Ferrate(VI) pretreatment before disinfection: An effective approach to controlling unsaturated and aromatic halo-disinfection byproducts in chlorinated and chloraminated drinking waters

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Abstract

Disinfection is an essential process of drinking water treatment to eliminate harmful pathogens, but it generates potentially toxic disinfection byproducts (DBPs). Ferrate (FeO₄²⁻, Fe(VI)) was used to pre-oxidize natural organic matter (NOM, the precursor of DBPs) in source water to control DBP formation in subsequent chlorine or chloramine disinfection. Currently, it is unclear how Fe(VI) changes the structure of NOM, and no information details the effect of Fe(VI) pretreatment on the aromatic DBPs or the speciation of overall DBPs generated in subsequent disinfection of drinking water. In the present paper, Fe(VI) was applied to pretreat simulated source water samples at a Fe(VI) to dissolved organic carbon mole ratio of 1:1 at pH 8.0. ¹³C nuclear magnetic resonance spectroscopy was newly employed to characterize NOM in simulated source waters with and without Fe(VI) treatment, and it was demonstrated that Fe(VI) converted unsaturated aromatic C functional groups in NOM to saturated aliphatic ones. High-resolution mass spectrometry (HRMS) and high performance liquid chromatography/triple quadrupole MS were applied to analyze the DBPs generated in chlorination and chloramination of the source waters with and without Fe(VI) pretreatment. It was confirmed that Fe(VI) pretreatment followed by chlorination (or chloramination), generated DBPs containing less unsaturated, halogenated, and aromatic moieties than chlorination (or chloramination) without pretreatment by Fe(VI). Finally, the cytotoxicity of disinfected drinking water samples were assessed with the human epithelial colorectal adenocarcinoma Caco-2 cell line (a model of the intestinal barrier for
ingested toxicants), and the results show that Fe(VI) pretreatment detoxified the chlorinated and chloraminated drinking waters.

Keywords
Ferrate; Disinfection byproduct; Chlorination; Chloramination; Toxicity

1. Introduction
Chlorine disinfection is an important step in drinking water treatment to eliminate harmful pathogens and prevent waterborne diseases. However, chlorine reacts with natural organic matter (NOM), bromide and iodide ions in drinking water to generate disinfection byproducts (DBPs) (Ding et al., 2019; Dong et al., 2019b; Ersan et al., 2019a; Zhang et al., 2019; von Gunten, 2018; Bond and Graham, 2018; Hu et al., 2018; Huang et al., 2018; Mao et al., 2018; Li and Mitch, 2018; Xu et al., 2018; Pan et al., 2017; Xue et al., 2017; Sharma et al., 2014; Zhai et al., 2014). It has been reported that certain DBPs are genotoxic, carcinogenic, and cytotoxic, and exposure to DBPs via ingestion of drinking water caused chronic adverse effects on humans (Dong et al., 2019b; Cortés and Marcos, 2018; Wagner and Plewa, 2017; Sayess et al., 2017; Li et al., 2016; Stalter et al., 2016; Sharma et al., 2014; Gängler et al., 2018; Villanueva et al., 2018). Five haloacetic acids (HAAs) and four trihalomethanes (THMs) are regulated by the U.S. Environmental Protection Agency (EPA) (U.S. EPA, 2006). To control the formation of the regulated HAAs and THMs, monochloramine is increasingly considered by water researchers and drinking water treatment plants as an alternative disinfectant (Ersan et al., 2019b; Dong et al., 2019b; Zhang et al., 2019; Hu et al., 2018; Selbes et al., 2018; Gong et al., 2017; Nihemaiti et al., 2017; Spahr et al., 2017; Yan et al., 2016; Zhai et al., 2014). However, chloramination enhanced the formation of iodo-DBPs in iodide-rich waters (Dong et al., 2019b; Yan et al., 2016; Ersan et al., 2019b) and favored the generation and accumulation of haloaromatic DBPs (Zhai et al., 2014). Iodo-DBPs are significantly more toxic than their corresponding chloro- and bromo-analogues, and haloaromatic DBPs are substantially more harmful than the regulated HAAs and THMs (Dong et al., 2019b; Wagner and Plewa, 2017; Sayess et al., 2017; Stalter et al., 2016; Sharma et al., 2014; Liu and Zhang, 2014).

Pre-oxidation of NOM in source water (before disinfection) is a common method to control the formation of DBPs. Ozone may be used to achieve pre-oxidation, which effectively decreased the levels of HAAs, THMs, and haloacetonitriles, but increased formation of bromate (which has been regulated by the U.S. EPA), haloketones, and chloropicrin in chlorinated and chloraminated drinking water (Hua and Reckhow, 2013; Jiang et al., 2019). An alternative pre-oxidant is ferrate (FeO$_4^{2-}$, Fe(VI)), which is reactive with NOM (Amano et al., 2018; Deng et al., 2018). Fe(VI) pre-oxidation was found to effectively lowered the formation of HAAs, THMs and bromate in subsequent disinfection of drinking water (Dong et al., 2019a; Jiang et al., 2019; Yang et al., 2015; Gan et al., 2015). Additionally, Fe(VI) is a multimodal action species that may simultaneously perform oxidation, disinfection, and coagulation (Zhang et al., 2020; Shao et al., 2020; Xie and Cheng, 2019; Manoli et al., 2019; Luo et al., 2019; Wu et al., 2019b; Feng et al., 2019; Feng et al., 2018; Jiang et al., 2018;
Existing studies on Fe(VI) pretreatment emphasized the production of volatile aliphatic DBPs (e.g., THMs, haloketones, haloacetonitriles), HAAs, or total organic halogen. Although some information on the oxidation mechanism of NOM by Fe(VI) was obtained with excitation-emission matrix (EEM) spectrometry (Dong et al., 2019a; Yang et al., 2015; Gan et al., 2015), it is largely unclear how Fe(VI) pretreatment changed the structure of NOM and the species of the organic (halogenated) DBPs, especially emerging aromatic DBPs, generated in subsequent disinfection. In this study, we applied $^{13}$C nuclear magnetic resonance (NMR) spectroscopy and high-resolution mass spectrometry (HRMS) together for the first time to elucidate changes of NOM after Fe(VI) treatment and to compare the organic (halogenated) DBPs mixtures generated from subsequent chlorination and chloramination of drinking water.

Additionally, the toxicity of a disinfected water sample is rendered by the combined effects of all DBPs and other organic and inorganic components (which depends on both the concentration and speciation). However, no such studies have been conducted to determine the toxicity of disinfected water with Fe(VI) pretreatment.

Accordingly, this study had three aims. The first aim was to quantify the changes in carbon functional groups of NOM caused by Fe(VI) treatment with $^{13}$C NMR spectroscopy. Second, we investigated the effect of Fe(VI) pretreatment on the species and quantities of the organic DBPs generated in subsequent chlorination and chloramination of drinking water using HRMS and high performance liquid chromatography/triple quadrupole mass spectrometry (HPLC/tqMS) techniques. Finally, we measured the cytotoxicity of water samples with different treatments (i.e., chlorination with and without Fe(VI) pretreatment, chloramination with and without Fe(VI) pretreatment), using the human epithelial colorectal adenocarcinoma Caco-2 cell. The Caco-2 cell line is proposed as a rapid and reliable method for toxicity studies, and it has been extensively used as a model of the intestinal barrier for in vitro toxicology studies for ingested toxicants including DBPs (Wu et al., 2019a; Melo et al., 2016).

2. Materials and methods

2.1. Chemicals, solvents and reagents

Suwannee River humic acid (SRHA, 3S101H) was purchased from the International Humic Substances Society. Ultrapure water (18.2 MΩ·cm) was obtained from a Milli-Q Element A10 water purification system. Solid potassium ferrate ($K_2FeO_4$) was chemically prepared based on previous studies (Dong et al., 2019a; Yang et al., 2015). A chlorine stock solution (~2500 mg/L as Cl$_2$) was prepared by bubbling a NaOH solution with chlorine gas in an ice bath, and stored at 4 °C. The chlorine concentration of the stock solution was measured prior to each experiment following the Standard Method (APHA et al., 2012). Monochloramine (NH$_2$Cl) stock solutions (55 and 200 mg/L as Cl$_2$) were prepared just before use by gradually adding the chlorine stock solution to an ammonium chloride solution at a chlorine to ammonium mole ratio of 0.8:1.0.
Standard compounds of halo-DBPs (Table SM-1) were ordered from Alfa Aesar or Sigma-Aldrich. HF Mega Bond Elut C18 cartridges (1 g, 6 mL) were ordered from Agilent Technologies. Prior to use, each C18 cartridge was conditioned with 5 mL methanol and equilibrated with 5 mL ultrapure water. Water (Optima LC/MS grade), acetonitrile (Optima LC/MS grade), methanol (Optima LC/MS grade), methyl tert-butyl ether (HPLC grade), and other chemicals and solvents were purchased from Fisher Chemical. Reagents used for Caco-2 cell incubation and cytotoxicity tests, including Dulbecco’s modified eagle medium nutrient mixture F-12 (DMEM medium), fetal bovine serum (FBS), penicillin-streptomycin solution (10,000 IU/mL), Dulbecco’s phosphate buffered saline (PBS), were of Gibco band and purchased from Thermo Fisher Scientific. The DMEM medium was supplemented with 10% FBS and 1% penicillin-streptomycin solution before use. CellTiter 96 AQueous One Solution Cell Proliferation Assay (containing 3-(4,5-dimethyl-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) inner salts) was ordered from Promega. Other experimental supplies for cell culture were acquired from Thermo Fisher Scientific.

2.2. Fe(VI) treatment of NOM and sample pretreatment for $^{13}$C NMR analysis

Simulated source water samples were prepared by dissolving 3.0 mg/L SRHA as C (0.25 mM C), 90 mg/L NaHCO$_3$ as CaCO$_3$, 2.0 mg/L KBr as Br$^-$ and 0.10 mg/L KI as I$^-$ in ultrapure water. The relatively high bromide and iodide concentrations were used to amplify the formation of bromo- and iodo-DBPs (Han et al., 2017). Each source water sample was adjusted to pH 6.2 ± 0.1 with HCl. A 28 mL Fe(VI) solution at 10 mM was freshly prepared by dissolving potassium ferrate in ultrapure water. The Fe(VI) concentration was quantified with the absorbance at 510 nm (using the coefficient of 1150 M$^{-1}$cm$^{-1}$) (Chen et al., 2018). This Fe(VI) solution was mixed with 1100 mL simulated source water. The volume change induced by Fe(VI) addition was negligible. The Fe(VI) initial concentration in the solution was 0.25 mM (14 mg/L as Fe), and the molar ratio of Fe(VI) to dissolved organic carbon (DOC) was 1:1. The Fe(VI) doses of 1–20 mg/L were used to treat source water samples containing 3 mg/L DOC in previous studies (Gan et al., 2015; Yang et al., 2015). The mixed solution was stirred at 400 rpm for 30 min, in which the pH was controlled at 8.0 ± 0.1 by adding dropwise HCl or NaOH. After 30 min, to completely consume Fe(VI), the solution was adjusted to pH 6.0 ± 0.1 with HCl, and kept stirring for another 10 min. Then, the sample was filtered with 0.45 μm filter.

From the filtered water sample, 20 mL was collected for DOC measurement with a Shidamzu total organic carbon analyzer, and the remaining solution was divided into six aliquots (~180 mL each), contained in 500 mL glass beakers and covered with aluminum foil. Samples were frozen at −20 °C and subjected to freeze drying at −56 °C and 0.2 mBar, in an ultra-low temperature upright freezer (Labconco) for 48 to 72 h until the volume of each was < 40 mL. Then, the six samples were thawed, combined and diluted to 250 mL by adding ultrapure water. The 1100 mL water sample was prepared in quadruplicate, and the four 250 mL concentrated samples obtained were combined to a 1000 mL solution. This 1000 mL concentrated solution was divided into five aliquots (200 mL each), and passed through five C18 cartridges, respectively. Then, each cartridge was rinsed with 6 mL methanol. Totally 30 mL methanol was collected and 60 mg silica gel was added into the
methanol. The mixture was dried at 25 °C in a TurboVap LV evaporator (Zymark). The solid obtained was packed in a rotor for $^{13}$C NMR analysis.

2.3. $^{13}$C NMR spectroscopy

NMR analysis was conducted with a standard bore 300 MHz Bruker Avance III spectrometer (Bruker BioSpin, Billerica, MA) equipped with a 4 mm magic angle spinning (MAS) probe, operating at a spinning frequency of 12,000 Hz, following the method by Longbottom et al. (2017). Spectra were acquired with a variable amplitude cross-polarization (CP) sequence with 1 ms contact time and composite pulse decoupling during signal acquisition. All spectra were exponentially apodized, zero filled to 16,384 data points, and Fourier transformed with 50 Hz line broadening. Dipolar dephasing experiments were carried out on each sample allowing a dephasing delay of 70 μs, following the methods by Smernik and Oades (2011).

2.4. Chlorination and chloramination after Fe(VI) pretreatment

As shown in Results and Discussion, Fe(VI) converted aromatic C in SRHA to aliphatic C. It was expected that less aromatic DBPs could be generated during subsequent chlorination or chloramination of the Fe(VI) treated water samples. A series of 1100 mL water samples were prepared with different treatments, i.e., chlorination with and without Fe(VI) pretreatment, chloramination with and without Fe(VI) pretreatment (with details shown in Text SM-1). The composition of simulated source water was the same as aforementioned; Fe(VI) treatment was conducted with 0.25 mM Fe(VI) for 30 min; chlorination was done with 5.0 mg/L NaOCl as Cl$_2$ for 6 h, and chloramination was with 5.0 mg/L NH$_2$Cl as Cl$_2$ for 96 h. The water samples were maintained at pH 8.0 during chlorination and chloramination. The relatively short contact time for chlorination and long contact time for chloramination were selected to enhance the formation of aromatic DBPs (Zhai et al., 2014). Prior to analysis, the chlorine residual in each water sample was quenched with 105% stoichiometric amount of Na$_2$S$_2$O$_3$. Multiple samples were prepared for chemical analysis with HRMS and HPLC/tqMS, and cytotoxicity measurement with Caco-2 cell.

2.5. Analysis of overall DBPs with high-resolution mass spectrometry (HRMS)

Each water sample was subjected to liquid-liquid extraction and solvent evaporation, and the organic compounds were transferred and concentrated in 1.0 mL methanol (with details shown in Text SM-2). The methanol solution was injected to an Orbitrap Fusion Lumos mass spectrometer (with a mass resolving power of 500,000 at $m/z$ 200, $R = m/Δm_{50%}$), equipped with an Ion Max NG electrospray ionization (ESI) source (Thermo Scientific). The flow rate was 5 μL/min and negative-ion ESI mode was applied to obtain full-scan mass spectra ($m/z$ 100–600) for each sample. Optimized ESI source conditions were as follows: sheath and auxiliary gas flow 5 and 2 units; heated capillary temperature 275 °C; electrospray voltage −2.1 kV; RF Lens 60 V. For each sample, data were collected for 400 scans with a maximum injection time of 300 ms and automatic gain control target of $1.0 \times 10^6$. Fluoranthene was used for internal mass calibration. This strategy achieved high mass accuracy with average root mean square error below 0.5 ppm (Table SM-2). Initial peak lists with predicted formulas ($m/z$ accuracy ≤ 1 ppm error) were generated using Thermo Xcalibur (Ver. 2.2) following elemental criteria: C ≤50, H ≤100, O ≤25, N ≤3, $^{35}$Cl ≤5,
37Cl ≤ 3, 79Br ≤ 5, 81Br ≤ 3, I ≤ 3. The detection limit was arbitrary chosen to be 100 counts. Elemental criteria described previously (Zhang et al., 2014) were applied and only formulas that are chemically feasible were included in subsequent analysis. For ion clusters predicted to be chlorine- and/or bromine-containing compounds, isotopic patterns were cross-checked to improve confidence of formula assignments.

2.6. Identification and quantitation of halo-DBPs using HPLC/tqMS

Each pretreated water sample (in methanol, Text SM-2) was injected to an ESI-tqMS (Thermo Scientific TSQ Quantum Access Max) at 10 μL/min. The iodo-, bromo- and chloro-DBPs were selectively detected with precursor ion scans (PISs) of m/z 126.9, 79/81 and 35/37, respectively (Zhai et al., 2014; Pan et al., 2017; Yang et al., 2019). The instrument was operated at negative ESI mode with the optimized parameters as shown in Table SM-3. The ESI-tqMS was coupled with a HPLC (Thermo Scientific Ultimate 3000). Five μL of the pretreated sample was injected into the HPLC with a Waters XSelect HSS T3 column (100 × 2.1 mm, 2.5 μm particle size). The run time was 18 min. The mobile phase was at 0.30 mL/min and composed of acetonitrile and water. The composition of acetonitrile/water (v/v) was 10/90 in the first 1 min, and changed linearly from 10/90 to 90/10 from 1 to 12 min. The ratio then returned to 10/90 in 1 min and stayed at 10/90 for 5 min for re-equilibration. Each ion or each pair of ion clusters detected by ESI-tqMS PISs m/z 126.9, 79/81 or 35/37 was further analyzed with HPLC/ESI-tqMS selected reaction monitoring (SRM) scan and product ion scan (with parameters in Table SM-3), to tentatively determine the structure. The corresponding standard compound was then purchased, and the DBPs were confirmed by comparing chromatographic congruence and mass fragments.

2.7. Cytotoxicity assessment with human epithelial colorectal adenocarcinoma Caco-2 cell

The Caco-2 cell line (ATCC, HTB-37, passages 40–42) was cultured in DMEM medium in T-75 flasks, in an incubator (37 °C, 5% CO2). The medium was changed every two days. Prior to toxicity assessment, each water sample was concentrated using freeze drying, which could effectively recover organic and inorganic DBPs (Han and Zhang, 2018). To generate toxicity test solutions (with different concentration factors relative to the initial water sample), the dry solids obtained from a water sample were re-dissolved in different volumes of cell culture medium. Caco-2 cells of 70–80% confluency in T-75 flasks were seeded into 24-well plates at the density of 4 × 10^4 cells/cm^2 in 0.75 mL medium per well. The cells were further incubated for 48 h to facilitate cell attachment. Then, the medium in each well was replaced by a 0.5 mL toxicity test solution or fresh medium (as control), and cells were incubated for another 24 h. After 24 h, the test solution was removed, and the cells were rinsed with 0.5 mL PBS. Then, 0.5 mL DMEM medium and 0.1 mL MTS assay were sequentially added to each well and the cells were incubated for an additional 2 h. The optical densities at 490 nm of all wells were measured using a BioTek Synergy H1 plate reader. The viability of Caco-2 cells in a test solution was calculated as the ratio of the optical density of the test solution to that of the control medium.

MTS cytotoxicity assay was conducted in four replicates. One-way Student’s t test was performed using the software Prism 8 (GraphPad) to determine the significant differences (p
< 0.05) between the cytotoxicity responses of chlorinated (or chloraminated) water samples with and without Fe(VI) pretreatment.

3. Results and discussion

3.1. Reaction between Fe(VI) and SRHA in source water

The reaction between Fe(VI) and SRHA decreased the DOC in water by 23.3% (Table SM-4). This amount of DOC could be removed from the dissolved phase as aggregates, due to the coagulation effect of Fe(VI), or converted to inorganic C due to the oxidation by Fe(VI) (Dong et al., 2019a; Yang et al., 2015). The removal of DOC depended on the dose of Fe(VI), concentration and characteristic of DOC in water and reaction conditions. It was reported that the DOC contents in real and simulated source water samples (initially 3 mg/L) decreased by 18% and 28%, respectively, after the reaction with 20 mg/L Fe(VI) (Gan et al., 2015; Yang et al., 2015). Fe(VI) treatment in the dosages of 2.5–10 mg/L to secondary effluent samples (containing 2.5–10 mg/L DOC) could remove up to 30% DOC (Yang et al., 2012). Zhang et al. (2020) applied 1.0–6.0 mg/L Fe(VI) to treat reservoir water (with 5.66 mg/L DOC) and river water (with 4.03 mg/L DOC), and obtained 5%–40% and 14%–24% decreases of DOC levels, respectively. Barışçi (2017) studied the reaction between Fe(VI) with humic acid in solution (with the initial concentration of 3.486 mg/L as C), and found that 60% DOC removal was achieved with 25 mg/L Fe(VI).

Figure SM-1 compares the $^{13}$C NMR spectra of SRHA and Fe(VI) treated SRHA, and Table 1 shows the carbon functional group relative abundances of the two samples. Significantly, Fe(VI) caused a large decrease in aromatic (including phenolic) C (from 32.0% to 6.3%), and minor decreases in N-alkyl and methoxyl C, di-O-alkyl C, amide and carboxyl C, and ketone and aldehyde C. These functional groups were converted to O-alkyl and alkyl C, which were dominant components in the Fe(VI) treated SRHA. Besides, the C functional groups with chemical shifts of 0–110 ppm were saturated, and those with chemical shifts ≥110 ppm were unsaturated. In the SRHA without Fe(VI) treatment, 50.3% C was saturated and 49.7% was unsaturated. With Fe(VI) treatment, 23.3% C was removed from the solution, saturated DOC increased to 60.1% and unsaturated DOC accounted for only 17.0%. These results indicate the conversion of unsaturated C constituent to saturated constituent. The lower degrees of aromaticity and unsaturation of SRHA resulted from Fe(VI) treatment may play a pivotal role in affecting the species of generated DBPs in subsequent disinfection as discussed below.

3.2. Effect of Fe(VI) pretreatment on DBP mixtures generated in subsequent chlorination and chloramination

In this study, HRMS was employed to analyze the overall organic DBPs in water samples with different treatments, i.e., chlorination with and without Fe(VI) pretreatment, and chloramination with and without Fe(VI) pretreatment. Summary of all detected ions, their assigned formulas, intensities and other relevant information are provided in spread sheet in Supporting Materials. Table 2 compares the numbers of halo-DBPs with various double bond equivalents (DBEs) in different water samples. Fe(VI) pretreatment decreased the numbers of detected halo-DBPs in chlorinated and chloraminated water samples by 80.5%
and 72.4%, respectively. In the chlorinated sample, the halo-DBPs with 0–6 DBE decreased by 71.6–75.5%; and the halo-DBPs with ≥7 DBE decreased by 91.1–95.2%. In the chloraminated sample, the highly unsaturated halo-DBPs (DBE ≥7) decreased to a greater extent than the moderately unsaturated halo-DBPs (DBE 4–6), and the relatively saturated halo-DBPs (DBE 0–3) increased by 9.5%. The average DBE of all the halo-DBPs in each water sample could be calculated as follows

\[
\text{Average DBE} = \frac{\sum I_i \times DBE_i}{\sum I_i}
\]

where \(I_i\) denotes the intensity the molecular ion (Andersson et al., 2019; Li et al., 2014). The average DBE values of chlorinated and chloraminated water samples without Fe(VI) treatment were 1.85 and 3.04, respectively, and the values of chlorinated and chloraminated samples with Fe(VI) pretreatment were 1.04 and 0.97, respectively. It has been reported that unsaturated sites of NOM, including olefins, phenolic and ketone moieties, are important precursors of halo-DBPs generated in chlorination and chloramination (Deborde and von Gunten, 2008; Yang et al., 2008; Bond et al., 2012; Önnby et al., 2018; Jiang et al., 2020). The formation mechanism of halo-DBPs mainly includes oxidation and halogen substitution, and the halo-DBPs generated were less likely to have higher degrees of unsaturation than the corresponding precursors (Deborde and von Gunten, 2008; Yang et al., 2008; Bond et al., 2012; Gong et al., 2017; Jiang et al., 2020). As shown in \(^{13}\text{C\ NMR\ results}, \text{Fe(VI)}\) pretreatment decreased the degree of unsaturation of SRHA in water, and this could lead to a lower average DBE of the halo-DBP mixture formed in subsequent chlorination or chloramination.

Table 3 shows that Fe(VI) pretreatment also decreased the numbers of overall organic compounds (including non-halogenated and halogenated DBPs) in chlorinated and chloraminated water samples. Similar selectivity was observed in the chloraminated water, i.e., highly unsaturated organic compounds (DBE ≥10) decreased more than moderately unsaturated compounds (DBE 4–9), and relatively saturated compounds (DBE 0–3) increased, but this selectivity in decreasing highly unsaturated compounds was not observed in the chlorinated water sample.

Table 4 compares the numbers of halo-DBPs based on the halogen type, and shows that Fe(VI) pretreatment decreased the formation of chloro-, bromo- and iodo-DBPs. Especially, iodo-DBPs were hardly detected in the chlorinated and chloraminated samples with Fe(VI) pretreatment. This is consistent with the finding by Jiang et al. (2019) that Fe(VI) pretreatment decreased the concentrations of total organic iodine (TOI, a collective parameter of all iodo-DBPs) in chlorine or chloramine disinfected waters. The reason could be that Fe(VI) oxidized the iodide in source water to iodate, which would not react with NOM to generate iodo-DBPs (Wang et al. 2018). Tables SM-5 and SM-6 further compare the numbers of halo-DBPs based on their halogen compositions. The chlorinated water sample without Fe(VI) pretreatment contained DBPs with 1–6 halogens (Table SM-5), and the chloraminated sample without Fe(VI) pretreatment contained DBPs with 1–4 halogens (Table SM-6). With Fe(VI) pretreatment, all types of DBPs decreased, and the DBPs with ≥3 halogens decreased to a greater extent than the DBPs with 1–2 halogens.
Figures SM-2–SM-5 are the spectra of ESI-tqMS PISs m/z 79 and m/z 35 of the chlorinated and chloraminated water samples with and without Fe(VI) pretreatment. Total ion intensities (TIIs) in the PIS spectra of m/z 79 (from m/z 100–500) and m/z 35 (from m/z 90–500) were reported to be positively related to the concentrations of total organic bromine (TOBr) and total organic chlorine (TOCl) in the water sample, respectively (Liu et al., 2015; Cai et al., 2016; Liu et al., 2017). TOBr and TOCl are collective parameters of all bromo- and chloro-DBPs. From the results, Fe(VI) pretreatment decreased the TIIs of all bromo-DBPs (from $1.89 \times 10^8$ to $7.76 \times 10^7$) and chloro-DBPs (from $6.36 \times 10^5$ to $1.52 \times 10^5$) in the chlorinated water sample, and the TII of all chloro-DBPs (from $5.62 \times 10^5$ and $2.44 \times 10^5$) in the chloraminated sample, but increased the TII of all bromo-DBPs (from $6.08 \times 10^7$ and $6.92 \times 10^7$) in the chloraminated sample. Jiang et al. (2019) studied the effect of Fe(VI) pretreatment on halo-DBPs formed in chlorination or chloramination, and found that Fe(VI) pretreatment could increase or decrease the TOBr concentration in the disinfected water under different reaction conditions. In this study, TII values in different m/z ranges were calculated to represent the total concentrations of DBPs with different molecular weights in each water sample (Fig. 1). Results show that Fe(VI) pretreatment decreased the formation of bromo- and chloro-DBPs in all m/z ranges in the chlorinated water sample, as well as the chloro-DBPs in all m/z ranges in the chloraminated sample. In the case of Fe(VI) pretreatment and subsequent chloramination, lower levels of high mass bromo-DBPs (m/z 301–500), and higher concentrations of low mass bromo-DBPs (m/z 100–300) were generated, compared with chloramination only.

3.3. Effect of Fe(VI) pretreatment on the formation of individual halo-DBPs

With HPLC/ESI-tqMS PIS, product ion scan, and SRM scan, 28 halo-DBPs were detected in the chlorinated and chloraminated water samples, in which 11 DBPs were confirmed with commercial standards (Table SM-7). The concentration of each DBP in each water sample was expressed as the SRM chromatographic peak area, and the peak area detected in the (chlorinated or chloraminated) water sample without Fe(VI) treatment was defined as 100% (Fig. 2). Fig. 2a illustrates the concentration differences of five aromatic and 13 aliphatic DBPs in the chlorinated water samples with and without Fe(VI) pretreatment. In the Fe(VI) pretreated sample, the concentrations of aromatic DBPs and iodo-DBPs were undetectable, and most bromoaliphatic- and chloroaliphatic-DBPs decreased, but bromopropionic acid and chloroacetic acid increased. Similarly, Fe(VI) pretreatment effectively inhibited the generation of aromatic DBPs and iodo-DBPs in chloramination, but enhanced the formation of some aliphatic DBPs, including bromopropenoic acid, bromopropionic acid, dibromoacetic acid, bromoacetic acid, dichloroacetic acid and chloroacetic acid (Fig. 2b). These data were consistent with the $^{13}$C NMR results, i.e., Fe(VI) treatment converted the aromatic C in SRHA to aliphatic C, and consequently switch the DBPs generated in subsequent disinfection from being aromatic to aliphatic.

3.4. Detoxification of chlorinated and chloraminated drinking waters by Fe(VI) pretreatment

Fig. 3 shows the viabilities of Caco-2 cells after 24 h exposure to the 50×, 40× and 25× concentrated chlorinated and chloraminated water samples with and without Fe(VI) pretreatment. A sample showing a lower viability was more cytotoxic than the sample
with a higher viability. The results from water samples with different concentration factors consistently show that Fe(VI) pretreatment significantly decreased the cytotoxicity of chlorinated water sample (Fig. 3a, c, e). The reason is that Fe(VI) pretreatment inhibited the formation of total chloro-, bromo- and iodo-DBPs, especially haloaromatic DBPs in the chlorinated water. Haloaromatic DBPs were reported to exhibit significantly higher toxicity than haloaliphatic acids (Liu and Zhang, 2014). In the case of chloramination, Fe(VI) pretreatment caused a higher total concentration of bromo-DBPs, but lower cytotoxicity of the water sample (Fig. 3b, d, f). This indicates that the control of iodo-DBPs and haloaromatic DBPs by Fe(VI) pretreatment played a dominant role in detoxifying the chloraminated water sample.

4. Conclusions

- The reaction of Fe(VI) and SRHA decreased the DOC concentration in water.
- Fe(VI) converted the unsaturated aromatic C functional groups of SRHA to saturated aliphatic ones.
- Fe(VI) treatment followed by chlorination (or chloramination) generated DBPs with lower degrees of unsaturation, aromaticity, and halogenation compared with chlorination (or chloramination) only.
- These changes of DBPs resulted in significantly lower cytotoxicity responses of the chlorinated and chloraminated drinking waters, indicating that Fe(VI) pretreatment is a promising strategy of controlling DBPs that possibly induced adverse effects on humans.

5. Author Statement

Jiaqi Liu collected most of the data of this paper. Henry Lujan assisted Jiaqi Liu in cytotoxicity assessment. Birendra Dhungana performed high resolution mass spectrometry (HRMS) analysis. William C. Hockaday helped Jiaqi Liu conduct $^{13}$C nuclear magnetic resonance (NMR) spectroscopy analysis. All authors discussed the interpretation of results and contributed to manuscript writing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Dr. Jiaqi Liu was supported by the U.S. National Institutes of Health institutional training grant T32 ES026568. The authors acknowledge the Baylor University Mass Spectrometry Center for support in HRMS analysis; Dr. Jeff Back for measuring DOC concentrations; Dr. Mingbao Feng for his assistance in the synthesis of Fe(VI) and freeze drying of water samples; Matthew Gibb for conducting statistical analysis of cytotoxicity data; and Sujan Shrestha for analyzing HRMS data.
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Fig. 1.
Total ion intensities (TIIs) of various m/z ranges of the ESI-tqMS PIS spectra of (a, b) chlorinated water samples with and without Fe(VI) pretreatment, and (c, d) chloraminated water samples with and without Fe(VI) pretreatment. (a) and (c) are comparisons of bromo-DBPs (detected by PIS m/z 79); (b) and (d) are comparisons of chloro-DBPs (detected by PIS m/z 35).
Fig. 2.
Halo-DBPs detected in different water samples: (a) chlorination without and with Fe(VI) pretreatment; (b) chloramination without and with Fe(VI) pretreatment. For each DBP, the peak area detected by HPLC/ESI-tqMS SRM scan in the water sample without Fe(VI) pretreatment, i.e., the chlorination sample in (a), or the chloramination sample in (b), was defined as 100%; the peak area detected in the sample with Fe(VI) pretreatment was expressed as the percentage of the peak area in the sample without Fe(VI) pretreatment. The DBPs marked with an asterisk were confirmed with commercial standards.
Viabilities of Caco-2 cells after 24 h exposure to (a, b) 50×, (c, d) 40×, and (e, f) 25× concentrated water samples: (a, c, e) chlorination without and with Fe(VI) pretreatment; (b, d, f) chloramination without and with Fe(VI) pretreatment. Each data point represents the average and standard deviation of quadruplicate measurements.
Table 1
Relative abundances (%) of carbon functional groups of SRHA in source waters without and with Fe(VI) treatment determined by $^{13}$C CPMAS NMR.

| Chemical shift (ppm) | Functional group assignment | SRHA sample | Without Fe(VI) treatment | With Fe(VI) treatment |
|----------------------|-----------------------------|-------------|--------------------------|----------------------|
| 0–45                 | Alkyl C                     |             | 23.9                     | 29.7                 |
| 45–60                | N-Alkyl and Methoxyl C      |             | 6.8                      | 4.3                  |
| 60–95                | O-Alkyl C                   |             | 13.0                     | 24.9                 |
| 95–110               | Di-O-Alkyl C                |             | 6.6                      | 1.2                  |
| 110–145              | Aromatic C                  |             | 21.9                     | 4.9                  |
| 145–165              | Phenolic C                  |             | 10.1                     | 1.4                  |
| 165–190              | Amide and Carboxyl C        |             | 13.4                     | 7.5                  |
| 190–215              | Ketone and Aldehyde C       |             | 4.3                      | 3.3                  |
| Summation$^a$        |                             |             | 100                      | 77.1                 |

$^a$The DOC concentration in source water decreased by 23.3% after Fe(VI) treatment.
Table 2

Numbers of halo-DBPs with various DBEs in different water samples detected by HRMS.

| Double bond equivalent (DBE) | Chlorination | Chloramination |
|-----------------------------|--------------|---------------|
|                             | Without Fe(VI) pretreatment | With Fe(VI) pretreatment | Change (%)<sup>a</sup> | Without Fe(VI) pretreatment | With Fe(VI) pretreatment | Change (%)<sup>a</sup> |
| 0–3                         | 184          | 45            | −75.5                  | 21            | 23            | 9.5                     |
| 4–6                         | 204          | 58            | −71.6                  | 101           | 32            | −68.3                   |
| 7–9                         | 147          | 7             | −95.2                  | 71            | 1             | −98.6                   |
| ≥10                         | 56           | 5             | −91.1                  | 17            | 2             | −88.2                   |
| Summation                   | 591          | 115           | −80.5                  | 210           | 58            | −72.4                   |

A negative number indicates Fe(VI) pretreatment decreased the number of halo-DBPs.

<sup>a</sup>The change was calculated as \( \frac{\text{Number of "with Fe(VI) pretreatment"} - \text{Number of "without Fe(VI) pretreatment"}}{\text{Number of "without Fe(VI) pretreatment"}} \times 100\% \).
Table 3

Numbers of organic (non-halogenated and halogenated) compounds with various DBEs in different water samples detected by HRMS.

| Double bond equivalent (DBE) | Chlorination Without Fe(VI) pretreatment | With Fe(VI) pretreatment | Change (%)$^a$ | Chloramination Without Fe(VI) pretreatment | With Fe(VI) pretreatment | Change (%)$^a$ |
|------------------------------|------------------------------------------|--------------------------|---------------|-------------------------------------------|--------------------------|---------------|
| 0–3                          | 259                                      | 121                      | −53.3         | 114                                       | 142                      | 24.6          |
| 4–6                          | 414                                      | 237                      | −42.8         | 339                                       | 325                      | −4.1          |
| 7–9                          | 388                                      | 240                      | −38.1         | 341                                       | 330                      | −3.2          |
| ≥10                          | 269                                      | 156                      | −42.0         | 354                                       | 189                      | −46.6         |
| Summation                    | 1330                                     | 754                      | −43.3         | 1148                                      | 986                      | −14.1         |

A negative number indicates Fe(VI) pretreatment decreased the number of the compounds.

$^a$The change was calculated as

\[
\text{Change} = \left( \frac{\text{Number of "with Fe(VI) pretreatment"} - \text{Number of "without Fe(VI) pretreatment"}}{\text{Number of "without Fe(VI) pretreatment"}} \right) \times 100\%
\]
Table 4

Numbers of halo-DBPs with various numbers of halogens in different water samples detected by HRMS.

| Number of specific halogen | Chlorination | Chloramination |
|----------------------------|--------------|---------------|
|                            | Without Fe(VI) pretreatment | With Fe(VI) pretreatment | Without Fe(VI) pretreatment | With Fe(VI) pretreatment |
| Chloro-DBPs                |              |               |                            |                          |
| 1Cl                        | 13           | 11            | 29                          | 6                         |
| 2Cl                        | 77           | 4             | 21                          | 1                         |
| 3Cl                        | 44           | 0             | 9                           | 1                         |
| 4Cl                        | 96           | 3             | 3                           | 0                         |
| Summation                  | 230          | 18            | 62                          | 8                         |
| Bromo-DBPs                 |              |               |                            |                          |
| 1Br                        | 367          | 93            | 93                          | 46                        |
| 2Br                        | 142          | 10            | 10                          | 4                         |
| 3Br                        | 23           | 4             | 0                           | 0                         |
| 4Br                        | 5            | 1             | 1                           | 0                         |
| Summation                  | 537          | 108           | 104                         | 50                        |
| Iodo-DBPs                  |              |               |                            |                          |
| 1I                         | 76           | 0             | 47                          | 1                         |
| 2I                         | 12           | 0             | 2                           | 0                         |
| 3I                         | 1            | 0             | 0                           | 0                         |
| Summation                  | 89           | 0             | 49                          | 1                         |