Environmental Science & Technology

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Detection and Occurrence of Chlorinated Byproducts of Bisphenol A, Nonylphenol, and Estrogens in Drinking Water of China: Comparison to the Parent Compounds

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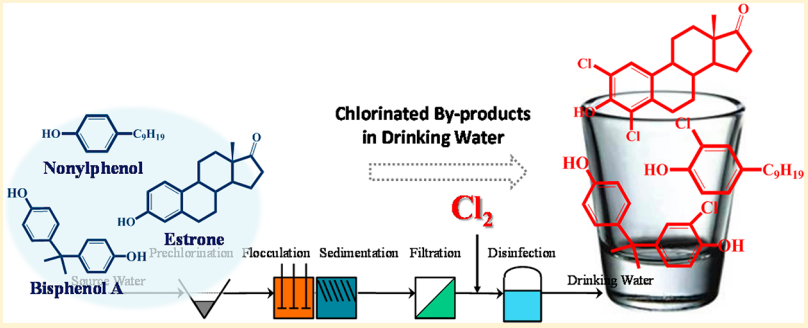
Supporting Information



ABSTRACT: This study applied a sensitive dansylation LC-MS/MS method to the investigation on the occurrence of bisphenol A (BPA), nonylphenol (NP), estrogens (E1 and E2), and their 11 chlorinated byproducts in 62 drinking water treatment plants (DWTPs) of 31 major cities across China. BPA (4.7−512 ng/L), NP (8.2−918 ng/L), and E1 (ND-9.9 ng/L) were widely detected in source waters, E2 was detected in less than half of the samples (ND-3.2 ng/L), while chlorinated byproducts were only detected in source waters of two DWTPs. In drinking water, chlorinated BPAs and monochloro-NP (MCNP) were detected in more than half of the samples with concentrations of 0.2−26.7 ng/L for monochloro-BPA (MCBPA), ND-6.3 ng/L for dichloro-BPA (DCBPA), ND-7.7 ng/L for trichloro-BPA (TCBPA), ND-4.8 ng/L for tetrachloro-BPA (TBBPA), and ND-13.3 ng/L for MCNP, while dichloro-E1 (DCE1, ND-0.2 ng/L) and dichloro-NP (DCNP, ND-1.6 ng/L) were less frequently detected (10/62 and 4/62). The production of chlorinated NPs in DWTPs was mainly influenced by the amount of NP in source water and chlorine added, while the concentrations of chlorinated BPAs in drinking waters were only found to be significantly correlated with those of BPA in source waters. Advanced treatment processes could be effective techniques for reducing target chlorinated byproducts in drinking water. This is the first report on the occurrence of chlorinated byproducts of BPA, NP, and estrogens in drinking water, and these chemicals should be considered when assessing the human risk of their parent compounds.

INTRODUCTION

Endocrine-disrupting compounds, represented by bisphenol A (BPA), nonylphenol (NP), and estrogens, have attracted considerable attention for their estrogenic activity in disrupting the endocrine systems of living organisms such as fish, wildlife, and human beings.[1−6] Among these compounds, natural estrogens including estrone (E1) and 17β-estradiol (E2) elicit high estrogenic activity and are mainly excreted by human and livestock as initial compounds and conjugates.[7,8] BPA and NP are both widely used in plastics as additives and antioxidants. BPA also plays an important role in the production of epoxy−resins and polycarbonate plastics, while NP can be produced in the environment[9] as a byproduct of nonylphenol ethoxylates, which are widely used in domestic detergents, pesticide formulations, and industrial settings.[10] Therefore, these two chemicals are continuously introduced into the aquatic environment via municipal wastewater and industrial discharge. Although the estrogenic potentials of BPA and NP are four and more orders of magnitude lower than that of E2,[11−13] the literature has documented the adverse effects on animals following exposure to low doses of NP and BPA, including developmental and reproductive toxicity, altered body weight, cancers, and so on.[14−17] In particular, BPA has been associated with disorders in women including obesity, recurrent miscarriages, and polycystic ovarian syndrome, etc. by epidemiological studies.[18]

Received: April 7, 2013
Revised: August 28, 2013
Accepted: September 6, 2013
Published: September 6, 2013

These compounds have been well investigated in environmental matrices and commonly detected in raw water and drinking water.[19−23] According to a survey on drinking water treatment plants (DWTPs) in Germany,[20] BPA and NP were detected in all 31 source water samples with a concentration range of 0.5−14 ng/L and 6.7−134 ng/L, respectively, and E1 was detected at 29 out of 31 sites surveyed with a maximum level of 4.1 ng/L. It is well-known that chlorination is an essential treatment in water supply systems, and phenolic compounds are reactive with hypochlorite.[24] Laboratory experiments have documented that phenolic compounds including BPA, E2, and NP can form chlorinated products during chlorination procedure, and MCBPA, DCBPA, TCBPA, TeCBPA, MCNP, DCNP, DCE2, and MCE1 as well as DCE1 have been identified.[25−27] All these emerging chlorinated byproducts show estrogenic activity,[28] and the estrogenic activities of MCBPA and DCBPA were even greater than their parent compound.[29,30] Thus the occurrence of these chlorinated byproducts is of concern, and three studies have made attempts to detect the chlorinated byproducts in DWTPs. LC-MS-MS analysis combined with solid phase extraction was used to analyze BPA, NP, and their halogenated derivatives in the effluents of DWTPs in France[31] and Spain,[32] and online solid phase extraction coupled with LC-MS analysis was adopted by another study to measure chlorinated BPA derivatives in water samples.[33] None of these studies detected chlorinated byproducts of BPA or NP in drinking waters, possibly due to the low concentrations, and a more sensitive analytical method is necessary.

Dansyl chloride is highly reactive with phenolic hydroxyl groups, and the dansyl derivatives of estrogens and BPA have been reported to exhibit greater sensitivities than estrogens and BPA when using the LC-MS(/MS) method.[34,35] In this study, we applied the sensitive dansylation UPLC-MS/MS method to the monitoring of chlorinated byproducts of BPA, NP, and estrogens in source water and drinking water, and we carried out a national investigation aiming at examining the occurrence of chlorinated BPAs, chlorinated NPs, and chlorinated estrogens in drinking water in comparison with their parent compounds. This paper fulfilled the data gap concerning the concentration distribution of these chlorinated byproducts across China, which provides a scientific basis for understanding and making policy decisions on the elimination of endocrine-disrupting phenolic compounds.

MATERIALS AND METHODS

Standards and Reagents. BPA, NP, E1, E2, and their 11 chlorinated byproducts are shown in Supporting Information Figure S1. E1 and E2 were purchased as powders from Wako Pure Chemical Industries, Ltd. (Tokyo, Japan). 4-NP was purchased as a technical-grade product from Hayashi (Tokyo, Japan, CAS 84852-15-3). BPA was obtained from Kanto Chemical Co., Tokyo. Tetrachloro-BPA (TeCBPA) was purchased from TCI Corp. (Tokyo, Japan). Surrogate standards including E1-d4, E2-d3, 4-n-NP, and BPA-d4 were supplied by C/D/N Isotope (Montreal, Canada).

Chlorinated byproducts including 4-chloro-BPA (MCBPA), dichloro-BPA (DCBPA, mixture of 2,6-dichloro-BPA and 2,6′-dichloro-BPA, 1/0.25), trichloro-BPA (TCBPA), 2-chloro-NP (MCNP), 2,6-dichloro-NP (DCNP), 2-chloro-E1, 4-chloro-E1, and 2,4-dichloro-E1 (DCE1) were synthesized and purified according to methods reported previously.[11,36] 4-Chloro-E2 (MCE2) and 2,4-dichloro-E2 (DCE2) were synthesized in our previous study.[27] The purity of all commercial and synthesized compounds was 95% or higher. The synthesized products were characterized by ESI-UPLC-MS. NMR spectra were taken on a Bruker A-VANCE III (1H, 400 MHz) spectrometer. Details of synthesis methods and NMR analytical results are described in the Supporting Information.

Dansyl chloride (DNS) was obtained from Sigma-Aldrich. Sodium sulfite, sodium chloride, sodium carbonate, sodium hydroxide, magnesium sulfate, hydrochloric acid (36−38 ω/%), and sodium hypochlorite solution (>8% available chlorine) were analytical grade and purchased from Beijing Chemical Works. Formic acid, methanol (MeOH), acetonitrile, ethyl acetate, acetone, dichloromethane, n-hexane, methyl tert-butyl ether (MTBE), tetrahydrofuran, diisopropyl ether, and diethyl ether were HPLC grade and purchased from Fisher Chemical Co. (Beijing, China). HPLC-grade water was prepared using a Milli-Q RC apparatus (Millipore, Bedford, MA, USA). A fresh water sample was loaded onto an Oasis HLB (200 mg, 6 mL) solid phase extraction (SPE) cartridge and eluted for derivatization. The cartridges were purchased from Waters (Waters, Milford, MA, U.S.).

Description of DWTPs and Sampling. Our investigation includes 62 DWTPs in 31 major cities across China. Information on source water, temperature, sampling time, and residual chlorine is provided in Supporting Information Table S1. DWTP locations are shown in Figure S2. All DWTPs employ treatments of prechlorination, flocculation, sedimentation, filtration, and disinfection. Most of the facilities used chlorine or sodium hypochlorite as the disinfectant, except one DWTP that used chlorine dioxide. The source water samples of 54 DWTPs were surface water, while 8 DWTPs used groundwater. From August 2011 to March 2012, grab source water and drinking water samples for each DWTP were collected in 4 L glass containers, previously rinsed with Milli-Q water and methanol. For drinking water, we added 20 mg of sodium thiosulfate to 1 L of water for the removal of residual chlorine. Afterward, the samples were stored with dry ice during transportation and extracted on the same day when they were sent to the lab.

Preparation of Samples and Working Standards. 100 mL of water samples spiked with 1 ng of each surrogate standard was extracted through an Oasis HLB cartridge, which was previously conditioned with 20 mL of MTBE, 20 mL of MeOH, and 5 mL of distilled water, at a flow rate of 5−10 mL/min. The cartridge was washed with 5 mL of distilled water and then was dried under a flow of nitrogen. A volume of 4 mL of MTBE/MeOH (1:1, v/v) was used to elute the analytes. The extracts were then dansylated according to the method reported in a previous paper[34] and redissolved with 0.5 mL of acetonitrile prior to UPLC-MS/MS analysis. Details of danslyation are provided in the Supporting Information. Working standard solutions were prepared at 1 ng/mL for each analyte by dilution and dansylation of the stock solutions. The same dansylation procedure was used for sample extracts and working standards.

UPLC-ESI-MS-MS Analysis. The UPLC apparatus was an Acquity Ultra Performance LC (Waters, Milford, MA, U.S.). Target analytes were separated using a Waters Acquity UPLC BEH C18 column (100 × 2.1 mm, 1.7 μm particle size) (Milford, MA, USA). The column was maintained at 40 °C and a flow rate of 0.3 mL/min, and the injection volume was 5 μL. Acetonitrile and water containing 0.1% formic acid were chosen as the mobile phases of HPLC. Gradient conditions were

Table 1. Comparison of Instrumental Detection Limits (IDLs, μg/L) and Signal Suppression (%) for Target Analytes by LC-MS-MS Methods with and without Dansylation

	IDL[a] dansylated	IDL[b] nondansylated	improvement ratio of IDL	signal suppression dansylated	signal suppression nondansylated
E1	0.001	0.03	30	−6%	61%
2-chloro-E1	0.004	0.2	50	−8%	20%
4-chloro-E1	0.003	0.3	100	−6%	9%
DCE1	0.008	0.05	6	−5%	9%
E2	0.001	0.2	200	−5%	75%
MCE2	0.002	0.5	250	−9%	37%
DCE2	0.002	0.6	300	−7%	17%
BPA	0.001	0.03	30	−9%	61%
MCBPA	0.001	0.01	10	−6%	50%
DCBPA	0.002	0.01	5	−5%	27%
TCBPA	0.001	0.005	5	−14%	41%
TeCBPA	0.001	0.005	5	−9%	30%
NP	0.005	0.05	10	−11%	45%
MCNP	0.01	0.04	4	−10%	33%
DCNP	0.02	0.04	2	−4%	74%

[a]Estimated by the injection of 5 pg standard analyte. [b]Estimated by the injection of 25 pg standard analyte.

initiated with 60% acetonitrile followed by a linear increase to 75% acetonitrile in 0.5 min. After being increased to 80% in 6 min, acetonitrile was increased to 95% in 0.5 min and then to 100% in 2 min and kept isocratic for 2 min.

Mass spectrometry was performed using a Premier XE tandem quadrupole mass spectrometer (Waters) equipped with a Z-Spray ionization (ESI) source and operated in the positive ion (PI) mode. The two most abundant multiselected reaction monitoring (MRM) transitions, cone voltages, and collision energies were optimized for each analyte by infusing dansyl derivatives of standards, which had been purified by hexane extraction, into the mass spectrometer (Table S2). Common MS parameters were as follows: capillary voltage, 3.2 kV (ESI +); source temperature, 120 °C; desolvation temperature, 450 °C; source gas flow, 50 L/h; and desolvation gas flow, 800 L/h.

Quantification and Quality Control. Identification of the target analytes was accomplished by comparing the retention time (within 2%) and the ratio (within 20%) of the two selected precursor ion-produced ion transitions with those of standards. Quantification was accomplished using the multi-selected reaction monitoring (MRM) transitions. One procedure blank (Mili-Q water, 100 mL) with sample loading was analyzed per 10 samples to determine the background contributed during the entire procedure. Field blanks were performed by adding 2 mg of sodium thiosulfate to 100 mL of the same Mili-Q water, transporting the glass bottle to a site, transferring the water to a sampling container, and processing it as a sample. A total of six field blanks were analyzed, and the results were compared with those of procedure blanks. In order to minimize contamination, only pretreated glassware (400 °C, 4 h) were used throughout the study. SPE cartridges were prerinsed with MTBE and MeOH to minimize the contamination of the SPE procedure.

The entire analytical procedures were checked for accuracy, precision, reproducibility, linearity, matrix effects, and limits of quantification (LOQs). Recoveries were estimated by triplicate analysis of field water samples spiked with 150 ng/L for each target chemical and with low levels similar to the concentrations found in samples previously analyzed (25 ng/L for BPA, 50 ng/L for NP, 1 ng/L for MCBPA, DCBPA, TCBPA, and 0.2 ng/L for other analytes), respectively. The interday variation of recoveries was determined by repeating the recovery experiments at low level with triplicate samples at three separate days. Accuracy was determined during interday and intraday assessments. The matrix effects of both dansylation UPLC-MS/MS method and nondansylation method were evaluated as the ratio of the slope of matrix-matched standard curves to that of standard solution curves as described in previous papers,[37,38] and the details were described in the Supporting Information. LOQs of all target analytes, except for BPA and NP, were estimated based on the water sample enrichment factor of 200 and the peak-to-peak noise of the baseline near the analyte peak obtained by analyzing field samples (spiked with each analyte at 0.2 ng/L) using ten as the minimal value of signal-to-noise. While the LOQs of BPA and NP were calculated as three times the highest blank value. The instrument was calibrated with each analyte at 0.005, 0.01, 0.05, 0.1, 0.5, 2, 10, 50, and 100 μg/L. Calibration curves of all target analytes provided adequate linearity as shown by the correlation coefficients, which are greater than 0.995. Appropriate dilutions were performed in order to obtain a signal within the linear range of NP. Quantification of the analytes was achieved using an internal standard method with calibration against standard solutions. BPA-d_4 was used as the surrogate standard for BPA and chlorinated BPAs; 4-n-NP for NP and chlorinated NPs; E1-d_4 for E1, 2-chloro-E1, 4-chloro-E1, and DCE1; and E2-d_3 for E2, MCE2, and DCE2.

Statistical Analysis. Pearson's correlation analysis was used to identify the significance of relationships between the concentrations of chlorinated byproducts and the concentrations of parent compounds, residual chlorine, total organic carbon (TOC), or temperature of water samples. The statistical level of significance is $p \leq 0.05$. When the concentrations were below the corresponding LOQs, one-half of the LOQs were used for calculation and statistical analysis.

RESULTS AND DISCUSSION

Derivatization and Method Validation. In this study, a dansylation LC-MS/MS method[34] was for the first time applied to the simultaneous determination of chlorinated byproducts of BPA, NP, and estrogens in source and drinking water samples to achieve high analytical sensitivity. Ionization and fragmentation of the isolated dansyl derivatives in electrospray tandem mass spectrometry resulted in protonated molecular ions of

their dansyl derivatives. Double DNS derivatives were observed at m/z 695, 729, and 763 for BPA, MCBPA, and DCBPA, respectively, while only single DNS derivatives were observed at m/z 566 and 600 for TCBPA and TeCBPA, presumably due to the steric hindrance as exemplified by the dansylation of triiodo- and tetraiodothyroacetic acids.[39] However, all molecular ions of dansylated target compounds produced the same major product ions at m/z 171 ([dimethylaminonaphthalene $+H]^+$) and m/z 156 ([dimethylaminonaphthalene-CH_3+H]$^+$) from the cleavage of a C−S bond in the dansyl portion of the molecule and the loss of a methyl group from the m/z 171. The instrument detection limits (IDLs) for danysl derivatives of chlorinated byproducts were defined as the concentration of standard solution producing a peak with a signal-to-noise (S/N) ratio of 3. The IDLs of the chlorinated products of BPA, NP, and estrogens were estimated to be 0.001−0.002, 0.01−0.02, and 0.002−0.008 ng/mL, respectively, by injecting 5 pg each target analyte (Table 1). As displayed in Table 1, the IDLs of chlorinated estrogens except for DCE1 were significantly lower (50−300 times) than those using direct UPLC-(ESI-)-MS/MS analysis without dansylation, and the IDL of DCE1 was decreased about 6 times. The sensitivity improvements for analyzing chlorinated BPAs and chlorinated NPs were limited to 5−10 times and 2−4 times, respectively, lower than those for analyzing BPA (30 times) and NP (10 times). UPLC-MS/MS MRM chromatograms of a water sample spiked with target analytes at low levels (0.05 ng/mL for NP and chlorinated NPs and 0.01 ng/mL for other analytes) were shown in Supporting Information Figure S3.

In the recovery experiment spiked with 150 ng/L for each analyte, several solvent mixtures were tested for elution from the HLB cartridge to optimize the simultaneous extraction of 11 chlorinated byproducts together with their parents. When pure MeOH was used as the elution solvent, BPA, estrogens, and their chlorinated products show good recoveries (73−133%), but the recoveries of NP and its chlorinated byproducts were lower than 48%; and when using pure MTBE as the elution solvent, chlorinated BPAs and chlorinated estrogens showed relatively lower recoveries (42−76%), while the recoveries for NP and its chlorinated byproducts (86−108%) were largely improved as displayed in Table S3. Ultimately, a mixture of MTBE and MeOH (v/v, 1:1) was chosen for the elution from the HLB cartridge to achieve satisfactory recoveries (72−123%) for all target analytes. Since matrix effects are a general problem in LC-MS/MS analysis, potential matrix effects were evaluated in this study. Less than 11% signal enhancement were observed for all target analytes when using the newly developed dansylation method combined with UPLC-(ESI+)-MS/MS (Table 1). This is significant since heavy levels of signal suppressions were found for target analytes and their chlorinated byproducts (9−75%) using direct UPLC-(ESI-)-MS/MS analysis (Table 1), while such improvement of signal suppressions would be partly contributed by the increase of retention time for some target analytes as reported in a previous paper.[40] The method recoveries of all target analytes spiked at low levels were between 67% and 110% in water samples with a relative standard deviation (RSD) of ≤12% from nine interday replicate determinations. Interday relative recoveries for all target analytes were all in the range of 92−109% with RSD ≤ 13% (Table 2). The LOQs were 0.02−0.05 ng/L for chlorinated BPAs, 0.1−0.3 ng/L for chlorinated NPs, and 0.02−0.08 ng/L for chlorinated estrogens and estrogens. BPA and NP were detected in both procedure and field blanks with less than 10% of the average concentrations in drinking water and their LOQs were 2.1 ng/L and 8.1 ng/L, respectively. Thus, the dansylation UPLC-MS-MS method was well applied for analyzing the chlorinated byproducts of BPA, NP, and estrogen, while this method needs a relatively long analysis time compared with UPLC-MS-MS analysis without derivatization.

Table 2. Method Quantification Limits (LOQs), Interday Absolute Recoveries, and Interday Relative Recoveries (n = 9) Spiked with Standards at Low Level[a]

	LOQ (ng/L)	interday absolute recoveries	interday relative recoveries
BPA	2.1	109 ± 4%	101 ± 8%
BPA-d_4	-	108 ± 6%	-
MCBPA	0.05	110 ± 6%	102 ± 7%
DCBPA	0.05	102 ± 5%	94 ± 7%
TCBPA	0.05	109 ± 10%	101 ± 10%
TeCBPA	0.02	105 ± 9%	97 ± 6%
NP	8.1	74 ± 7%	102 ± 11%
4-n-NP	-	72 ± 4%	-
MCNP	0.1	69 ± 10%	94 ± 7%
DCNP	0.3	67 ± 12%	92 ± 8%
E1	0.05	102 ± 8%	101 ± 10%
E1-d_4	-	101 ± 6%	-
2-chloro-E1	0.04	104 ± 9%	103 ± 5%
4-chloro-E1	0.08	99 ± 8%	98 ± 8%
DCE1	0.04	94 ± 10%	93 ± 10%
E2	0.02	82 ± 7%	109 ± 13%
E2-d_3	-	75 ± 3%	-
MCE2	0.02	69 ± 4%	92 ± 8%
DCE2	0.04	76 ± 3%	101 ± 12%

[a]25 ng/L for BPA, 50 ng/L for NP, 1 ng/L for MCBPA, DCBPA, and TCBPA, and 0.2 ng/L for other analytes.

In addition, technical NP is a mixture of approximately 20 para-substituted isomers with differently branched alkyl chains.[41] It has been reported that the isomeric composition of NP differs among producers,[42,43] and environmental degradation can lead to a shift in isomeric composition of NP, which may consequently lead to uncertainty of the quantification of NP in samples.[44] In this study, the signal differences between Hayashi-NP and NP standards from other producers were compared and found to be less than 8% (details in the Supporting Information).

Occurrence in Source Waters. The concentrations of target analytes in source water are shown in Table 2. BPA, NP, and estrogens were widely detected in source water samples of DWTPs. BPA and 4-NP were detected in all 62 source water samples, and the detection frequencies of E1 and E2β were 98% (61/62) and 61% (38/62), respectively. The mean concentrations of BPA, NP, E1, and E2 were 87.2 ng/L (4.7−512 ng/L), 204 ng/L (8.2−918 ng/L), 1.7 ng/L (0.1−9.9 ng/L), and 0.2 ng/L (ND-3.2 ng/L), which are generally higher than those detected in source water samples by most other studies.[18,32,45,46] The concentrations of BPA, NP, E1, and E2 in river water used for production of drinking water reported by a comprehensive investigation of 19 DWTPs across the U.S were <5−14 ng/L for BPA, <80−130 ng/L for NP, and <0.2−0.9 ng/L for E1.[45] Similar levels of BPA and NP were also found in the surface water of South Germany,[20] Canada,[46] and France,[31] while a study of 6 DWTPs in Spain revealed exceptionally high levels of NP (1.1−1.2 μg/L) in source waters.[32] The relative

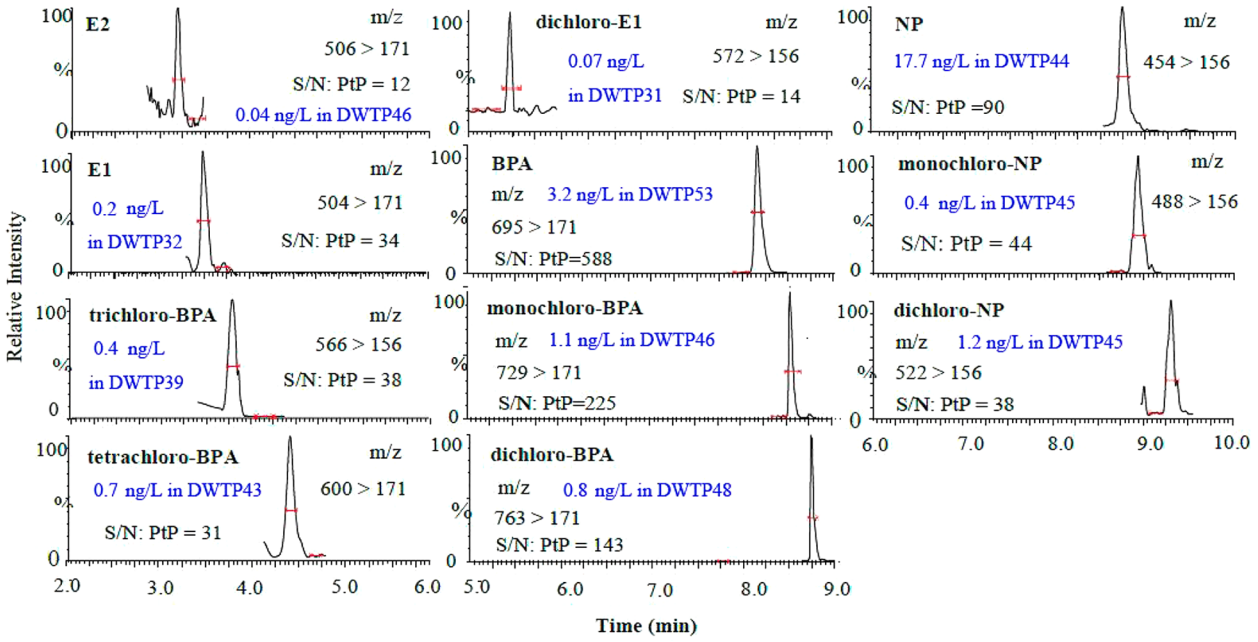


Figure 1. UPLC-MS/MS MRM chromatograms of the selected ions used for identification of analytes detected in drinking water samples.

high concentrations of these endocrine disrupting compounds in source water of China possibly due to the fact that BPA and NP have already been restricted in countries including Canada, France, and United States as hazards to human and environmental safety for several years,[47−51] while they were just listed as chemicals in need of control in the 2013 planning report of Chinese Environment Protection Department.[52] On the other hand, chlorinated analytes were hardly detected in source waters, except for two samples collected from DWTP17 and DWTP26 which were located at the downstream of sewage treatment plant. In DWTP17, MCBPA, DCBPA, and TCBPA were detected with the concentrations of 18.5 ng/L, 3.6 ng/L, and 1.9 ng/L, respectively. In DWTP26, DCBPA, TCBPA, TeCBPA, and MCNP were detected, and the concentrations were 0.4 ng/L, 2.2 ng/L, 0.2 ng/L, and 1.6 ng/L, respectively. There is no report on the occurrence of chlorinated phenolic compounds in natural waters which limited our comparison of concentrations.

Of the 62 source water samples, 8 were collected from groundwater, 31 were from reservoirs, and 23 were from river water. The average concentrations of BPA (106 ng/L) and NP (248 ng/L) in river water were the highest followed by those in reservoir water (79.8 ng/L for BPA and 190 ng/L for NP) and in groundwater (62.8 ng/L for BPA and 133 ng/L for NP). As for E1 and E2, the highest concentrations (2.5 ng/L for E1 and 0.4 ng/L for E2) were found in groundwater, and the concentrations in river water (1.4 ng/L for E1 and 0.1 ng/L for E2) were similar to those (1.6 ng/L for E1 and 0.1 ng/L for E2) in reservoir. Such different concentration distributions of estrogens and BPA, NP would be due to their different sources: estrogens in water environment mainly stem from animal manure and area pollution in agriculture,[53] while BPA and NP mainly originated from industrial discharging.[15,54,55] As expected, the concentrations of BPA and NP in the river source water for DWTPs were lower than the previously reported concentrations of BPA (2.2−1030 ng/L) and NP (130−8890 ng/L) in Chinese river since source waters are well protected in China.[56−59]

Occurrence in Drinking Water. Seven chlorinated chemicals (MCBPA, DCBPA, TCBPA, TeCBPA, MCNP, DCNP, and DCE1) and their parent compounds, BPA, NP, E1, and E2, were detected in at least one sample. Figure 1 shows the typical MRM LC-MS/MS chromatograms of field water samples. For detected analytes, BPA, NP, E1, and 4 chlorinated byproducts including MCBPA, DCBPA, TCBPA, and MCNP were detected in more than half of the drinking waters, and their concentrations in each DWTP are available in Supporting Information Table S4. Table 3 displays the detection frequencies, median, and maximum concentrations of all analytes in drinking waters.

Chlorinated BPAs and BPA. As displayed in Figure 2(a), the concentrations of BPA and its chlorinated byproducts MCBPA,

Table 3. Concentrations (ng/L) of Analytes Detected in Source and Drinking Water Samples (n = 62)

	source water			drinking water		
	median	max	number of detection	median	max	number of detection
BPA	51.3	512	62	10.8	128	60
MCBPA	ND	18.5	1	2.8	26.7	62
DCBPA	ND	3.6	2	0.7	6.3	61
TCBPA	ND	2.2	2	1.5	7.7	37
TeCBPA	ND	0.2	1	0.3	4.9	31
NP	123	918	62	27	558	55
MCNP	ND	1.6	1	0.5	13.3	57
DCNP	ND	ND	0	0.8	1.6	4
E1	1.1	9.9	62	0.3	1.7	53
2-chloro-E1	ND	ND	0	ND	ND	0
4-chloro-E1	ND	ND	0	ND	ND	0
DCE1	ND	ND	0	0.07	0.2	10
E2	0.1	3.2	38	0.04	0.1	31
MCE2	ND	ND	0	ND	ND	0
DCE2	ND	ND	0	ND	ND	0

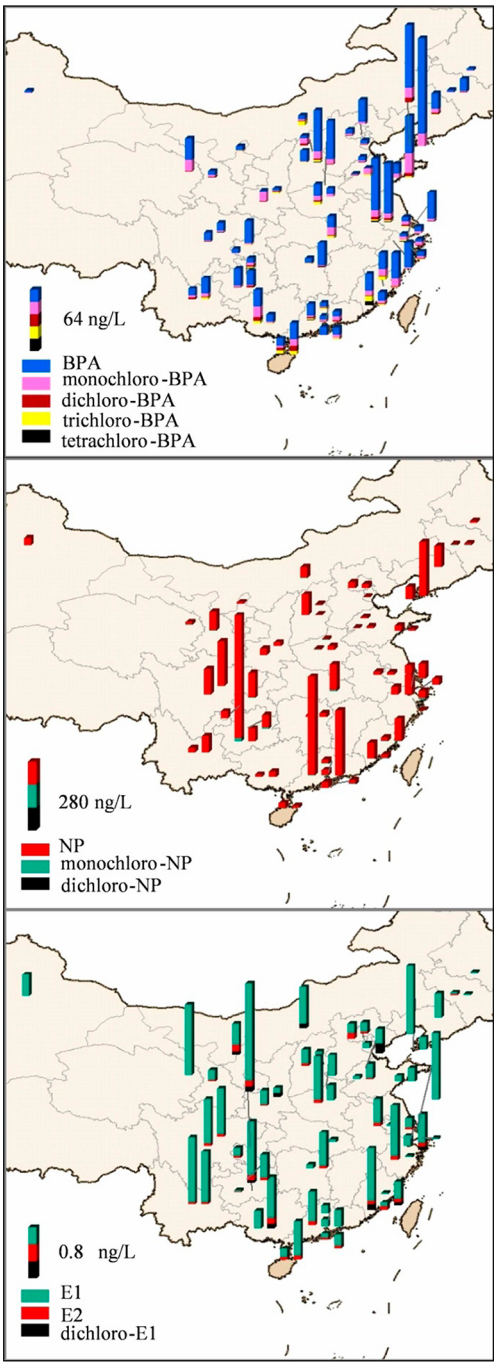


Figure 2. Concentrations of chlorinated byproducts of bisphenol A (BPA), nonylphenol (NP), and estrogens in the drinking water of different DWTPs: comparison to the parent compounds.

DCBPA, TCBPA, and TeCBPA in drinking water samples from 62 DWTPs in 31 cities in China were determined, and their detection frequencies were 97% (60/62) for BPA, 100% (62/62) for MCBPA, 98% (61/62) for DCBPA, 60% (37/62) for TCBPA, and 50% (31/62) for TeCBPA. Similar with BPA in source water, the concentration levels of BPA in drinking water (<2−128 ng/L) were higher than those in Southern Germany (0.5−2 ng/L), the French Poitou-Charentes area (2−16.9 ng/L), Malaysia (14 ng/L), Canada (<0.1 ng/L), and the U.S. (ND-25 ng/L).[20,45,46,60] Chlorinated BPAs occurred in drinking waters with average total concentration of 7.1 ng/L, which was more than 2 times lower than that of BPA. The concentrations of four chlorinated byproducts in drinking waters were in the range of 0.2−26.7 ng/L for MCBPA, ND-6.3 for DCBPA, ND-7.73 for TCBPA, and ND-4.9 ng/L for TeCBPA. It was demonstrated by the result of correlation analysis that the concentrations of both BPA (r = 0.66, p < 0.001) and chlorinated BPAs (p < 0.001, Figure 3(a)) in drinking waters were significantly influenced by the occurrence of BPA in source waters. The high total concentrations of BPA and its chlorinated byproducts were generally found in DWTPs located in more developed coastal cities such as DWTP55 (128 ng/L), DWTP54 (83.7 ng/L) and DWTP37 (68.2 ng/L).

Since chlorinated BPAs were not detected in most source water samples except for DWTPs 17 and 26 but were detected in drinking water samples, chlorinated BPAs must have been formed by the chlorination of BPA during the drinking water treatment process. As for DWTP 26, the sum of chlorinated BPAs in drinking water (5.8 ng/L) was 2-fold higher than that (2.8 ng/L) in source water. In DWTP 17, while the total concentration of chlorinated BPAs in drinking water (22.4 ng/L) was similar with that in source water (24.6 ng/L), obvious differences in the profiles for chlorinated BPAs were observed: MCBPA in drinking water (13.8 ng/L) became low compared with source water (18.5 ng/L) and vice versa for DCBPA, TCBPA, and TeCBPA (5.1 ng/L, 3.4 ng/L, 0.1 ng/L for drinking water, respectively, and 3.6 ng/L, 1.9 ng/L, <0.02 for source water, respectively). These results observed in the two plants also suggested the occurrence of chlorination of BPA. In addition, it has been reported that BPA and its chlorinated derivatives were eluted from pipes coated with epoxy resins during water chlorination as described in a recent study,[61] and BPA derivatives such as bisphenol A diglycidyl ether, which has been detected in environmental water,[62] might decompose to BPA during water treatment and then convert to chlorinated byproducts. Among the four chlorinated BPAs, MCBPA was the predominant compound in most drinking water samples (55/62) with an average level of 4.9 ng/L. However, in the remaining seven drinking water samples, TCBPA was the predominant chlorinated byproduct of BPA in six samples, and DCBPA was the most abundant in one water sample (Table S4).

Chlorinated NPs and NP. NP and MCNP were frequently detected in drinking water with the detection frequencies of 89% (55/62) and 92% (57/62), respectively, but DCNP was hardly detected in drinking water samples with detection frequency of 6.5% (4/62). Significant differences in the concentration of NP and its chlorinated byproducts among DWTPs (4.1−572 ng/L) are shown in Figure 2(b). The highest total concentrations were observed in DWTP12 (558 ng/L) in Southwest China and DWTP19 (446 ng/L) along with DWTP24 (296 ng/L) in South China. Statistical analysis result showed that the concentrations of both NP (r = 0.71, p < 0.001) and MCNP (r = 0.33, p < 0.01) in drinking waters were significantly correlated with the concentrations of NP in source waters. Since NP concentration in source waters positively correlated with the amounts of gross industrial production[63] of different located cities (p = 0.012), more attention should be paid to the NP pollution in developed areas. Similar with BPA, NP occurred in drinking water at relatively high levels (ND.-558 ng/L) compared with those in France (ND.-59.4 ng/L), Spain (25−90 ng/L), and the U.S. (ND.-100 ng/L).[32,33,36] The concentrations of MCNP ranged from <0.1 ng/L to 13.3 ng/L, which were much higher than those of DCNP (ND-1.6 ng/L) but far less than that of NP. In laboratory experiment, NP can

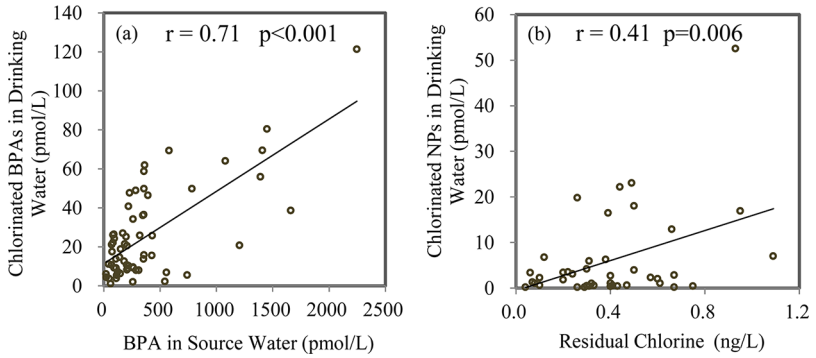


Figure 3. Correlation between (a) total molar concentrations of chlorinated BPAs in drinking water and those of BPA in source water and (b) total molar concentrations of chlorinated NPs and residual chlorine in drinking waters.

also reacted with hypochlorite but with a relatively slow reaction rate compared with BPA,[25,26] which could explain the relatively low concentrations of chlorinated NPs compared with NP. On the other hand, it has been reported that nonylphenol ethoxylates could be aerobically degraded to lower ethoxymers and then anaerobically biodegraded to NP in sewage treatment plant.[15] Considering nonylphenol ethoxylates have been well detected in source water,[57] anaerobic bacteria in a drinking water distribution system[64] might biotransform the nonylphenol ethoxylates with short chains to NP and contribute to NP and chlorinated NPs in drinking water.

Chlorinated Estrogens and Estrogens. E1 was detected in 85% (53/62) of the drinking water samples, while E2 was detected in less than half of the samples (31/62). Of the five chlorinated estrogens, only DCE1 was detected in 10 out of 62 samples. As shown in Figure 2(c), the variance in total concentrations of estrogens and DCE1 among DWTPs was not as significant as for NPs and BPAs. The highest total concentrations of estrogens and their chlorinated byproducts occurred in DWTP9, where the concentrations of E1, E2, and DCE1 were 1.7 ng/L, 0.1 ng/L, and 0.1 ng/L, respectively. The mean concentrations of E1 and E2 in drinking water were 0.4 ng/L and 0.05 ng/L, respectively, which were slightly higher than those reported in the U.S. (<0.5 ng/L for E1 and E2) but comparable with Southern Germany (ND-0.6 ng/L for E1 and ND-2.1 ng/L for E2).[20,45] Trace levels of DCE1 were detected in drinking water samples (ND-0.1 ng/L) compared to E1 and E2.

It has been demonstrated that various factors such as chlorine content, TOC, and temperature can also affect the formation of chlorinated byproducts.[65] Therefore, we made an attempt to correlate the total molar concentration of chlorinated BPAs and chlorinated NPs with residual chlorine, TOC, or temperature. It was found that the total molar concentrations of chlorinated NPs significantly increased with the levels of residual chlorine (p = 0.006) in drinking waters (Figure 3(b)), while no correlation was found with the content of TOC in source waters or the average temperature of source and drinking waters (Table S5), suggesting the amount of chlorine added could be an important influencing factor. However, no significant correlation was found between the concentrations of chlorinated BPAs and residual chlorine or other factors by linear correlation analysis (p > 0.5) (Table S5). It is well-known that advanced water treatment processes such as ozonation and granular activated carbon (GAC) can effectively remove trace hydrophobic organic compounds including BPA, NP, and MCNP.[32,66−69] In this study, BPA, NP, E2, TCBPA, TeCBPA, and chlorinated estrogens were not detected in the drinking water of DWTP49 in which ozone was used, and the concentrations of E1, MCBPA, DCBPA, and MCNP were relatively low (0.05 ng/L, 1.0 ng/L, 0.6 ng/L, and 0.4 ng/L) compared with DWTP48, even though the concentrations of BPA and NP in source water of DWTP49 were higher than those in DWTP48 (Table S4). Therefore, advanced treatment processes are expected for reducing these endocrine disrupting compounds and chlorinated byproducts in DWTPs.

BPA, NP, and estrogens have been paid tremendous attention from research scientists and government panels due to their environmental ubiquity and potential health impacts. Besides BPA, NP, and estrogens, some of their chlorinated byproducts were also widely detected in drinking water samples although they occurred at lower levels than the parent compounds. It has been reported that MCNP elicited antiestrogenic activity,[26] and the estrogen receptor binding activities of MCBPA and DCBPA were reported to be much higher than that of BPA.[25,30] When calculating BPA equivalent (EQ_{BPA}) estrogenic activity (details in the Supporting Information), the average EQ_{BPA} value in drinking water was found to be higher than that in source water (Figure S4). Besides, a recent paper also reported that TCBPA and TeCBPA could elicit higher thyroid hormone activities than MCBPA and DCBPA.[70] Thus, it is necessary to consider the occurrence chlorinated BPAs and chlorinated NPs in the future risk assessment and standard making for drinking water safety. On the other hand, although DCE1 exhibits higher estrogenic activity than chlorinated BPAs, a low contribution to the total estrogenic activity could be expected in drinking waters considering its lower potency compared to E1 and E2[36] and its relatively low concentration and low detection frequency.

Thus, this work provides the first description of the occurrence of chlorinated byproducts of BPA, NP, and estrogens in DWTPs of major cities across China by applying the dansylation LC-MS/MS analysis method. The present work showed that humans are being exposed to chlorinated byproducts of BPA, NP, and estrogens together with their parent chemicals via intake of drinking water, and therefore monitoring of these chlorinated byproducts is recommended in future epidemiological studies for better understanding of their risk. Further studies on the detailed behaviors of endocrine-disrupting compounds and their chlorinated byproducts in water supply plants are needed to control the formation of chlorinated estrogenic chemicals.

■ ASSOCIATED CONTENT

Supporting Information

Detailed descriptions of target analytes, synthesis, dansylation procedure, nonylphenol standards and estimation of matrix effects and BPA equivalent estrogenic activity, figures and tables addressing method validation, parameters of drinking water treatment plants (DWTPs), correlations between analytes and parameters of DWTPs, and between concentrations of BPA, NP, estrogens, and their chlorinated byproducts in source water and drinking water of all DWTPs. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the National Special Funding Project for Water Pollution Control and Management of China [2009ZX07419-001] and the National Basic Research Program of China [2012BAD20B05] is gratefully acknowledged.

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