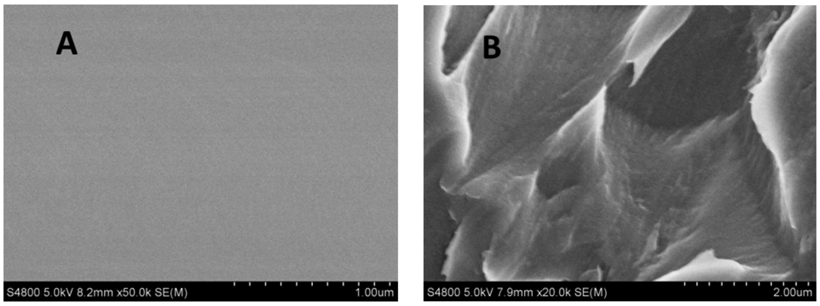


Figure 2. SEM images of sample surface: (A) sample without treatment; (B) sample treated for 1 min.

the methods is low. In addition, LC-MS is not easy to use for the rapid screening of **1** and its analogues in food packaging products because the separation is time-consuming.

Ambient mass spectrometry (AMS) is a new technology. It can directly analyze sample or sample surface without or with less sample pretreatment. After Cooks's group presented desorption electrospray ionization (DESI),[25] AMS has been developed rapidly because of its rapid, high-throughput merits.[26−28] It is a potential high-throughput screening method for hazardous ingredients. Now, more than 30 ambient ionization methods have been developed.[29] Among different AMS techniques, paper spray MS (PS-MS) has unique advantages, e.g., in situ analysis and simple instrumental construction for ionization. In addition, PS-MS has good quantitation ability (<15% RSD) when using proper internal standards.[30,31]

AMS has been used in food safety analysis to analyze hazardous substances and contaminants in foodstuffs and food packaging products.[32−40] Ambient ionization accurate mass spectrometry (AMI-AMS) was employed to successfully detect and identify compounds from print set-off.[33] Wang et al.[34] also developed a rapid method for the direct detection of **1** in food packaging materials based on desorption corona beam ionization (DCBI) tandem mass spectrometry. In 2016, a comparison of LC-high-resolution/accuracy-time-of-flight (TOF) MS with different ionization sources and ambient mass spectrometry with direct probe (DP)-APCI for the screening of additives in plastics was completed. These techniques proved to be complementary, providing different selectivity and sensitivity for the different compound classes.[39]

In this study, a PS-MS method for rapid screening and quantitation of **1**, **2**, **3**, and **4** in food packaging products was developed. The method is less time-consuming, requires less sample treatment, and is convenient for high-throughput testing.

■ MATERIALS AND METHODS

Chemicals and Materials. HPLC-grade methanol was obtained from Tedia Company Ltd. (Fairfield, OH). Analytical grade ethanol, ethyl ether, and benzene were purchased from Tianjin HengXing Chemical Reagent Ltd. (Tianjin, China). Analytical grade dichloromethane was purchased from Tianjin Chemical Reagent Research Institute (Tianjin, China). **1**, **2**, **3**, and **4** were purchased from Aladdin Company (Shanghai, China). Bisphenol A-d_{16}, obtained from Sigma-Aldrich (St. Louis, MO), was used as an internal standard (I.S.). Ultrapure water (>18 MΩ) used for the experiments was purified by a Milli-Q system.

The samples, including mineral water bottles, energy drink bottles, plastic cups, paper cups, and baby bottles, were purchased from Wal-Mart (Changsha, China). One baby bottle was an imported product produced by Philips Avent Corporation (U.K.).

Apparatus. A ZQ 2000 single-quad mass spectrometer with a scan speed range of 197 to 3980 Da/s (Manchester, U.K.) was used to record the signal for PS-MS analysis. The resolution was as follows: the peaks at 1080.8 and 1081.8 from an infusion of β-cyclodextrin resolved with a valley between them of no more than 10% of the average height of the two peaks. An XYZR (three-dimensional plus angle adjustment) moving platform was made in-house and used to accurately control location of the spray tip.

LC-MS/MS analysis was accomplished using an LCMS-8050 liquid chromatograph mass spectrometer (Shimadzu, Kyoto, Japan) coupled with two LC-20AD HPLC pumps, a SIL-20A autosampler, a DGU-20A3R degassing unit, and a CTO-20A column oven. System control and data processing were performed with the Labsolutions chromatography workstation, version 5.75 (Shimadzu).

Rapid Screening Analysis by Direct Sample Spray MS. Samples were cut into triangle-like shapes with dimensions of 4 mm at the base and 10 mm in height for paper spray. Before direct sample spray MS analysis, the plastic piece was soaked in dichloromethane for 1 min. After being dried under nitrogen, the sample was fixed on the XYZR moving platform by an alligator clamp; the triangular tip was held 5 mm from the ion cone of the MS. Ten microliters of methanol was used as a spray solvent and dropped on the sample surface, and then −2.5 kV was applied to form the sample spray ionization. The spray process lasted for 10−15 s. For paper product analysis, the method was the same but without soaking in dichloromethane.

The MS parameters for the working negative ion mode of the ZQ 2000 for PS-MS analysis were as follows: cone voltages, −40 V; extractor voltage, −1 V; ion energy, 0.5; source temperature, 100 °C; RF lens voltage, −0.5 V; cone gas (N_2), 5 L/h.

Rapid Quantitative Analysis by PS-MS. For rapid quantitative analysis by PS-MS, triangular filter paper (base, 6 mm; height, 12 mm) was employed as PS substrates. The triangular paper was cut by a CUTOK DC 330 craft cutting plotter (Hefei CNC Equipment Co., Hefei, China). The sample volume for PS-MS analysis was 10 μL.

Bisphenol A-d_{16} was used as I.S. at 10 μg/mL in a series of standard solutions using methanol as solvent. The calibration curves of **1**, **2**, **3**, and **4** were constructed with ratios of abundance of target ions (m/z of **1**, **2**, **3**, **4** was 227, 249, 199, 335, respectively) to I.S. (m/z: 241) vs the concentrations of **1**, **2**, **3**, and **4**, respectively. The concentration range was 1−100 μg/mL. The limits of detection (LOD) were determined by injecting diluted standards. The least concentrated standard yielding a signal/noise ratio >3 was considered as the LOD.

For polymer samples for analyses, the sample treatment method was similar to the FDA method.[41] The detailed procedures are as follows: 0.10 of cut sample was mixed with 2 mL of methylene chloride in a flask. The flask was placed in an ultrasonic water bath for 30 min to dissolve the sample. Eight milliliters of methanol was added in the flask to precipitate the polymer completely. The polymer precipitate was allowed to settle for 10 min. Five milliliters of the sample filter liquor was dried by N_2 stream. The residue was redissolved in 0.2 mL of methanol including 10 μg/mL of bisphenol A-d_{16}.

For paper products, the sample, cut into small pieces, was extracted by shaking with methanol. After filtering, 1 mL of the sample solution was dried by N_2. The residual **1** and its analogues were redissolved in 1 mL of methanol including 10 μg/mL of bisphenol A-d_{16}.[40]

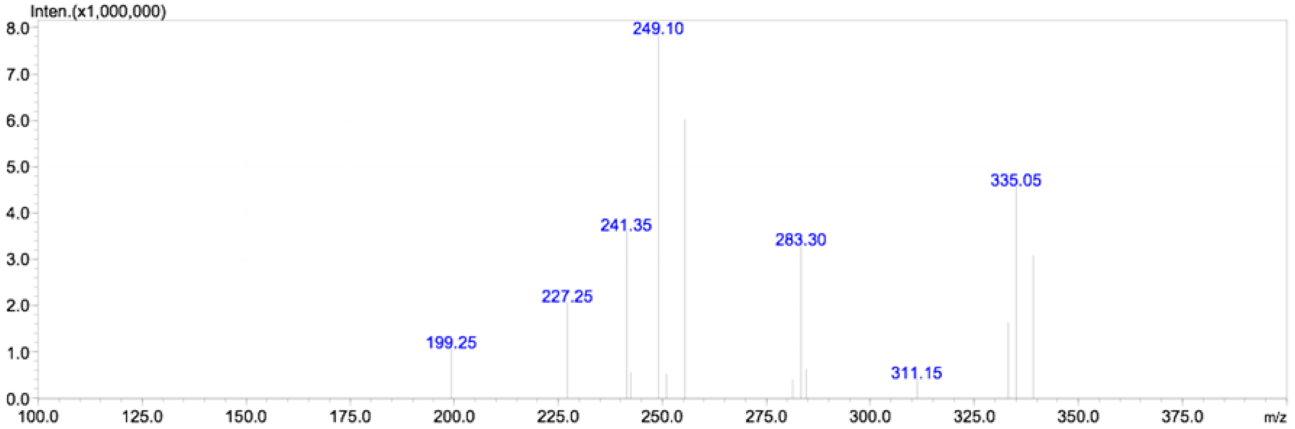
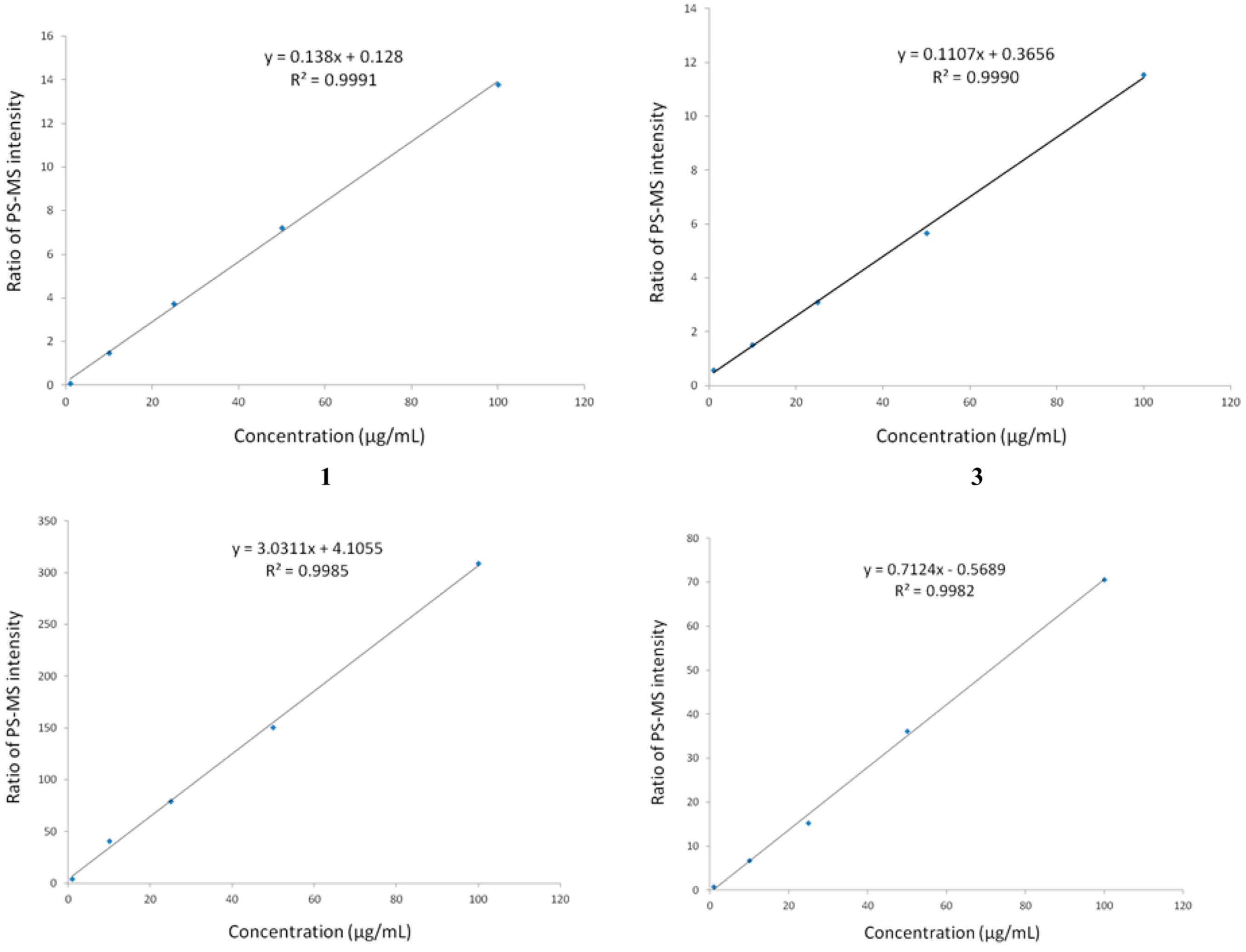


Figure 3. PS-MS spectra of **1** and its analogues (10 μg/mL). *m*/*z*: **3**, 199; **1**, 227; bisphenol A-d_{16}, 241; **2**, 249; **4**, 335.



1 **3**

2 **4**

Figure 4. Calibration curves of **1**, **2**, **3**, and **4** in the range of 1−100 μg/mL using bisphenol A-d_{16} as I.S.

LC-MS/MS Analysis. The samples were also analyzed by LC-MS/MS to investigate the accuracy of PS-MS. The sample pretreatment methods were similar to those of the PS-MS analysis. LC-MS/MS conditions were similar to those in the literature.[22]

The column used was a 150 mm × 2.0 mm i.d., 5 μm, Shim-pack VP-ODS (Shimadzu). The mobile phase was methanol:water, with 0.1% ammonium hydroxide (v/v). A gradient elution was adopted starting with 30% MeOH and reaching 90% MeOH in 3 min, maintaining this percentage for 2 min, and finally taken to 30% MeOH and held for 4 min prior to the next injection. The column temperature was kept at 50 °C. The mobile phase flow rate was set at 0.4 mL/min, and the injection volume was 10 μL. MS conditions were as follows: MS scan range was *m*/*z* 100−500 using electrospray ionization (ESI) working in negative ion mode. Interface, DL, and heat block temperatures were 300, 250, and 400 °C, respectively. Nitrogen was used as a sheath gas, ion sweep gas, and auxiliary gas at flow rates of 40, 10, and 55 arbitrary units, respectively. Argon used as a collision-induced dissociation (CID) gas was approximately 1.5 mTorr, and the collision energy was 3.5 V. The deprotonated molecule $[M - H]^-$ was used as the precursor ion. Quantitation was made in MRM mode. The following channels were utilized: 227 > 211 for **1**; 249 > 108 for **2**; 241 > 223 for bisphenol A-d_{16}; 199 > 93 for **3**; and 335 > 265 for **4**. All collision energies (CE) were 25 V.

■ RESULTS AND DISCUSSION

Optimization of PS-MS Conditions. To study the effect of different solvents on the PS-MS response, different solvents, i.e., water, methanol (MeOH), ethanol (EtOH), ethyl ether (EtOAc), benzene, and their mixtures, were investigated using **1** as a model target on a filter paper matrix. Ten microliters of **1** standard solution in methanol (10 μg/mL) was dropped on triangular filter paper. After being dried by N_2, spray solvent was dropped on the paper, and voltage was then applied to finish PS-MS. The results showed that the MS signal of **1** was too low when ethyl ether and water were used as solvents, and the result with benzene as the solvent was lower than with methanol and ethanol. Methanol was the best solvent for PS-MS analysis of **1**. The responses in all mixed solvents were lower than that in methanol.

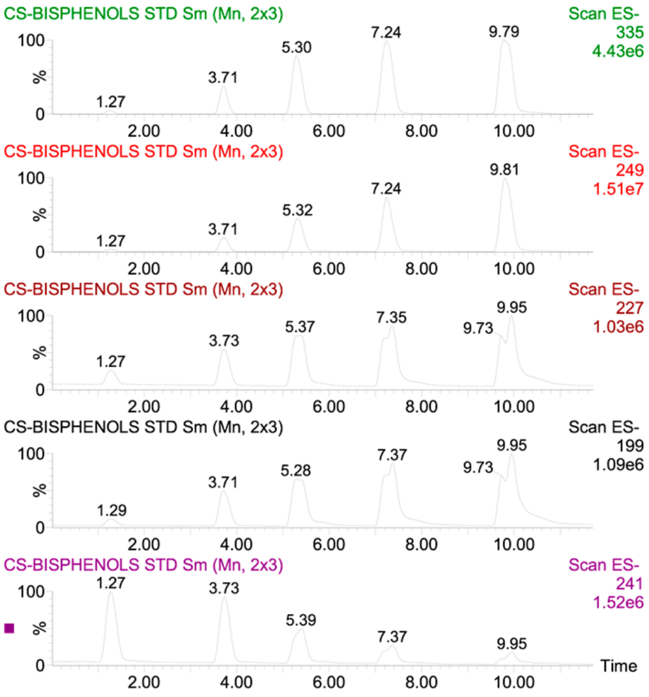


Figure 5. Chromatograms of **1**, **2**, **3**, **4**, and bisphenol A-d_{16} by PS-MS.

Table 1. Comparison Results between PS-MS and HPLC-MS/MS

sample	PS-MS (mg/kg) (*n* = 5)		HPLC-MS/MS (mg/kg) (*n* = 5)	
	1	2	1	2
paper cup	12.2 ± 0.7	nd[a]	11.8 ± 0.3	nd
baby bottle 1	nd	7.9 ± 0.3	nd	8.5 ± 0.2
baby bottle 2	34.6 ± 2.5	nd	36.2 ± 1.3	nd
food packaging paper	67.2 ± 5.7	nd	69.9 ± 2.4	nd
food packaging film	32.3 ± 1.7	nd	33.7 ± 0.9	nd

[a] Not detected.

Table 2. Sample Analysis Results by PS-MS

				PS-MS quantitative results (*n* = 5) (μg/g)	
sample no.	sample	1	2	1	2
1	PC 1	positive	negative	12.2 ± 0.7	nd[a]
2	PC 2	positive	negative	22.7 ± 1.2	nd
3	PC 3	positive	negative	14.5 ± 0.9	nd
4	PC 4	positive	negative	18.7 ± 1.2	nd
5	PC 5	positive	negative	25.6 ± 1.4	nd
6	PlC 1	positive	negative	20.6 ± 1.3	nd
7	PlC 2	positive	negative	42.7 ± 3.0	nd
8	PlC 3	positive	negative	27.8 ± 1.3	nd
9	PlC 4	positive	negative	32.2 ± 0.9	nd
10	BB 1	negative	positive	nd	7.9 ± 0.3
11	BB 2	positive	negative	34.6 ± 2.5	nd
12	BB 3	negative	negative	nd	nd
13	BB 4	positive	negative	30.1 ± 3.0	nd
14	MWB 1	positive	negative	67.2 ± 5.7	nd
15	MWB 2	positive	negative	43.4 ± 3.9	nd
16	MWB 3	positive	negative	35.1 ± 1.9	nd
17	MWB 4	positive	negative	10.3 ± 0.7	nd
18	EDB 1	positive	negative	22.2 ± 1.3	nd
19	EDB 2	positive	negative	10.7 ± 1.0	nd
20	EDB 3	positive	negative	34.1 ± 1.6	nd
21	EDB 4	positive	negative	9.2 ± 0.8	nd
22	FPF 1	positive	negative	32.3 ± 1.7	nd
23	FPF 2	positive	negative	34.7 ± 2.9	nd
24	FPF 3	positive	negative	18.9 ± 1.1	nd
25	FPF 4	positive	negative	24.3 ± 1.1	nd
26	FPF 5	positive	negative	13.2 ± 0.9	nd
27	IPC 1	positive	negative	42.7 ± 2.7	nd
28	IPC 2	positive	negative	40.3 ± 2.9	nd
29	IPC 3	positive	negative	35.1 ± 1.4	nd
30	IPC 4	positive	negative	37.9 ± 2.1	nd
31	IPC 5	positive	negative	46.8 ± 2.7	nd
32	IPC 6	positive	negative	27.3 ± 2.0	nd
33	FPP 1	positive	negative	67.2 ± 5.7	nd
34	FPP 2	positive	negative	43.4 ± 3.9	nd
35	FPP 3	positive	negative	46.1 ± 2.7	nd
36	FPP 4	positive	negative	27.5 ± 1.8	nd
37	FPP 5	positive	negative	38.1 ± 2.7	nd
38	FPP 6	positive	negative	21.4 ± 1.5	nd
39	FPP 7	positive	negative	17.8 ± 1.5	nd
40	DS 1	positive	negative	51.9 ± 3.7	nd
41	DS 2	positive	negative	45.2 ± 2.6	nd
42	DS 3	positive	negative	47.8 ± 3.2	nd

[a] Not detected.

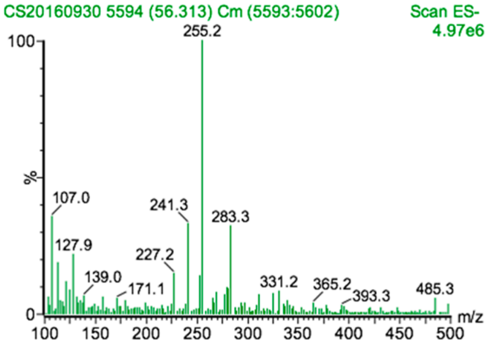


Figure 6. PS-MS spectra of baby bottle with bisphenol A-d_{16}.

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The selection of spray volume plays an important part in PS-MS detection. The effect of different spray volumes of methanol, i.e., 5, 10, 15, and 20 μL, on the MS signal of **1** at the same concentration (10 μg/mL) was investigated at a −2.5 kV spray voltage using filter paper as the matrix. The results showed that the response intensity of **1** was minimized when the spray volume was 5 μL. When the spray volume was 10 μL, the response intensity was good, but when it was 15 μL, the response started to drop off. At 20 μL, the response was close to the minimum. When the volume was too small (5 μL), the formation of stable Taylor cone jets was difficult. However, a larger volume will form multiple Taylor cone jets, reducing the sensitivity.[30] Ten milliliters of spray volume was selected for subsequent experiments.

The spray voltage of PS-MS must be chosen carefully in the negative ion mode. Optimization of the spray voltage for the detection of bisphenols was completed. The effects of different spray voltages on PS-MS responses showed that −2.5 kV was optimal for the detection of bisphenols. When the voltage was low, ionization efficiency was limited. A higher voltage will also affect the sensitivity because the onset voltage of electrical discharge is always lower than that of electrospray ionization, seriously degrading ESI performance.

Because the temperature of the MS source of ZQ 2000 also affects the sensitivity due to the formation of solvent adduct ion and its effect on ion transmission, different source temperatures, i.e., 50 °C, 70 °C, 85 °C, 100 °C, 120 °C, and 150 °C, were investigated. The results demonstrated that 100 °C gave the best PS-MS response at $[M - H]^-$ of **1**. Because there was a small spray solvent volume, a higher source temperature was adverse during ion transmission due to thermal degradation. In addition, ion transmission efficiency will also be reduced when the temperature is low. Therefore, 100 °C was selected for subsequent experiments.

Pretreatment of the Plastic Surface for in Situ PS-MS Analysis for Rapid Screening. For in situ PS-MS analysis, different sample matrixes, such as plastic and paper products, significantly affected the sensitivity. For paper products, such as paper cups, bisphenols in the thin coating can be easily extracted by methanol and spray ionization. However, plastic was difficult to analyze by PS-MS only using methanol as the spray solvent. Its surface was smooth (Figure 2A), and methanol cannot effectively extract bisphenols from the matrix. To effectively analyze plastic products in situ by PS-MS, we used dichloromethane to destroy the smooth surface and extract bisphenols to the surface. The SEM images of untreated and treated surfaces of a baby bottle containing **1** are presented in Figure 2, which shows that the surface rugosity is completely different. After treatment, the specific surface area increased dramatically. In addition, bisphenols can also be extracted to the surface, increasing the detection sensitivity. To further optimize the experimental conditions, in situ PS-MS responses of **1** were compared over different treatment times, such as 30 s, 1 min, 3 min, 5 min, and 10 min. The results showed that the response of 1 min treatment was the highest. With increased treatment time, the response decreased. With 5 min of treatment, the response reduced substantially, and at 10 min there was no PS-MS response. When treated with dichloromethane, there are two procedures: (1) The smooth surface is destroyed and more **1** is exposed on the surface; and (2) **1** on the surface diffuses into the solvent. Competition between the two procedures affects the amount of **1** on the surface. When the treatment time was long, almost all the **1** on the surface diffused into the solvent. Therefore, there was no PS-MS response.

Quantitative Analysis by PS-MS. A typical PS-MS mass spectrum of mixed standards is shown in Figure 3. The calibration curves of bisphenols are shown in Figure 4. The chromatograms of standards at different concentrations and I.S. are shown in Figure 5.

In the range of 1−100 μg/mL for **1**, **2**, **3**, and **4**, the correlation coefficients are greater than 0.998. The limits of detection (LODs) were 0.1, 0.1, 0.3, and 0.1 μg/mL for **1**, **2**, **3**, and **4**, respectively. Using baby bottle extract without bisphenols as the matrix, the LODs were almost the same as those of the diluted standards, i.e., 0.1, 0.2, 0.3, and 0.2 μg/mL for **1**, **2**, **3**, and **4**, respectively. A comparison of typical samples analyzed by PS-MS and HPLC-MS/MS is given in Table 1.

The quantitative results of PS-MS are similar to those of HPLC-MS/MS, suggesting that PS-MS quantitative analysis is useful for the rapid determination of bisphenols in food packaging products. However, the repeatability by PS-MS (RSD: 8.4%), especially for plastic products, is lower than that of HPLC-MS/MS (RSD: 3.5%). Nonvolatile plastic matrix effects may be a major factor affecting effective ionization. Therefore, more effective sample pretreatment is necessary for accurate quantitation by PS-MS.

Application of PS-MS for the Analysis of Bisphenols. Forty-two samples were analyzed after in situ rapid screening and then quantitated by PS-MS. The results are listed in Table 2. A typical PS-MS spectrum of a sample is shown in Figure 6.

The results demonstrate that **1** is still a major chemical contaminant in food packaging products, including paper products and plastic products. **2** likewise appeared in products. **3** and **4** were not been detected.

The increasing awareness regarding safety to bisphenol A and its analogues requires methods capable of handling numerous samples in a short time frame. From the results obtained in this study, the PS-MS method presented is capable of rapidly screening for **1**, **2**, **3**, and **4** at a rate of approximately 1 min/sample. Moreover, it has been demonstrated that quantitation of bisphenols in food packaging products by PS-MS using deuterated internal standards is feasible. The results of sample analyses showed that the food packaging products still use **1** in raw material in China, and as a replacement for **1**, **2** has entered the market in China.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jafc.7b02061.

Picture of the XYZR moving platform and PS-MS response under different conditions (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

PS-MS, paper spray ionization mass spectrometry; BPA, bisphenol A; BPS, bisphenol S; BPF, bisphenol F; BPAF, bisphenol AF; EFSA, European Food Safety Authority; CEF, Food Contact Materials, Enzymes, Flavourings and Processing Aids; t-TDI, temporary tolerable daily intake; AMS, ambient mass spectrometry; DESI, desorption electrospray ionization; DCBI, desorption corona beam ionization

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