Suspect and nontarget screening of aromatic halogenated disinfection byproducts with emerging contaminants as possible precursors in drinking water distribution systems

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1 KEYWORDS

2 disinfection byproducts, drinking water, emerging contaminants, nontarget screening

ABSTRACT

The presence of emerging contaminants (ECs) is increasingly discharged into the aquatic environment and often cannot be removed by conventional water treatment processes. This presents challenges in detecting the various disinfection byproducts (DBPs) originating from ECs as possible precursors. This study used liquid chromatography coupled with time-of-flight mass spectrometry for suspect and non-target screening of ECs and DBPs simultaneously in the effluent of drinking water treatment plants and drinking water distribution systems (DWDS). A total of 41 ECs and 27 DBPs were identified with different confidence levels (levels 1-3). Among the identified ECs, pesticides, pharmaceuticals and personal care products accounted for approximately 63% of the ECs. Among the aromatic DBPs, halo-phenols and halonitrophenols are the predominant categories. Three ECs species (4-nitrophenol, 3-methyl-4-nitrophenol, and Enrofloxacin) and six of their confirmed DBPs (2,6-dichloro-4-nitrophenol, 2-bromo-6-chloro-4-nitrophenol, 2,6-dibromo-4-nitrophenol, 2-bromo-4-nitrophenol, 3-chloro-5-(chloromethyl)-4-nitrophenol) were simultaneously detected in the DWDS. A sudden increase in the intensity of ECs was observed in the DWDS. In branch DWDS, the intensity of aromatic DBPs initially increased and then decreased along with transportation, consistent with the quantification results. The results indicate that the transportation process in DWDS has a noticeable impact on DBP formation.

SYNOPSIS:

Emerging contaminants existed in the drinking water distribution system contribute to the formation of aromatic disinfection byproducts.

INTRODUCTION

Disinfection of drinking water is essential to remove and inactivate pathogens[1]. Chlorine, chloramine, and chlorine dioxide are widely used disinfectants due to their cost-effectiveness and accessibility[2]. However, chlorine-based disinfectant reacts with organic and inorganic substances in water, leading to undesirable halogenated disinfection by-products (DBPs), which could cause adverse health effects[3]. Numerous studies have focused on the formation of regulated DBPs, such as trihalomethanes (THMs)[4], haloacetic acids (HAAs)[5], and nitrosamines (NDMA)[6]. Nevertheless, there appears to be a gap between the toxicity of regulated DBPs and the observed toxicity of water samples, suggesting that a large number of new and potentially important DBPs remain unknown. With advancements in analytical methods, an emerging class of DBPs, known as aromatic halogenated DBPs, has been newly detected and attracted widespread attention[7, 8].

Aromatic DBPs are defined as DBPs with planar cyclic structures following Hückel's Rule, primarily include halophenols, halo-hydroxybenzaldehydes, halo-hydroxybenzoic acids, halo-hydroquinones, halo-salicylic acids and halo-anilines[9, 10]. Aromatic DBPs often exhibit higher toxicity than haloaliphatic DBPs[11, 12]. Specifically, the acute toxicity of halobenzoquinone was up to hundreds of times more potent than that of HAAs when using zebrafish embryos as a developmental toxicity model[13], emphasizing the importance of understanding aromatic DBP formation. Numerous studies have sought to investigate aromatic DBPs in drinking water distribution systems

(DWDS) by chlor(am)inating authentic drinking water under well-controlled laboratory conditions[7, 14]. However, these studies have limitations in fully elucidating the variation in the occurrence and abundance of aromatic DBPs in real DWDS. This is primarily due to the influences and contribution of multi-factors toward DBP formation remain unknown, such as long transportation distances, prolonged reaction time, and, notably, unsuspected precursors. Consequently, challenges persist in gaining a comprehensive understanding of the formation of aromatic DBPs in DWDS.

Emerging contaminants (ECs), including pharmaceuticals and personal care products (PPCPs), pesticides, industrial chemicals, food additives, and their transformation products (TPs), have been demonstrated to serve as precursors for aromatic DBPs[15-19]. For instance, bisphenol A, an extensively used industrial product, can react with chlorine and the co-existed bromine ions in aqueous environment to form various intermediates like 2,4,6-tribromophenol and 2,6-dibromo-4-chlorophenol[20]. ECs have been quantified utilizing target analysis, with concentrations typically ranging from tens to hundreds of nanograms per liter in drinking water[21, 22]. Even at low concentrations compared to natural organic matter (NOM), ECs and their TPs exhibit notable diversity and possess a high potential for specific DBP formation[23, 24]. This highlights the undeniable connection between ECs and aromatic DBPs. Unfortunately, the co-occurrences of ECs/TPs and their corresponding aromatic DBPs are scarcely addressed in real DWDS.

To simultaneously identify ECs, TPs, and aromatic DBPs in real DWDS,

appropriate analytical techniques are crucial. The development of quadruple time-of-flight mass spectrometry (QTOF-MS) has dramatically facilitated the application of suspect and non-targeted screening protocols for micropollutant identification[25-27]. MS analyzers coupled with liquid chromatography (LC) are particularly suitable for ECs and aromatic DBPs as these chemicals are typically soluble and polar. In terms of post-acquisition data processing, suspect screening is a commonly employed method[28]. Mass spectrometric datasets (including MS data and MS/MS data~~M~~[1/2]) are matched against a suspect list originating from in-house libraries or mass spectral libraries such as mzClound, European MassBank, and MassBank of North America (MoNA)[29, 30]. The list can also be expanded by predicting molecular structure using in-silico tools such as MetFrag, CFM-ID[31], and Global Natural Products Social Network[32, 33]. Although the suspect screening approach has been successfully applied for the identification of ECs, such as per- and polyfluoroalkyl substances and PPCPs in rivers or landfill leachate[34], the variations in the species and intensities of ECs-derived DBPs in DWDS are still largely unexplored[35].

Consequently, to enhance the understanding of the aromatic DBP formation with ECs as possible precursors, this study investigates the co-occurrence of ECs and aromatic DBPs in real DWDS using suspect and non-target screening analysis. The main objectives of the present study are as follows: (i) to qualitatively identify the intensity variations of ECs and DBPs, (ii) to quantitatively characterize the spatial variation of aromatic DBPs in DWDS, and (iii) to explore the aromatic DBP formation

taking possible ECs as precursors.

MATERIAL AND METHODS

2.1 Chemicals and reagents

The reference standards of aromatic DBPs were of analytical grade, as shown in **Table S1**, purchased from Macklin (Shanghai, China) and used to build an in-house DBP MS database. Detailed information on ECs standards, including antibiotics, biocides, drugs, endocrine-disrupting chemicals, and steroid hormones were given by Wang, et al. [36]. The standard and internal standard solutions were prepared in methanol and stored in the refrigerator at -20℃. The ultrapure water was obtained from a Milli-Q system (Veolia, UK). Methanol and acetonitrile were purchased from Merck (Darmstadt, Germany).

2.2 Sampled site and water sample collection

The sampling campaign was conducted in two independent DWDS that served four districts with a population of nearly 5,000,000, namely Dongjiang (DJ) and Beijiang (BJ), in Guangzhou, China. As shown in **Fig. S1**, the treated water supplied to the DJ network originated from the drinking water treatment plants (DWTPs) of DJ, while the BJ network was supplied by the treated water from the DWTP of BJ. The treatment process for DJ included sand filtration and chlorination, whereas the BJ treatment process involved sand filtration, ozonation, granular activated carbon filtration (GAC), and chlorination. At the water treatment plants, the unchlorinated water (sample taken before the chlorination process) was collected for analysis of ECs, which are referred to as DJ-B and BJ-B, while the water samples taken after

chlorination are referred to as DJ-A and BJ-A, respectively. In DWDS, five sampling sites (DJ-1 to DJ-5) were located in the branched DJ network, and four sites (BJ-1 to BJ-4) in the looped BJ network were selected for both ECs and DBPs measurements. The distance between sampling site and DWTP in DJ area are ranging from 6.3 to 38.5 km, corresponding to 1.8 h to 10.7 h retention time. The distance of sampling site in BJ areas ranges from 5.5 to 12.4 km, corresponding to the retention time of 2.6 to 13.3 h. The measured DOC concentrations of DJ-A and BJ-A were 2.29±0.60 mgL^{-1} and 2.77±0.80 mgL^{-1}, respectively.

The amber glass bottles were pre-cleaned with methanol and ultrapure water. Tap water was flushed with running water for 3–5 min before sampling. Three replicate water samples (1 L for each) were collected for EC analysis. Sulfuric acid (4 mL of 4 M sulfuric acid) and 50 mL of methanol were immediately added to water samples to adjust samples to pH = 3 and inhibit microbial activity, respectively[36]. Three replicate water samples (3 L for each) were collected for aromatic DBP screening. The residual chlorine of samples was quenched with ascorbic acid at 2 g/L. After collection, the water samples were transported to the cold storage of the laboratory at 4℃ in the dark and extracted within 24 hours.

2.3 Water sample pretreatment

2.3.1 Extraction of the ECs

All the samples were filtered through glass fiber filters (GF/F, 140 mm, 0.7 μm, Whatman) to remove suspended particulate matter before extraction. The filtered

samples were spiked with 0.4 g Na_4EDTA to mitigate the effects of heavy metal. A solid-phase extraction (SPE) procedure was applied to enrich ECs according to the established methods[15, 36]. Detailed information is described in the Supplementary Information (**SI, Section 1**).

2.3.2 Extraction of aromatic DBPs

All the prepared samples were pretreated with a previously established liquid-liquid extraction (LLE) to extract the aromatic DBPs[7, 37]. In brief, a 3 L water sample was acidified to pH 0.5 using sulfuric acid (70%) and saturated with 100 g sodium sulfate. Subsequently, 100 mL of methyl tert-butyl ether (MtBE) was added. After vigorous shaking in a separating funnel, the organic layer was transferred to a rotary evaporator and concentrated to 1 mL. Then, the 1 mL MtBE layer was mixed with 10 mL methanol and re-concentrated to 100 μL under a gentle nitrogen stream (<5 psi). Following this, it was reconstituted with 400 μL of ultrapure water. The extract was filtered with a 0.22 μm membrane filter before being transferred into injection vials. It was then stored at 4°Cin the dark until MS analysis.

2.4 Analytical methods

2.4.1 Suspect and non-target screening of ECs

We used an Agilent Infinity II LC system coupled with an Agilent 6545 QTOF-MS featuring an electrospray ionization (ESI) source to detect the presence of ECs. For each sample, three μL was injected into an Agilent InifinityLab Poroshell 120 EC-C18 column (2.1×150 mm, 2.7 μm) at the rate of 300 μL/min, with the column oven

temperature maintained at 40°C. Detailed instrument settings for high-resolution mass spectrometry (HRMS) and the mobile phase can be found in the Supplementary information (**SI, Section 2**) based on the previously published method[34, 38].

The mass spectrometer was operated in both negative and positive ionization modes. A data-dependent acquisition mode (DDA) was employed. In the DDA acquisition mode, five precursors with the highest response at a given moment were fragmented, while precursors of potential interest with lower responses were excluded. To address this challenge, we implemented an additional iterative injection method. This allowed us to acquire data on other features while protecting the high-response features that had already been fragmented.

2.4.2 Suspect and non-target screening of DBPs

Suspect screening analysis of aromatic DBPs was performed using ACQUITY I-Class UPLC system combined with a Xevo G2-XS-QTOF MS (Waters, Milford, MA, USA) equipped with an electrospray ionization source (ESI). The mass spectrometer can operate in both positive and negative ionization modes. An HSS T3 column (2.1 × 50 mm, 1.7 μm, Waters) was applied for the chromatographic separation. The MS^E mode was applied for the full scan analysis of the water samples. MS^E is a data acquisition technique in LC-MS that simultaneously collects low-energy and high-energy mass spectrometry data, which can be valuable for identifying compounds. The mobile phase gradient elution program and mass parameters are provided in the **SI Section 3**[9, 39]. The mass data were collected under both positive and negative modes.

2.4.3 Quantification of aromatic halogenated DBPs

Aromatic halogenated DBPs were quantified using an Agilent Infinity II UPLC system (1290) coupled with a triple-quadrupole mass spectrometry (6495) equipped with an ESI source. Samples of 2 μL were injected into an Agilent InifinityLab Poroshell 120 EC-C18 column (2.1×150 mm, 2.7 μm) at a flow rate of 300 μL/min. The oven temperature was set to 40°C. Detailed parameters for quantifying aromatic halogenated DBPs were shown in the **SI Section 4**.

2.5 HRMS data mining

2.5.1 HRMS data mining for ECs

The in-house database was created by initially gathering spectral information from available reference standards, including MS, tandem mass spectra (MS^2), and retention time (RT). To ensure the accuracy of RT, mixture standards were analyzed under the same conditions as the samples. Subsequently, the "metID" R package was used to establish the in-house database for EC identification. Additionally, two online public databases, i.e., Massbank and MoNA, are used to aid in identifying ECs.

The initial step in the HRMS data analysis involved converting the raw sample data into "mzxml" format. Subsequently, a portion of the data was selected to optimize the parameters for peak detection and extraction using the *XCMS* package[40]. Features with intensities less than 5000, which were attributed to instrument noise signal, features with relatively low intensities, procedural and solvent blanks, were excluded from further consideration. The remaining chromatographic peaks corresponding to these

features were examined manually to ensure accurate identification. Finally, features with mass errors of less than five parts per million (ppm) were matched against the in-house and publicly available databases.

A previous study established confidence levels (CLs) for compound identification ranging from CL 1 (confirmed with a reference standard) to CL 5 (confirmed only with ~~extract~~ exact mass)[41]. Based on the rules, we considered only compounds with CL 1-3 confidence levels in the present study.

2.5.2 HRMS data mining for DBPs

The Unifi platform (Version 1.9.3, Waters, USA) was used to analyze the MS^E data. An in-house library of DBPs containing DBP information was created, including accurate molar weight, RT, and structural formula. The DBPs with CL 1 are shown in **Table S1**. Simultaneously, another referential library was built using the Unifi platform based on an online DBPs suspect list CHLORINE_TPs database (comptox.epa.gov, accessed May 2023). We selected DBPs amenable to LC-ESI-HRMS from the suspect list and saved their corresponding structure files in mol format in Unifi. In total, there are 916 DBPs, with 231 in positive mode and 685 in negative mode. For the in-house DBP library, compounds can be identified if they meet the following criteria: mass error of less than five ppm and a retention time bias of under 0.5 min[42, 43]. For the referential library, unknown chemicals were identified if they meet the following specifications: detection counts exceeding 3000, isotope match intensity RMS (root mean square)

percent less than 20, isotope match mass-to-charge (~~Mz~~m/z) RMS ppm less than 6, and a mass error within the range from -3 ppm to 3 ppm[44].

2.6 Statistical analysis

To visualize the variation in the levels of detected compounds across different sampling sites, a principal coordinate analysis (PCoA) was conducted using R (version 4.3.2) along with the 'factoextra' (version 1.0.7) and 'FactomineR' packages (version 2.10). A hierarchical clustering analysis was performed to determine the distribution of the ECs and DBPs across different networks supplied by two water sources. This analysis was conducted using the"pheatmap" R package (version 1.0.12).

RESULTS

3.1 Suspect and non-target screening of ECs

The Centwave algorithm of *XCMS* was used to extract features from the data file. A detailed explanation of the algorithm can be found in the previous study by Tautenhahn, et al. [45]. Initially, 19,383 characteristics were obtained, encompassing both positive and negative modes from the detected samples. After subtracting the features observed in blank samples, 9304 features were retained. A total of 738 features were acquired following a matching process with the in-house and public databases containing MS^2 fragmentation information. Out of these, 476 and 262 features were detected in the positive and negative ion modes, respectively. Subsequently, only features with intensities exceeding 1.0×10^5 and devoid of any additive forms other than protonated or deprotonated ions were retained to minimize the likelihood of false

positives. The additive forms included $M+Na^+$, $M+K^+$, or $M+NH4^+$ were excluded manually according to the mass information provided by the database. To ensure the unambiguous detection of each suspected feature, the chromatographic peak was manually extracted using Agilent Qualitative Navigator (version B.08.00) to confirm that each feature corresponded to a single chromatographic peak.

Feature No. 162 (m/z=138.0198, RT=8.678 min) was detected in the negative mode and is presented here as an illustrative example of substance identification at CL 1a (**Figure 1**). The extracted ion chromatograms and MS^2 fragmentation patterns of feature No. 162 closely matched those of the in-house-library standard, with an acceptable criteria i.e., mass tolerance of less than five ppm and RT deviation of under 0.2 min[43]. Consequently, feature No. 162 was conclusively identified as 4-nitrophenol ($C_6H_5NO_3$, CAS No. 100-02-7). Using the approach, 41 ECs were identified within CL1 and CL2a, with 30 detected in the positive mode and 11 in the negative mode.

The identified ECs were categorized into five categories, as illustrated in **Fig 2a**: PPCP (n = 10, n denotes the number of species), pesticides (including herbicides, fungicides, insecticides, and transformation product of pesticides, n = 16), industrial chemicals (comprising industrial raw materials and additives, n = 8), food additives (n = 2) and intermediates (n = 5). **Fig 2b** depicts the variation of EC categories across different sampling sites. Among the identified chemicals, pesticides were the most prevalent, constituting 38% of the total species, and were detected in the entire DWDS. The category included four herbicides, nine fungicides, and one insecticide, along with

the detection of a metabolic transformation product of an organophosphorus pesticide, diethyl phosphate. PPCPs accounted for 25% of the detected species, encompassing seven pharmaceuticals and three personal care products. Detailed information on compound names and confidence levels is given in **Table S3**.

3.2 Variation in composition and intensity of ECs

3.2.1 Composition and intensity of ECs in DWTP

According to the PCoA analysis using the Bray–Curtis metric (**Fig. S2**), the compositional differences in ECs between the effluents of two DWTPs were more pronounced than those observed in the corresponding tap water samples within their respective DWDS. These results indicate significant variations in the composition of ECs between the two treatment plants. These disparities can be attributed to differences in the water sources and treatment processes. In other words, the origin of contaminants and the efficiency of removal processes collectively shape the species composition of treated water[46].

Regarding the specific species of detected ECs with standardized intensity in the effluent of DWTP BJ, as shown in **Fig. 3**, climbazole, cyproconazole, perfluorooctanoic acid, and 4-nitrophenol were the main species. In a prior study conducted by our research group[47], cyproconazole (biocide) and climbazole (fungicide), originating from domestic wastewater and surface runoff, were detected in the source water. Despite the application of GAC at DWTP BJ, known to be effective in pesticide attenuation during the drinking water treatment process [48], cyproconazole and climbazole persisted in the

BJ effluent. It is speculated that certain pesticides may leach from GAC into the effluent after long operation time due to the instability in GAC performance[49].

The predominant species in the effluent of DWTP DJ were sorbic acid, telmisartan, and deoxyvasicinone. It was reported that telmisartan and deoxyvasicinone, categorized as PPCPs, exhibited a high detection frequency in wastewater treatment effluent[50], potentially leading to the contamination of the drinking water source. While the exact extent of their removal during processes such as sand filtration and chlorination is not available, in general, conventional drinking water processes are often ineffective in removing PPCPs[15].

3.2.2 Composition and intensity of ECs in DWDS

Despite the significant differences in the composition and intensity of ECs at the two DWTPs, the PCoA analysis revealed that the composition and intensity of ECs in BJ and DJ networks shared many similarities, except BJ-2 (**Fig. S2**). This suggests that the influence of DWTP-treated water quality is limited to tap water. Conversely, variations in the composition of ECs in district water supply networks are likely attributed to microbiological and chemical reactions occurring during the water transportation process.

Regarding the specific species as depicted in **Fig. 3**, certain pesticides, such as paclobutrazol and diuron, exhibited relatively higher intensities in the DJ water network than BJ. Industrial chemicals such as 5-methyl-2H-benzotriazole and benzoguanamine in the BJ area showed higher signal intensities than in the DJ area. It is worth noting

that 5-Methyl-2H-benzotriazole, identified as the ozonation byproduct, may explain the higher intensity observed at the BJ DWTP where the ozonation was applied. The intensity of pharmaceuticals showed comparable levels in both supply areas. Given that the BJ network features a pressurized system with a looped structure, there is no reasonable explanation for the abrupt increase in intensity at BJ-2. We speculate that this is caused by the grab sample and EC concentration entering DWDS vary over time.

3.3 Suspect and non-target screening of DBPs

The Waters Unifi Platform extracted features from the original MS data file. An identified aromatic DBP 2,6-dibromo-4-nitrophenol, which was detected in negative mode and identified as CL1a, was chosen as an illustrative example for the validation of DBPs. As shown in **Fig. S3**, a sample feature was detected at RT = 5.62 min, which exhibited a slight RT deviation (≤0.02 min) compared to a standard used to build the in-house-library, ~~standard~~ 2,6-dibromo-4-nitrophenol (RT = 5.64min). Subsequently, the mass-to-charge ratio (m/z) and isotope relative response of the sample feature were checked with those of the in-house library standard. Ultimately, the feature was confidently identified as 2,6-dibromo-4-nitrophenol and classified as a CL 1 compound.

Based on the aforementioned identification process, a total of 27 DBPs were identified, as shown in **Fig. 4a**. Detailed information about the detected species can be found in **Table 1**. Among these DBPs, 52% of DBPs were chloro-DBPs (Cl-DBPs), 19% were bromo-DBPs (Br-DBPs), 15% were non-halogen DBPs, followed by bromo-chloro-DBPs (Br, Cl-DBPs) at 11%, and iodo-DBPs (I-DBPs) at 3%. Furthermore, the

identified DBPs were categorized into eight groups based on the functional groups present in their chemical structures. These categories include halo-hydroxybenzoic acid (n = 3, where n donates the number of DBP species), halo-hydroxybenzaldehydes (n = 4), halo-ketones (n = 2), halo-phenols (n = 1), halo-carboxylic acids (n = 4), halo-nitrophenols (n = 5), halo-anilines (n = 1), and others (n = 7).

As depicted in **Fig. 4b**, BJ and DJ effluents contained 10 and 12 DBP species, respectively. The DBP categories exhibited a decreasing trend in tap water across all sampling sites, except for BJ-3 and DJ-4 for respective BJ and DJ networks. The trend may be attributed to the decomposition of aromatic DBPs, leading to the formation of volatile and non-polar DBPs[9, 51]. The sudden increase in intensity and the detection of DBP species at BJ-3 and DJ-4 were consistent with the findings related to ECs.

3.4 Variation in composition and intensity of DBPs

Fig. 5 illustrates the occurrence and relative signal intensity of the detected DBPs. Among these DBPs, halo-phenols and halo-nitrophenols were the predominant groups of DBPs found in both DWDS. Specifically, 2-bromo-4-nitrophenol, 2,6-dibromo-4-nitrophenol, and 2,6-dichloro-4-nitrophenol exhibited higher intensity in the BJ supply area, while 3-chloro-5-(chloromethyl)-4-nitrophenol and 4-chlorophenol showed higher intensity in the DJ supply area. Moreover, 2-bromo-6-chloro-4-nitrophenol was detected in chlorinated effluents of both DWTPs.

A significant increase in signal intensity of halo-phenols and halo-nitrophenols was observed in the tap water at BJ-1, BJ-3, and DJ-4. It illustrates the need for special

attention to tap water quality, even when the water quality of DWTP effluent has been well controlled. Similarly, a rising trend was identified for halo-hydroxybenzaldehyde from chlorinated effluent to tap water. This includes compounds like 3-bromo-4-hydroxybenzaldehyde, 3-bromo-5-chloro-4-hydroxybenzaldehyde, and 2,4-dichloro-6-hydroxybenzaldehyed. Additionally, three halogenated salicylic-acid compounds were detected at high intensity in BJ-1 and DJ-4 (**Table 1**). In a previous study, 5-chlorosalicylic acid and 3-bromo-5-chlorosalicylic acid were found as DBPs by chlorinating simulated drinking water using Suwannee River humic acid as a surrogate [7].

3.5 Aromatic DBP concentration

Based on the suspect and non-target screening, it was evident that the category of halo-nitrophenol (HNPs) DBPs exhibited the highest frequency at all sampling sites. Consequently, the concentration of HNPs was proceeded to quantitatively determined, including six distinct species, i.e., 3-chloro-4-nitrophenol, 2-chloro-4-nitrophenol, 3-bromo-4-nitrophenol, 2,6-dichloro-4-nitrophenol, 1,6-dibromo-4-nitrophenol, 2-bromo-4-nitrophenol, as illustrated in **Fig. 6**. The average concentration of HNPs in the BJ DWDS (61.13±28.34 $ng \cdot L^{-1}$) exceed that in the DJ network (32.99±10.00 $ng \cdot L^{-1}$). Among the quantified HNPs, 2,6-dibromo-4-nitrophenol showed the highest concentration, ranging from 14.2 to 43.36 $ng \cdot L^{-1}$, followed by 2,6-dichloro-4-nitrophenol ranked as the second-highest in terms of concentration, with a range of 8.71

± 4.93 ng L^{-1}. The brominated HNP concentration is higher than chlorinated HNP, possibly due to the seawater intrusion during the sampling period.

In the case of the branch network (DJ DWDS), a slight increase in HNPs was observed along with the transportation direction, specifically from DJ-1 to DJ-4, followed by a decrease from DJ-4 to DJ-5. It implies the presence of HNP's precursors within the DWDS, as well as the prolonged reaction time, both contributing to an increased HNP formation. On the other hand, the decomposition of aromatic DBPs into regulated DBPs in the presence of chlorine, as discussed by Chen, et al. [52], likely became a predominant factor leading to the decrease in HNPs observed at DJ-5. DJ-5 is the furthest sampling site from the DWTP. It is worth noting that the HNP concentrations at BJ-1, BJ-3, and DJ-4 were higher than those at other sampling sites, which is consistent with the intensities` distribution obtained through non-target analysis.

DISCUSSION

While direct evidence for the formation of aromatic DBPs from ECs as precursors is limited, substantial support exists for the role of metabolites and transformation products of ECs as major precursors for halogenated DBPs. In this context, the relationships between ECs, transformation products, and DBP formation are discussed. Based on the author's knowledge, there is a lack of methods to isolate the contribution of NOM, ECs, or extracellular polymeric substances secreted by biofilm to DBP formation in a real DWDS. Therefore, the possible EC precursor can be only qualitatively discussed in the present study.

Halo-nitrophenols. 4-nitrophenol, commonly used as an industrial intermediate in pesticide and dye manufacturing, was detected in BJ-treated water at a relatively higher intensity before chlorination (**Table 1**). Notably, 4-nitrophenol has been substantiated as the primary precursor that reacts with halogen atoms to form halo-nitrophenol[53, 54]. As shown in **Figure S4**, the benzene ring of 4-nitrophenol possesses both an activating group (-OH) and a deactivating group (-NO_2). The nitro group on the benzene ring encourages substitution at its meta-positions, while the hydroxy group on the ring directs substitution at its ortho- and para-positions. Consequently, the 2- and 6-positions of 4-nitrophenol are susceptible to halogenation, resulting in the formation of halo-nitrophenols such as 2-bromo-4-nitrophenol, 2,6-dibromo-4-nitrophenol, 2,6-dichloro-4-nitrophenol, and 2-bromo-6-4-nitrophenol. All of these DBPs were detected in the present study (**Table 1**).

Halo-salicylic acids. Salicylic acid (SA), the principal metabolite of acetylsalicylic acid (aspirin, PPCP), has been identified as a precursor of chlorinated DBPs[55]. It has been detected in various environmental sources, including wastewater treatment plant effluent[56, 57], groundwater[58], and certain tap water[59]. However, it is worth noting that the conversion of salicylic acid into halo-salicylic acid accounted for less than 1% of the halo-salicylic acid formation, indicating salicylic acid plays a minor role as an intermediate[7]. In the present study, neither the parent compound aspirin nor the transformation product of salicylic acid was detected. Instead, products like 3-chlorosalicylic acid and 3,5-dichloro-salicylic acid exhibited significantly higher intensities at several sampling points (**Fig. 5**). These findings support the inference that the salicylic acid is not a major precursor, and the presence of halo-salicylic acid in tap water may originate from the decomposition of ECs or the NOM containing halogenated moieties.

Halo-hydroxybenzaldehyde. 4-hydroxybenzaldehyde has been identified as the major intermediate in the formation of halo-hydroxybenzaldehyde. It is also confirmed as the transformation product of bisphenol A in an advanced oxidation system[60] and is a metabolite product of tetracycline. To our knowledge, 4-hydroxybenzaldehyde has not been reported as a transformation product of the ECs listed in **Table 1**. However, the ester-type moieties were found in detected ECs. These ester moieties may undergo nucleophilic chlorine attack and subsequent hydrolysis, potentially leading to the formation of 4-hydroxybenzaldehyde. Further validation of this hypothesis is required.

Others. Based on the literature, we have summarized the precursors of the detected DBPs, which are presented in **Table 1**. Enrofloxacin and its halogenated DBP, 3,8-dichloro-1-cyclopropyl-7-(4-ethylpperazin-1-yl)-6-fluoroquinolin-4(1H)-one were both identified. DBPs associated with antibiotics such as sulfamethoxypyridazine, sulfamerazine, and sulfamethazine were found. For example, 4-(2-imino-4,6-dimethylpyrimidin-1(2H)-yl) aniline was identified as the DBP of sulfamethazine[61], and 7-((2-aminoethyl)amino)-2,8-dichloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid was validated as the DBP of ciprofloxacin[62]. Moreover, 1-(2-chloro-3-hydroxy-6-methylphenyl)-3-(5-hydroxy-2-methylphenyl) guanidine and 6-imino-4,8-dimethyl-6,7-dihydro-5H-dibenzo[d,f][1,3]diazepin-1,9-diol have been reported to be the DBPs of a rubber accelerator known as 1,3-di-o-tolylguanidine (DTG)[63].

It should be noted that a significant portion of the detected DBPs in DWDS still have unknown precursors. Meanwhile, the intensity of detected ECs decreases along with the water transportation, but their chlorination transformation products remain unclear. Based on the non-targeted screening results, we recommend conducting chlorination experiments with specific-detected ECs as precursors to establish the reaction pathways of DBP formation.

CONCLUSIONS

In this study, we conducted a comprehensive analysis to detect ECs and aromatic DBPs simultaneously in both the effluent of DWTP and the corresponding DWDS. The

suspect screening and non-target methods based on high-resolution mass spectrometry are employed, which enables the identification of a wide range of compounds. The spatial distribution characteristics of these ECs and DBPs are revealed, as well as the existence of DBPs with ECs as precursor are explored.

A total of 41 ECs and 27 aromatic DBPs were detected and identified in the DWDS. Among these, pesticides and PPCPs constituted the majority, accounting for 64% of the identified ECs. Nearly half of DBPs were chlorinated DBPs, followed by brominated DBPs, with a smaller proportion of non-halogen DBPs or those containing chlorine and bromo atoms. Remarkably, 22% of DBPs were identified as EC-DBPs, with their corresponding precursor ECs also identified within the DWDS. Specifically, four detected halo-nitrophenols were the transformation products of 4-nitrophenol. Enrofloxacin and its chlorinated DBPs were identified simultaneously.

The data provided herein indicates that emerging contaminants significantly influenced the occurrence and categories of DBPs. As anthropogenic chemicals are increasingly produced and consumed, the potential connections of ECs and DBPs deserve a deeper understanding of DWDS.

ACKNOWLEDGEMENT

This work was jointly supported by the National Natural Science Foundation of China (Grant No.: 42377059) and Guangdong Basic and Applied Basic Research Foundation (Grant No.: 2022A1515010499, 2021B1515120055). Mentioning trade names or commercial products does not constitute endorsement or recommendation.

This manuscript has not been subjected to the above agencies' required peer and policy review and, therefore, does not reflect the views of the above agencies, and no official endorsement should be inferred.

Table 1 Detected DBPs and reported precursor ECs.

Category	Name	Formula	CAS	Precursor	Literature
halo-salicylic acid	3-chlorosalicylic acid	$C_7H_5ClO_3$	1829-32-9	-	-
	5-bromosalicylic acid	$C_7H_5BrO_3$	89-55-4	-	-
halo-hydroxybenzaldehydes	2-bromo-3-chloro-6-hydroxybenzoic acid	$C_7H_4BrClO_3$	1934463-24-7	-	-
	2,4-dichloro-6-hydroxybenzaldehyde	$C_7H_4Cl_2O_2$	78443-72-8	-	-
	3-bromo-5-chloro-4-hydroxybenzaldehyde	$C_7H_4BrClO_2$	1849-76-9	-	-
	2,3-dibromo-4-hydroxybenzaldehyde	$C_7H_4Br_2O_2$	NA	-	-
	3-bromo-4-hydroxybenzaldehyde	$C_7H_5BrO_2$	2973-78-6	-	-
halo-phenols	4-chlorophenol	C_6H_5ClO	106-48-9	Bisphenol S[b]	[64]
halo-nitrophenols	2,6-dichloro-4-nitrophenol	$C_6H_3Cl_2NO_3$	618-80-4	4-nitrophenol[a,b]	[53, 54]
	2-bromo-6-chloro-4-nitrophenol	$C_6H_3BrClNO_3$	20294-55-7	4-nitrophenol[a,b]	
	2,6-dibromo-4-nitrophenol	$C_6H_3Br_2NO_3$	99-28-5	4-nitrophenol[a,b]	
	2-bromo-4-nitrophenol	$C_6H_4BrNO_3$	5847-59-6	4-nitrophenol[a,b]	
	3-chloro-5-(chloromethyl)-4-nitrophenol	$C_7H_5Cl_2NO_3$	NA	3-methyl-4-nitrophenol[a,b]	[65]
halo-ketones	3,5,5-trichloro-4-hydroxycyclopent-3-ene-1,2-dione	$C_5HCl_3O_3$	NA	-	-
	2,6-dichloro-3-hydroxy-5-methylcyclohexa-2,5-diene-1,4-dione	$C_7H_4Cl_2O_3$	NA	Dichloromethylbenzoquinone[b]	[66]
Halo-carboxylic acids	3,4,5-trichlorofuran-2-carboxylic acid	$C_5HCl_3O_3$	32417-81-5	-	-
	6,7-dichloro-3-oxo-4H-1,4-benzoxazine-8-carboxylic acid	$C_9H_5Cl_2NO_4$	NA	-	-
	2-iodo-3-methyl-2-butenedioic acid	$C_5H_5IO_4$	NA	-	-
	7-((2-aminoethyl)amino)-2,8-dichloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid	$C_{15}H_{14}Cl_2FN_3O_3$	NA	-	-
Halo-anilines	1-(2-chloro-3-hydroxy-6-methylphenyl)-3-(5-hydroxy-2-methylphenyl)guanidine	$C_{15}H_{16}ClN_3O_2$	NA	1,3-di-o-tolylguanidine (DTG)[b]	[63]

Others	7-((2-aminoethyl)amino)-3-chloro-1-ethyl-6-fluoroquinolin-4(1H)-one	$C_{13}H_{15}ClFN_3O$	NA	Norfloxacin[b]	67
	3,8-dichloro-1-cyclopropyl-7-(4-ethylpperazin-1-yl)-6-fluoroquinolin-4(1H)-one	$C_{18}H_{20}Cl_2FN_3O$	NA	Enrofloxacin[a,b]	68
	N-chloro-2-methoxybenzo[4,5]imidazo[1,2-b]pyridazin-8-amine	$C_{11}H_9ClN_4O$	NA	Sulfamethoxypyridazine[b]	69
	6-imino-4,8-dimethyl-6,7-dihydro-5H-dibenzo[d,f][1,3]diazepin-1,9-diol	$C_{15}H_{15}N_3O_2$	NA	1,3-di-o-tolylguanidine (DTG)[b]	63
	4-amino-N-(aminomethyl)benzenesulfonamide	$C_7H_{11}N_3O_2S$	NA	Sulfamerazine[b]	70
	3-((4-cyclopropyl-6-methylpyrimidin-2-yl)amino)phenol	$C_{14}H_{15}N_3O$	NA	Cyprodinil[b]	71
	4-(2-imino-4,6-dimethylpyrimidin-1(2H)-yl)aniline	$C_{12}H_{14}N_4$	NA	Sulfamethazine[b]	61

Fig. 1.

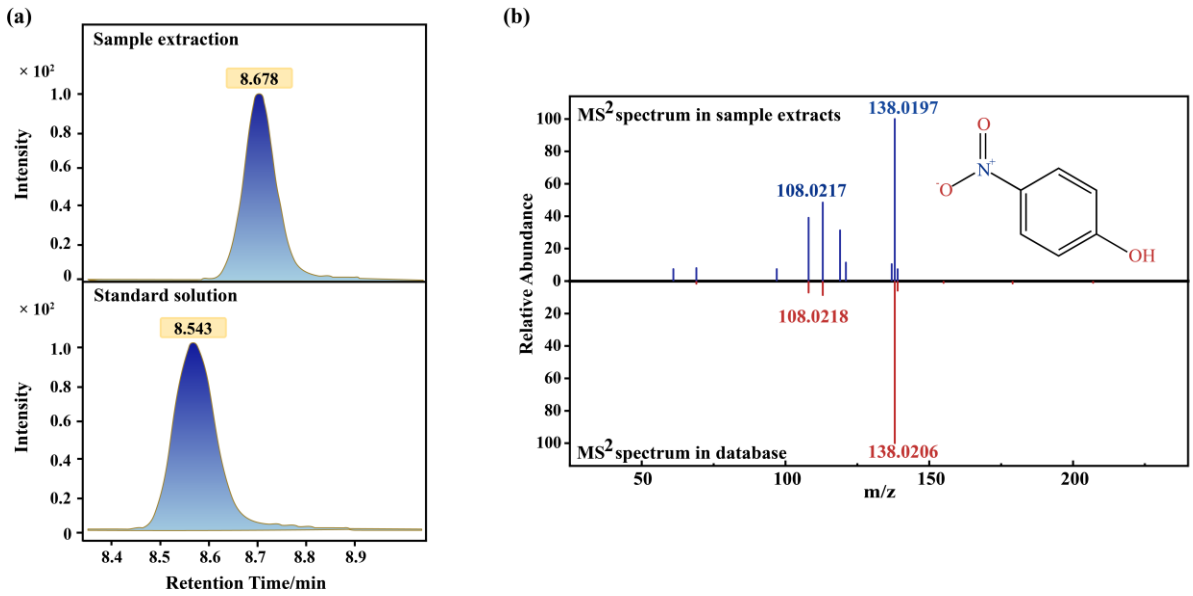

Figure 1 Illustration on the identification of feature No.162 extracted from samples in negative mode. a) Comparison of chromatographic peak shape and their retention time with the standard of 4-Nitrophenol in full scan mode. b) Comparison of MS^2 fragmentation patterns of 4-Nitrophenol in the sample extracts and library record.

Fig. 2.

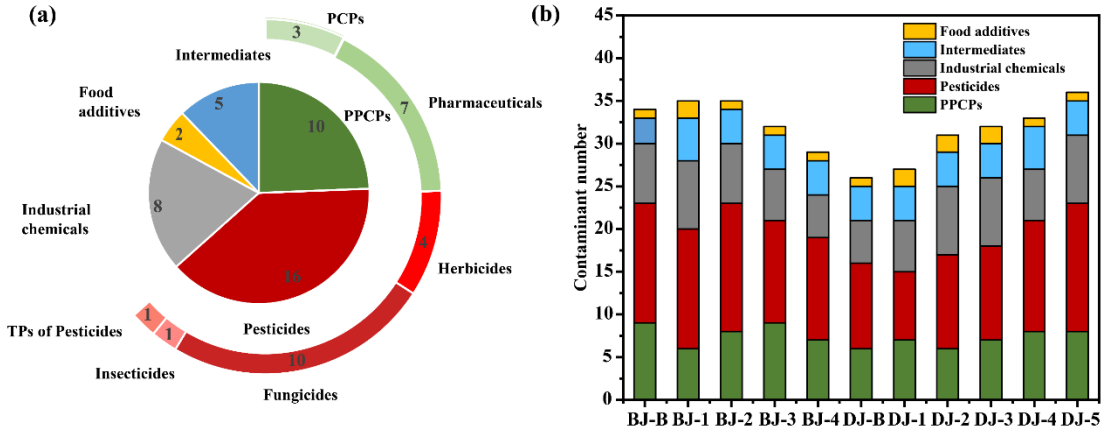

Figure 2 Spatial occurrence and distribution of different categories of CL1 and CL2a compounds in the DWDS. a) Categories of CL1 and CL2a identified ECs; b) ECs detected in sampling sites.

Fig. 3.

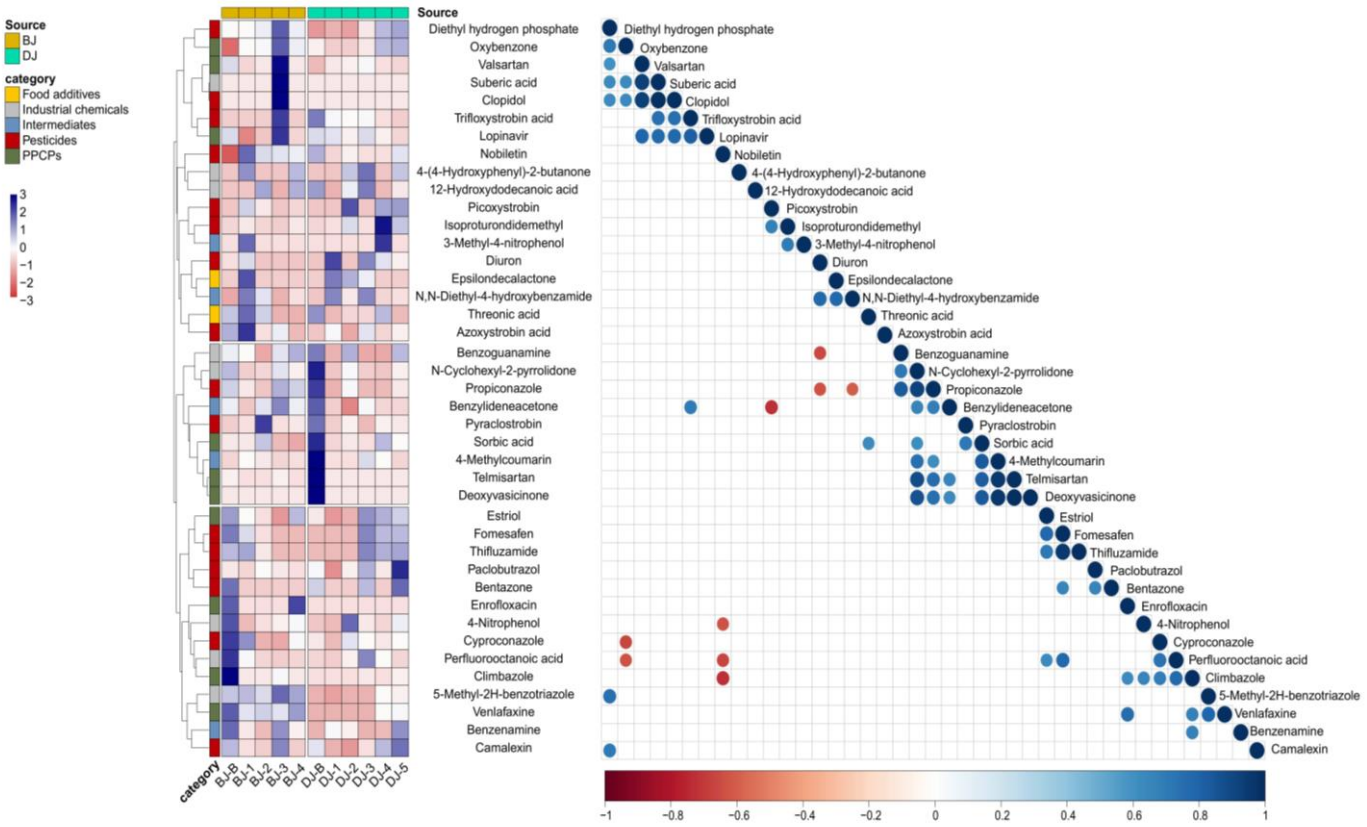

Figure 3 Occurrence and intensity of CL1 and CL2a ECs identified in different sampling sites. The sample BJ-B and DJ-B were collected from DWTP (without chlorination), while the others were collected in DWDS . The color units in the top row represent samples of different DWDS.

Fig. 4.

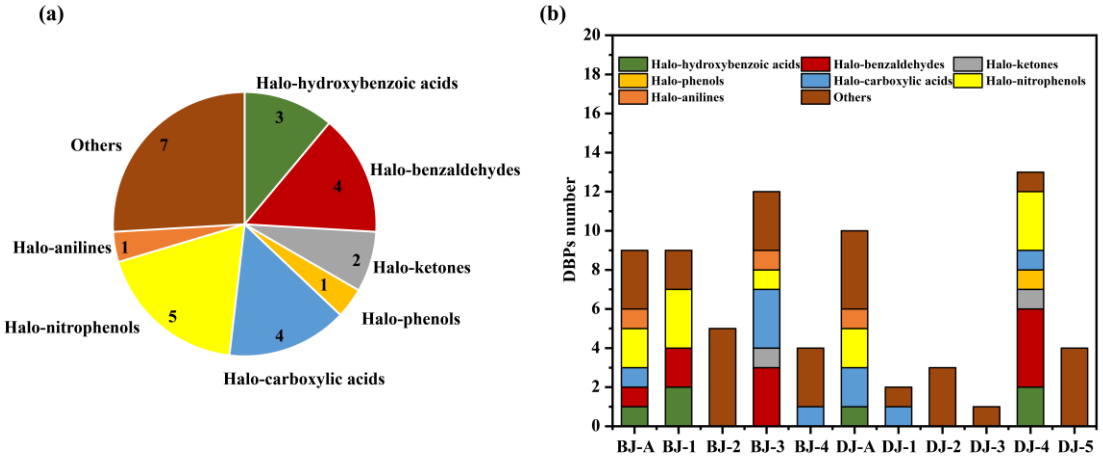

Figure 4 Spatial occurrence and distribution of different categories of DBPs in the DWDS. a) Categories of DBPs; b) DBPs detected in sampling sites.

Fig. 5.

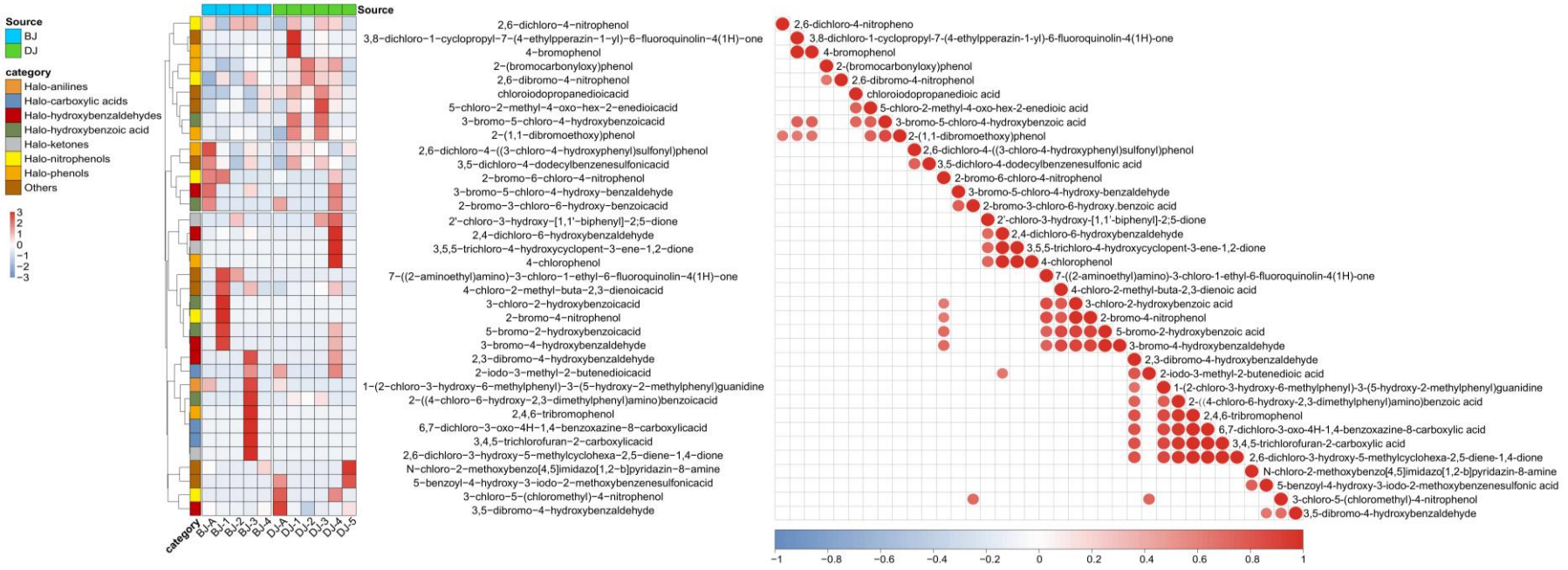

Figure 5 Occurrence and intensity of DBPs identified in different sampling sites. Sampling site codes are shown in the x-axes; the samples BJ-A and DJ-A were collected from DWTP (after chlorination), while the others were collected in DWDS. The color units in the top row represent samples of different DWDS.

Fig. 6.

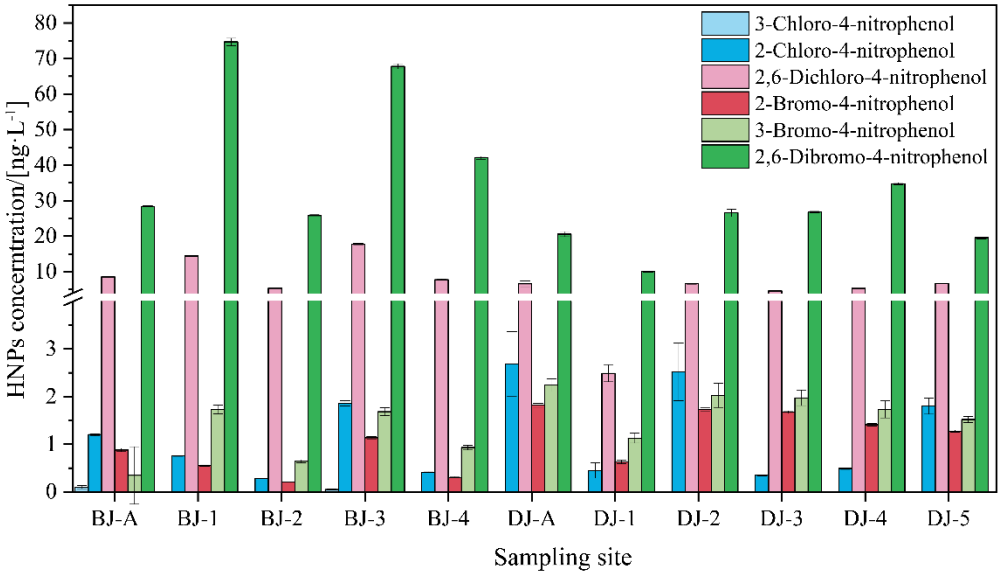

Figure 6 Concentrations (ng/L) of halonitrophenols (HNPs) detected in the DWDS.

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