Research progress of disinfection and disinfection by-products in China

Xuefeng Sun[1,2], Miao Chen[1,2], Dongbin Wei[1,2,*], Yuguo Du[1,2,*]

1. State Key Laboratory of Environmental Chemistry and Eco-Toxicology, Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences, Beijing 100085, China
2. University of Chinese Academy of Sciences, Beijing 100049, China

ARTICLE INFO

ABSTRACT

Disinfection is an indispensable water treatment process for killing harmful pathogens and protecting human health. However, the disinfection has caused significant public concern due to the formation of toxic disinfection by-products (DBPs). Lots of studies on disinfection and DBPs have been performed in the world since 1974. Although related studies in China started in 1980s, a great progress has been achieved during the last three decades. Therefore, this review summarized the main achievements on disinfection and DPBs studies in China, which included: (1) the occurrence of DBPs in water of China, (2) the identification and detection methods of DBPs, (3) the formation mechanisms of DBPs during disinfection process, (4) the toxicological effects and epidemiological surveys of DBPs, (5) the control and management countermeasures of DBPs in water disinfection, and (6) the challenges and chances of DBPs studies in future. It is expected that this review would provide useful information and reference for optimizing disinfection process, reducing DBPs formation and protecting human health.

© 2019 The Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences.
Published by Elsevier B.V.

Contents

* Corresponding authors. E-mails: weidb@rcees.ac.cn, (Dongbin Wei), duyuguo@rcees.ac.cn. (Yuguo Du).

Introduction

Disinfection is a necessary water treatment unit for killing harmful pathogens and protecting public health from infectious water-borne diseases. Disinfection has been adopted as a standard treatment for drinking water, swimming pool water and reclaimed water. The commonly used chemical disinfectants include chlorine, ozone, chlorine dioxide, chloramine, and so on (Richardson, 1998). Among these, chlorine is the predominantly used disinfectant due to its efficient bacteria-killing ability, convenient operation and low cost (Li et al., 2013a). Chlorine-containing disinfectants mainly include chlorine gas (Cl_2), sodium hypochlorite (NaClO) and calcium hypochlorite (Ca$(ClO)_2$) (WHO, 2006). The typical concentration of available chlorine in WTPs of China was about 0.3–0.5 mg/L. Although chemical disinfectants are effective for killing harmful pathogens, they may react with natural organic matter (NOM), anthropogenic contaminants in water and generate unexpected DBPs. The studies on disinfection and DBPs has drawn much attention in the last decades due to their significant toxicological effects.

Trichloromethane (TCM) was the first DBP identified from chlorinated drinking water in 1974 (Rook, 1974; Bellar et al., 1974). Two years later, the reports from the U.S. EPA and the National Cancer Institute showed that, trihalomethanes (THMs) were ubiquitous in chlorinated drinking water, and TCM was carcinogenic in laboratory animals. Since then, disinfection and DBPs became a hot research field, and lots of efforts have been directed toward increasing our understanding on DBPs formation, occurrence, and health effects. Up to September 2018, more than 8700 articles and 1000 patents on DBPs have been published around the world. Among them, the United States had the largest contribution, accounting for ca. 30% of all related publications worldwide. Water Research and Environmental Science & Technology were the most popular journal sources in this field, in which more than 1000 research articles on DBPs were published.

Although the study on disinfection and DBPs in China was about 10 years later than in the USA, the Chinese scientists and engineers have paid more attention to this topic. Based on the statistical data of publications and researchers in the past 40 years, China has the second largest contribution in the world. More than 1700 scientists and engineers from about 200 institutions in China have achieved fruitful work on DBPs related science research and engineering practices. Up to now, more than 1600 publications can be searched from the ISI Web of Science database, and about 1800 Chinese publications can be searched from the China National Knowledge Infrastructure (CNKI) database. Among them, more than 80% articles were published during the last 10 years. The Chinese Academy of Science, Tongji University and Tsinghua University were the top three institutions that had the highest numbers of publications in China. The studies on the disinfection and DBPs in China mainly include: occurrence of DBPs, identification and detection of DBPs, formation of DBPs, toxicity and toxicological mechanisms of DBPs, and control and management of DBPs. A summary of DBPs studies in China during 1974–2018 is shown in Fig. 1.

1. Occurrence of DBPs in China

Considering the potential adverse biological effects, some DBPs have been regulated by several national and international agencies, named as regulated DBPs. For example, China has regulated TCM, dichloromethane (DCM), bromodichloromethane (BDCM), dibromochloromethane (DBCM), dichloroacetic acid (DCAA), trichloroacetic acid (TCAA), etc. in the "Standards for drinking water quality of China (GB/T5749-2006)". And the others, have not been regulated in the standards are named as "unregulated DBPs". The first report on DBPs in China was published in 1986, which showed the TCM levels in three drinking water treatment plants (disinfected with bleaching powder) ranged from 7.5 to 24 μg/L (Yang and Cai, 1986). The total concentration of four THMs (TCM, tribromomethane (TBM), DBCM and DCBM) in the drinking water collected from 24 large and medium-sized cities in China in 1984 ranged from 0.01 to 86 μg/L (Huang et al., 1987). A survey on THMs and haloacetic acids (HAAs) in drinking water from China mainland showed that the total concentrations of THMs and HAAs were generally present at not detected (ND) to 92.8 and ND-40 μg/L, respectively (Deng et al., 2008). However, Chang et al. (2010) reported that THMs levels in drinking water from Taiwan were occasionally beyond 100 μg/L. A total of 155 water samples were collected in 2011 and 2012 from Guangzhou, Foshan and Zhuhai. The median (range) levels of THMs and HAAs were 17.7 (0.7–62.7) μg/L and 8.6 (0.3–81.3) μg/L, respectively (Gan et al., 2013). Ding et al. (2013) detected 28 DBPs in 70 drinking water treatment plants from 31 cities across China, and the average detection frequency of 21 DBPs was 50%. Of these, THM_4 and HAAs were the predominant species, with median concentrations of 10.53 and 10.95 μg/L, respectively. Two iodine-containing THMs (I-THMs) ranged from
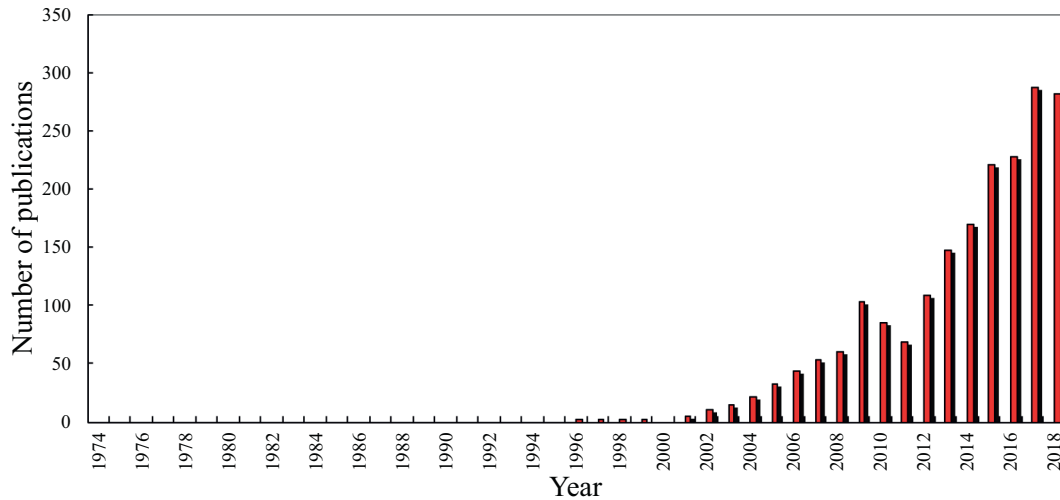
Fig. 1 – A summary of DBPs studies in China during 1974–2018

ND to 5.58 μg/L. The total median concentration of haloace-tonitriles (HANs) was 1.11 μg/L (ND to 39.20 μg/L). The maximum concentrations of chloronitromethane (CNM) and TCNM were 0.96 and 0.28 μg/L, respectively. A recent survey on DBPs occurr-ence in 8 counties in Jinhua Region of Zhejiang Province in China shows that median (range) of THMs, HAAs, HANs, haloketones (HKs) and halonitromethanes (HNMs) were 23.2 (9.1–40.9), 15.3 (5.8–38.6), 2.2 (0.7–7.6), 2.1 (0.2–6.4) and 0.7 (0.2–2.9) μg/L, respectively (Zhou et al., 2019). Bei et al. (2016) detected 9 nitrosamines (NAs) in 164 drinking water samples from 44 large-, medium-, and small-size cities of 23 Chinese provinces. It was found that N,N-dimethyl-nitrosamine (NDMA) was the domi-nant species, whose mean levels in finished water of plants and tap water were 11 and 13 ng/L, respectively. Compared to the California notification level of 10 ng/L, ~26% of the finished waters and ~29% of the tap waters exceeded this value. The percentage of detects of NDMA was 37% in Chinese water samples (based on using the same maximum residue limit (MRL) as in the U.S.), which was 3.6 times that in the U.S. (Bei et al., 2016). Another similar survey on N-DBPs (nitrogen-containing DBPs) occurrence in drinking water from six cities was performed from June 2015 to January 2016. It was found that the N-DBPs levels in coastal cities were higher than in inland ones, and in southern cities were higher than those in northern ones, which may because the source water in southern China has the characteristics of low turbidity, high algae and micro-pollution. Sewage discharge and algae activities will increase the concen-tration of nitrogen-containing precursors, promote the produc-tion of N-DBPs, result in the average level of N-DBPs in drinking water in southern cities is higher than that in northern cities. The concentration of trichloronitromethane (TCNM) was less than 1.21 μg/L in six cities. For Shenzhen city, the total concentrations of NAs in pipe water were 10.65–55.80 ng/L, and the concentration of predominant species NDMA was 37.76 ng/L. For Xiamen city, dichloroacetonitrile (DCAN) was the predominant species (5.25 μg/L) among the total HANs (ND – 9.36 μg/L) in pipe water (Dong et al., 2016). NDMA, N-nitrosodiethylamine, N-nitrosopiperidine, TCNM and four

HANs had higher concentrations in dry season than in wet season in Shenzhen, Fuzhou, Xiamen and Harbin. And Br-HANs (brominated HANs) had similar seasonal trend in three coastal cities (Dong et al., 2016). A survey on DBPs in swimming pool of China showed that the median concentrations of THMs, HAA9, chloral hydrate (CH), HAN4 and 1,1-dichloropropanone (DCP) and 1,1,1-trichloropropanone (TCP) were 33.8, 109.1, 30.1, 3.2, 0.8 μg/L and below detection limit, respectively (Zhang et al., 2015a). A recent survey found that the levels of TCM, BDCM, DBCM, and TBM in drinking water of Xi'an city ranged from ND to 52.50 mg/L (mean: 12.67 mg/L), ND to 12.80 mg/L (mean: 1.42 mg/L), ND to 8.50 mg/L (mean: 0.60 mg/L), and ND to 5.30 mg/L (mean: 0.13 mg/L) (Zhang et al., 2018). A survey on haloacetamides (HAcAms) concentrations of five DWTPs which use the Yangtze River or Yellow River as source water showed that the rank order of HAcAms was: Cl-HAcAms (15.3 μg/L) > > Cl-Br-HAcAms (1.2 μg/L) > Br-HAcAms (1.0 μg/L). Among the three Cl-HAcAms, dichloroacetamide (DCAcAm) had the highest concentration (10.7 μg/L), followed by trichloroacet-amide TCAcAm (3.1 μg/L) and chloroacetamide (CAcAm) (1.5 μg/L) (Yang et al., 2014b). The concentration data of some representative DBPs in China are listed in Appendix A Table S2. These results imply that the DBPs pollution in drinking water of China should be noticed.

2. Identification and detection of DBPs

About 700 DBPs have been identified, while more DBPs are unknown yet. Therefore, the identification and detection of regulated and unregulated DBPs is still an emergent task in disinfection practices. The identification of DBPs is mainly dependent on target analysis and non-target analysis. The target analysis for known DBPs was performed by using gas phase chromatography in tandem with mass spectrometer (GC–MS), high performance liquid phase chromatography in tandem with mass spectrometer (HPLC–MS) and related techniques (APHA, 1998). Wang et al. (2011) developed an improved liquid–

liquid extraction-gas chromatography-electron capture detector (LLE-GC-ECD) method for THMs detection, the detection limit for TCM, CCl$_4$, BDCM, DBCM and TBM were 0.002, 0.004, 0.008, 0.0012 and 0.011 μg/L, respectively. The study of Li et al. (2007) showed that the detection limit of improved GC-ECD for monochloroacetic acid (MCAA), monobromoacetic acid (MBAA), DCAA, trichloroacetic acid (TCAA), and dibromoacetic acid (DBAA) were 1.25, 0.10, 0.07, 0.05 and 0.05 μg/L, respectively. Except for the recommended or standard detection methods, researchers have also developed some analytical methods for DBPs to gain satisfactory sensitivity and detection limit. A cold on-column (COC) injection in track-oven mode coupled with a GC–MS system was developed for HNMs analysis (Chen et al., 2016b). The advantage of COC method over the conventional split/splitless injection was minimizing thermal degradation of HNMs, especially dibromochloro- and tribromo-nitromethanes in water. Huang et al. (2013) developed a fast and sensitive LLE method for HNMs analysis, which had good linearity (*r* > 0.9925), high recovery (81%–120%, RSD% < 6.7), and low detection limit (MDL: 0.017–0.217 μg/L).

As for the unknown DBPs, the common identification methods are GC–MS and HPLC-MS. For example, more than 600 peptides in drinking water samples were identified using HPLC-MS/MS method with multiple reaction monitoring (MRM) mode (Huang et al., 2017a). To identify more DBPs, the present instruments and methods should be optimized. A non-targeted screening method involving comprehensive two-dimensional GC × GC-qMS combined with OECD QSAR Toolbox Ver. 3.2 was developed for identifying and prioritizing the volatile and semi-volatile DBPs in drinking water (Li et al., 2016a). The method was successfully applied to identify DBPs formed during chlorination, chloramination or ozonation of raw water, more than 500 DBPs were tentatively identified in each sample. Recently, the application of ultra high resolution mass Fourier transform ion cyclotron resonance mass spectrometry coupled with electrospray ionization (ESI FT-ICR MS) has a rapid development and plays an important role in identifying the molecular composition of unknown DBPs and their precursors in water (Wang et al., 2016b; Zhang et al., 2012a; Zhang et al., 2012b; Zhang et al., 2014). By aiding of ESI FT-ICR MS, 659 mono-chlorinated products, 348 di-chlorinated products, 441 mono-brominated products, 37 di-brominated products, 178 mono-iodinated products, 13 di-iodinated products and 15 mono-chlorinated and iodinated products were indentified in the chlorinated drinking water sample, while only tens of products have been reported in previous studies (Wang et al., 2016b; Zhang et al., 2012a; Zhang et al., 2012b; Zhang et al., 2014). These results demonstrate that the ESI FT-ICR MS method can provide valuable molecular composition and structure information on unknown DBPs. Except for instrumental analysis, bioassay was also used to screen the formation of DBPs based-on their toxicity effects. The mammalian cell toxicity test was a useful tool for profiling the occurrence of toxic DBPs. For example, bacterial studies have shown that bromoacetic acid is approximately 20 times more cytotoxic and 200 times more mutagenic in *Salmonella typhimurium* strain TA100 than chloroacetic acid (Zhang et al., 2014). Xiao et al. (2013)) found that tens of disinfection by products were formed during chlorination treatment on benzophenone-4, and chlorinated

products exhibited high genotoxicity. The study of Li et al. (2013a) showed that the chlorination of cefazolin would produce sulfoxide products with high genotoxicity. The detection methods of main DBPs and detection limits in drinking water of China are shown in Table S3.

3. Formation mechanisms of DBPs

Among the identified 700 DBPs, the frequently detected DBPs in drinking water include THMs, HAAs, HANs, HAcAms, HKs, TCNM, trichloroacetaldehyde (CH), NAs and so on (Huang et al., 2017b; Wang et al., 2015b; Serrano et al., 2015). Recently, more and more researches have been conducted to identify DBPs and explore their formation mechanisms, toxicity effects, exposure characteristics, and potential health risk. In fact, how the DBPs form in disinfection treatment seems to be the first question that should be answered. Up to now, several chemical reactions involved in DBPs formation have been disclosed, which are summarized as following.

3.1. Substitution

Substitution is the most commonly occurring chemical reaction in chlorination disinfection process. The disinfectant hypochlorous acid is easily polarized as Cl$^{\oplus}$–OH$^{\ominus}$, the chlorine atom with partial positive charge will readily attack carbon atoms with partial negative charge, and form chlorinated products. During chlorine disinfection process, resorcinol can easily transform into mono-, di-, and tri-chlorinated resorcinol via substitution reaction (Fig. 2). Since the hydroxyl groups on 1- and 3-position of benzene ring have strong electron-donating effects, the carbon atoms on their *o*-, and *p*-position (2-, 4-, and 6-position of benzene ring) have more negative charge, which would be easily attacked by Cl$^{\oplus}$ to form chlorinated products. It has been reported that chlorinated resorcinol could be quickly transformed into TCM (Boyce and Hornig, 1983). When bromine or iodine ions are present in water chlorination, aqueous chlorine will easily oxidize the halides to hypobromous acid or hypoiodous acid respectively and, form some brominated or iodinated products. Chloramine is another disinfectant used widely, and substitution would also occur during chloramination treatment. During the chloramination of iodide-containing water, NOM would be converted into iodoform (CHI$_3$), iodoacetonitrile (IAN), diiodoacetonitrile (DIAN), iodoacetamide (IAcAm), diiodoacetamide (DIAcAm), iodoacetic acid (IAA) and TIAA. The important formation mechanism of these DBPs is iodine substitution. As shown in Appendix A Fig. S1, iodine will substitute both hydrogen atoms of the intermediate R-CH$_2$-CN to form R-CI$_2$-CN, which will be further hydrolyzed into DIAN (Liu et al., 2017). And the transformation pathways of NOM and formation of DBPs was provided in Appendix A Fig. S2.

3.2. Reduction–oxidation reaction

Reduction–oxidation (Redox) is a chemical reaction in which the oxidation states of atoms are changed. Any such reaction involves both a reduction process and a complementary
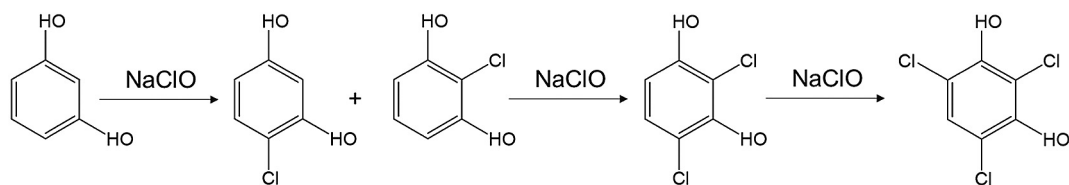
Fig. 2 – Chlorination substitution and formation of chlorinated resorcinol

oxidation process, two key concepts involved with electron transfer processes. Generally, redox reactions involve the transfer of electrons between chemical species. Redox reactions often occur during the disinfection process because most of chemical disinfectants are oxidative agents. NOM contains various function groups, such as carboxylic, aromatic, amino and hydroxyl, which easily react with oxidative disinfectants. Phenolic chemicals are often present in water, they would be oxidized into hydroquinone intermediate during disinfection and further formed benzoquinone, one kind of DBPs with high toxicity (Guan et al., 2018). Some reductive anions, such as iodide ions in source waters are easily oxidized to HOI, which can react with natural organic matter (NOM) to form various I-DBPs. As shown in Fig. S3, the tri-iodocarbonyl compound (R-CO-CI$_3$) can either be hydrolyzed to CHI$_3$ and a corresponding acid (R-COOH) or be oxidized to TIAA if the R- is an oxidizable group (Liu et al., 2017).

Except for the conventional redox reaction, Baeyer-Villiger oxidation was found by Xiao et al. in chlorination disinfection system (Fig. 3), the UV-filter benzophenone-4 (2-hydroxy-4-methoxy- benzophenone-5-sulfonic acid) was converted into phenyl ester derivatives (Xiao et al., 2013). Similarly, Liu et al. (2016b)) found Baeyer-Villiger oxidation could occur in the chlorination of 4-hydroxyl benzophenone. Baeyer-Villiger oxidation is an organic reaction that forms an ester from a ketone or a lactone from a cyclic ketone, using peroxy acids or peroxides as the oxidant (Baeyer and Villiger, 1899). First, peroxy acid protonates the oxygen of the carbonyl group, making the carbonyl group more susceptible to attack by peroxy acid. Second, peroxy acid attacks the carbon of the carbonyl group forming Criegee intermediate. Third, one of the substituents on the ketone migrates to the oxygen of the peroxide group while a carboxylic acid leaves. Finally, deprotonation of the oxocarbenium ion produces the ester (Baeyer and Villiger, 1899; Kürti and Czakó, 2005).

3.3. Hydrolysis

Hydrolysis usually means the cleavage of chemical bonds by the addition of water. Acid- or base-catalyzed hydrolysis is

very common. Take amides and esters as example, their hydrolysis occurs when nucleophile (a nucleus-seeking agent, e.g., water or hydroxide ions) attacks the carbon of the carbonyl group. In alkaline system, hydroxide ions are stronger nucleophiles than polar molecules such as water. In acid system, the carbonyl group is protonated resulting in easier nucleophilic attack. The final hydrolysis products contain carboxylic acid group. The chlorinated cytosine (a) is easily hydrolyzed to form (1-amino-1,2-dichloro-2-hydroxy-3-iminopropyl)- chlorocarbamic acid (b). And (b) would further take place hydrolysis and form chloromethanamine, 1-chloro-2-iminoethan-1-ol and chlorocarbamic acid after hydrolyzing (Appendix A Fig. S4) (Zhang et al., 2017a).

In the chlorination transformation of Tyr–Tyr–Tyr, two products DCAcAm and dichloroacetonitrile (DCAN) were detected. DCAN could transform to DCAcAm via hydrolysis, which would be further hydrolyzed into DCAA (Chu et al., 2015b). Another report showed that HAAs and some other trihalogenated DBPs (e.g., chloral hydrate) would take place hydrolysis and form THMs (Zhang et al., 2015a) (Fig. 4).

The esters compounds are also easily hydrolyzed under acid or alkaline conditions. Since HClO is a nucleophilic agent, it would promote the hydrolysis of esters. As mentioned above, UV filter benzophenone-4 was oxidized into ester via Baeyer-Villiger oxidation first, and the ester would be further hydrolyzed into corresponding phenolic and benzoic products (Appendix A Fig. S5) (Xiao et al., 2013).

3.4. Others

Substitution, redox, and hydrolysis are most predominant reactions during disinfection treatment. In addition, there are many kinds of unsatured chemical bonds in NOM and anthropogenic compounds, such as alkenes (C=C), alkynes (C≡C), ketones (C=O), imines (C=N), nitriles (C≡N) and so on. These compounds readily undergo addition reactions with disinfectants HClO or NH$_2$Cl and form addition products or its isomer during the chlor(am)ination process. Within the chlor(am)ination of acrylamide (Fig. 5), an initial Cl$^{\oplus}$ transferred to the double bonds and generated a chloronium ion,
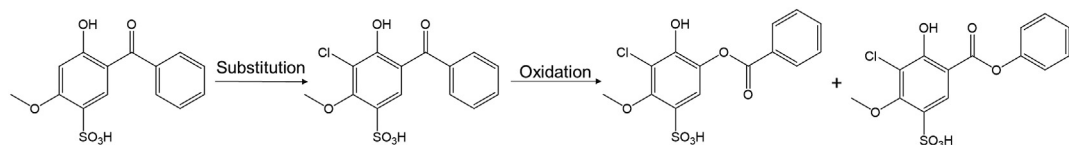

Fig. 3 – Baeyer-Villiger oxidation of benzophenone-4 during chlorination disinfection.
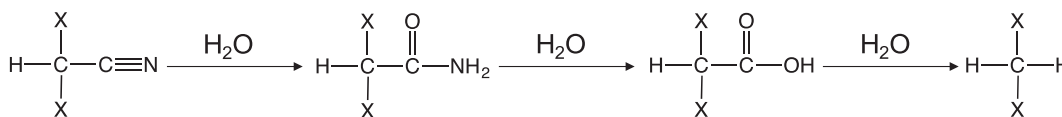
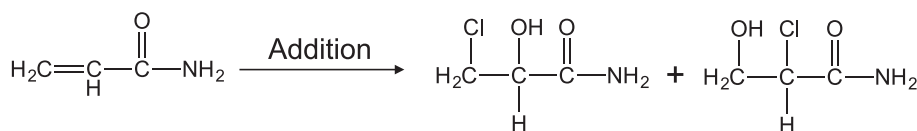Fig. 4 – Hydrolysis reactions of HANs and formation of THMs.

Fig. 5 – Addition reactions of acrylamide during chlorination process.

which is followed by the addition of $OH^{\square}$ (Ding et al., 2018). As shown in Fig. 5, addition also occurred in the process of dichloroacetic acid (DCAN) hydrolyzing and producing DCAcAm.

Along with the substitution reaction, some function groups such as carboxyl, amino, alkanes and sulfonic acid groups would be easily eliminated. Decarboxylation is a chemical reaction that removes a carboxyl group and releases carbon dioxide (CO_2). A study on chlorination of dipeptide Tyr–Ala showed that the carboxyl group in the chlorinated products of Tyr–Ala would be removed and form DCAN (Fig. 6) (Chu et al., 2015b). Furthermore, the results of tripeptide Tyr–Tyr–Tyr chlorination showed that trichloroacetonitrile (TCAN) could be produced through a dehydration reaction (Appendix A Fig. S6) (Chu et al., 2015b).

Xiao et al. (2013) found that product (A), formed from UV filter benzophenone-4 via chlorination and oxidation, would take place hydrolysis, chlorination and decarboxylation to form product (B). And product (B) would be further converted into product (C) via chlorination and desulfonation (Fig. 7).

Similarly, as shown in Fig. S7, the chlorination cytosine could transform into DCAA via hydrolysis and deamination (Zhang et al., 2017a).

In fact, the chemical reactions involved in disinfection process are very complex, and many of them take place simultaneously. Pan et al. (2016) found a new group of DBPs, trihalo-hydroxy-cyclopentene-diones, which would be easily decomposed to THMs and HAAs in the presence of excessive free chlorine. The possible reactions included bromine substitution on the benzene rings, further oxidation, addition and decarboxylation (Fig. 8).
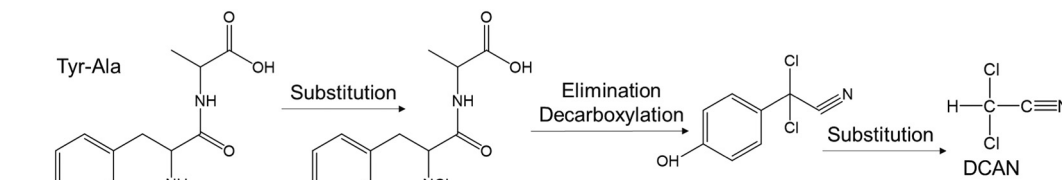
4. Toxicology and health effects of DBPs

DBPs having attracted much attention since more and more adverse biological effects were observed. In 1976, the US National Cancer Institute published the first toxicological results linking TCM to kidney epithelial tumors in laboratory rodents (Page and Saffiotti, 1976). Thereafter, the potential health impacts of DBPs became a sensitive but important issue. In the past decades, cytotoxic, genotoxic, mutagenic, teratogenic, carcinogenic, endocrine disrupting effects and some other toxicological effects of DBPs have been explored by scientists in China and other countries.

4.1. Cytotoxicity

Cytotoxicity is the quality of being toxic to cells. It is widely used to evaluate the adverse biological effect of DBPs. The cells treated with DBPs may undergo necrosis, losing membrane integrity and dying rapidly as a result of cell lysis. These processes of cell fates can be detected by staining method, luminescence method and so on. For example, MTT (3-(4,5-dimethyl-2-thiazolyl) -2,5-diphenyl-2-H-tetrazolium bromide) assay was used to measure the cytotoxicity of a new DBP phenazine. It was found that phenazine had significant cell-specific toxicity toward T24 (inhibitive concentration-50 (IC_{50}) 0.50 mmol/L) and HepG2 (IC_{50} 2.04 mmol/L) cell lines (Zhou et al., 2012a). A new real-time cell-electronic sensing (RT-CES) technique using T24 cell line as a probe was developed to analyze the comparative cytotoxicity of new DBPs halobenzoquinones (HBQs). The 72 hr-IC_{50} value of

Fig. 6 – The possible reactions occurred in chlorination of dipeptide Tyr–Ala.
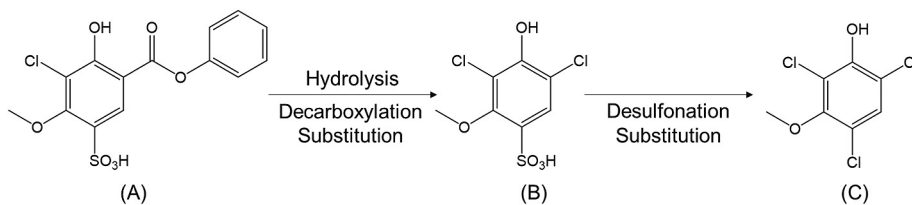
Fig. 7 – The possible reactions ocurred in benzophenone-4 chlorination.

dichlorobenzoquinone (DCBQ) was 3.1 mmol/L. This result fit well with those data measured with the conventional neutral red uptake (NRU) and MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) assays (for NRU, $R^2 = 0.9480$, $p < .05$) (Du et al., 2014). In addition, membrane integrity of cells is also an evaluation index of cytotoxicity. Lactate dehydrogenase (LDH) release was used to reflect the cytotoxicity of DBPs. When Neuro-2a cells were treated with CA (chloroacetic acid) for 24 hr, a significant increase in the release of LDH was observed. And the lethal dose-50 (LD_{50}) was determined as 1.5 mmol/L, which indicated that exposure of CA to neuronal cells can cause apoptosis (Lu et al., 2015).

Although MTT assay has been widely used in cytotoxicity assessment, it is not always suitable for measuring cytotoxicity of complex wastewater samples. Yang et al. (2015c) found that the signal of MTT assay with Chinese hamster ovary (CHO) cells treated with high concentration of secondary effluent samples (250–500 times concentrated) was quite lower than that of the control. The possible reason was attributed to the reaction of dye and phenolics in wastewater interfering the signal of MTT assay. Subsequently, the ATP assay with Luminescent Cell Viability Assay kit was used to measure the cytotoxicity of wastewater. The human liver hepatoma was treated with the same wastewater sample even at a lower concentration (50–130 times concentrated), the ATP decreased by 50%, which were consistent with those from flow cytometry determination (Yang et al., 2015c). Therefore, in order to avoid the interferential reactions of dyes with some substances in real environmental water, some cells with autologous luminescence or color were often adopted (Du et al., 2017b). For example, a marine bacteria strain *Photobacterium phosphoreum* was used to measure the acute toxicity variation of benzophenones UV-filters during disinfection processes, the results showed that the toxicity had significant increase after chlorination disinfection treatment (Chen et al., 2016c; Xiao et al., 2014).

In addition, some biological active molecules were chosen as biomarkers to reflect the adverse biological effects of DBPs.

The colorimetric protein phosphatase inhibition assay was used to evaluate the adverse effects of DBPs formed from the disinfection of microcystin-LR (MCLR-DBPs). The results showed that MCLR-DBPs had higher toxicity ($IC_{50} = 0.8$ μg/L) than their parent MCLR ($IC_{50} = 2.6$ μg/L), implying the secondary pollution of MCLR-DBPs in drinking water disinfection should be a concern (Zong et al., 2013). Interestingly, Pan et al. (2014b) conducted chronic cytotoxicity assay of DBPs with the CHO cells, and found cytotoxicity was reduced by 77% after boiling for 5 min. A survey on cytotoxicity and occurrence of 28 DBPs in 70 drinking water treatment plants from 31 cities across China showed that, HANs had the strongest cytotoxicity contribution in spite of their much low concentration (median value was 1.11 mg/L) in drinking water (Ding et al., 2013). Appendix A Table S4 shows the cytotoxicity information of main DBPs.

4.2. Genotoxicity and carcinogenicity (tumorigenicity)

Genotoxicity means the DNA damage induced by physical or chemical factors. The common genotoxicity assays can be classified into two major categories: DNA damage/repair assay (e.g., Ames test, comet assay and SOS/umu test) and chromosomal damage assay (micronucleus assays). With comet assay in HepG2 cell lines, the DNA-damaging potency of HAAs was ranked as: I-HAAs > Br-HAAs > Cl-HAAs according to their minimal effective concentrations (MECs) 0.01, 0.1, and 100 μmol/L, respectively (Zhang et al., 2012c). Using umu test with the genetically modified strain TA1535/pSK1002 of *S. typhimurium*, the genotoxicity variation during the chlorination disinfection of wastewater was evaluated. It was found that after disinfection treatment, the genotoxicity decreased for water with low NH_3-N level (<10–20 mg/L), while it increased for water with high NH_3-N level (>10–20 mg/L) (Wang et al., 2007a). Micronucleus (MN) assay is one of essential methods for assessing chromosome damage (Fenech, 2000). Hu et al. (2017) evaluated the genotoxicity potential of HAAs and HANs in chlorinated drinking water by the combination of *Vicia faba* MN test and comet assay, the
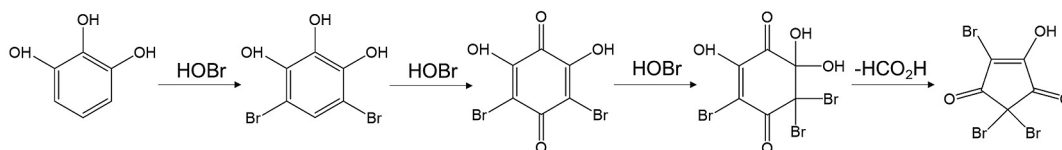

Fig. 8 – Multiple reactions involved in the formation of trihalo-hydroxy-cyclopentene-diones.

positive ratio was 75% in MN test and 100% in comet assay. In order to investigate the impact of recycling of combined filter backwash water (CFBW) to drinking water treatment plant (WTP), comet and MN assays with zebra fish (*Danio rerio*) were selected to evaluate the genotoxicity of water samples from two WTPs, one with recycling of CFBW, the other with a conventional process. The results showed that there was no statistically significant difference (P > 0.05) between the conventional and recycling processes. However, for each WTP, the water sample after disinfection treatment had higher DNA strand breaks and MN frequency (Hu et al., 2017).

Mutagenicity and carcinogenicity of DBPs may be attributed to the damage of genome, promotion of cells transformation, disturbance of cell cycle and gene expression or disruption of cellular metabolism. Studies have showed that exposure to the NAs-mixture doubled the revert ants in TA98 and TA100 *S. typhimurium* strains, increased DNA double-strand breaks and micronuclear frequency in NIH3T3 cells compared to a single exposure, indicating NAs-mixture exposure increased mutagenicity (Wang et al., 2017b). The ability to transform NIH3T3 cells to tumorigenic lines of iodoacetic acid (IAA) and iodoform (IF) in Shanghai drinking water was tested. It was found that IAA but not IF had carcinogenic potential because IAA was a potent inducer of NIH3T3 cell transformation with a positive response at 2 μmol/L (3.7×10^{-4} mg/mL), however, IF was negative in the transformation assay (Wei et al., 2013b).

In addition, the computer-based method was also applied to analyze the genotoxicity of unknown DBPs and avoid cumbersome and inconvenient biological experiments. QSAR (quantitative structure–activity relationship) is the most commonly used modeling method to predict biological activity by physico-chemical properties. Li et al. (2016a) used two-dimensional gas chromatography quadrupole mass spectrometry and OECD QSAR Toolbox to evaluate the genotoxicity of volatile and semi-volatile DBPs in drinking water, the results showed that the total volumes of genotoxic DBPs in chlorination (6.44×10^{7}) was higher than those in chloramination (4.23×10^{7}) and ozonation (3.19×10^{7}) processes. Li et al. (2016b) investigated the genotoxicity variation (SOS/umu assay with *S. typhimurium*) and 2D-, 3D-QSAR of 20 quinolones during chlorination disinfection. The results revealed that quinolones bearing hydrophilic substituents with less H-bond donors and negative charge at the 1-position of the quinolone ring exhibited a positive correlation with genotoxicity elevation.

Some other model methods such as RfD/C, slope factor approach developed by the USEPA ((2005), and disability-adjusted life years (DALYs, developed by World Health Organization, 2006) method were combined with the disease models to assess the potential cancer risk (e.g. renal and bladder cancer) resulting from DBPs exposure (Wang et al., 2007b). For example, DALYs method was used to assess the total cancer incidence caused by THMs and HAAs in drinking water of China based on water quality survey in 35 major cities. The ingestion exposures contributed 93.6% of risk, which was the most important pathway for the total risk, and TCAA produced the highest risk (2.12×10^{-7} DALYs ppy) among the DBPs considered (Pan et al., 2014a). The

genotoxicity of main DBPs in drinking water of China is shown in Table S5.

4.3. Other toxicities

Besides the cytotoxicity and genotoxicity, some other toxicity effects of DBPs were also found recently. For example, the antiestrogenic effect of the secondary effluent during chlorination disinfection was evaluated by using two-hybrid yeast cells containing rat estrogen receptor. After chlorination disinfection, the antiestrogenic activity of the sample spiked with bromide was 1.75 times than sample without bromide, indicating that bromide increased the anti-estrogenic activity of the secondary effluent during the chlorination disinfection (Wu et al., 2014). Developmental toxicity is the structural or functional alteration of the developmental processes (e.g., organogenesis, morphogenesis). The embryos of marine polychaete *Platynereis dumerilii* (PPD) and the marine green algal *Tetraselmis marina* were used to evaluate the developmental effects of DBPs (Yang and Zhang, 2013). It was surprisingly found that chlorinated saline wastewater effluents (effective concentration-50 (EC_{50}) was 51.7%) were less toxic than a chlorinated freshwater wastewater effluent (EC_{50} was 36.5%) using PPD, and this result was also confirmed by the tests using marine alga *Tetraselmis marina* (Yang et al., 2015a). In addition, the neurotoxicity of chloroacetic acids (CAA) was tested, and the possible mechanism was proposed that CAA could trigger apoptosis in neuronal cells via a reactive oxygen species-induced endoplasmic reticulum stress signaling pathway (Lu et al., 2015).

4.4. Toxicity test *in vivo*

Obeying the "3R" principle of animal experiment, convenience, and cost saving, most toxicity experiments were often conducted in vitro. However, the in vivo experiment is essential to confirm the toxicity effects and investigate the complex metabolic process of toxic chemicals. For example, metabonomics, histopathology and oxidative stress analysis on bromoacetonitriles (BANs) and HAcAms were conducted. It was found that BAN and HAcAms could induce oxidative stress by disrupting metabolism of amino acid, energy, and lipid in mice (Deng et al., 2014; Deng et al., 2017). Furthermore, the high-throughput sequencing and metabonomics were combined to explore the effects of trichloroacetamide (TCAcAm) exposure on the gut microbiome and urine metabolic profiles in mice. TCAcAm exposure not only altered the abundance level of gut microbiome but also disrupted the metabolic function of the gut microbiota, corresponding to metabolic dysfunction (Zhang et al., 2015b). *Caenorhabditis elegans* was used as model organism to determine the in vivo toxicity of 2,6-dichloro-1,4-benzoquinone (DCBQ). lethal concentration-50 (LC_{50}) and EC_{50} of DCBQ were 3.28×10^{2} and 6.37 μmol/L, respectively, which was more toxic than some regulated DBPs such as MBA, DBA, TCA, and DCA (LC_{50} and EC_{50} were 7.71×10^{2}–5×10^{4} μmol/L and 11.82–83.13 μmol/L, respectively). The results of in vivo tests were similar to those of in vitro tests, HBQs were up to 1000-fold more cytotoxic than some regulated DBPs in CHO test (Zuo et al., 2017).

4.5. Epidemiological survey

The epidemiological survey is an effective tool to connect DBPs with human diseases. In the last decades, tens of epidemiological surveys have been performed in China for the relationship between DBPs and newborn health, reproductive capacity and cancer morbidity. A survey on 1184 pregnant women recruited in Hubei province was conducted from 2011 to 2013. It was found that the TTHMs (sum of TCM, BDCM, BDCM, and TBM) in maternal blood during late pregnancy were slightly associated with lower mean birth weight, and BDCM and DBCM exposures were weakly associated with smaller birth length (Cao et al., 2016). Another survey on 398 women who had given birth showed that, the mean birth weight of the newborns in the third and top quartiles of urinary creatinine adjusted TCAA concentrations was less than those in the lowest quartile (Zhou et al., 2012b). A total of 418 male partners were recruited from the Tongji Hospital in Wuhan China, and an investigation of DBPs exposure and impaired male reproductive health was conducted. A suggestive but inconclusive association between decreased sperm mobility and increased urinary TCAA levels was observed (Xie et al., 2011).

Series of epidemiological surveys on the relationship between TTHMs levels in public water supplies and risk of esophageal, colon, bladder and kidney cancer were carried out in Taiwan. (Chang et al., 2007; Kuo et al., 2009; Liao et al., 2012; Tsai et al., 2013). It was found that there was no significant correlation between death risk of colon cancer and TTHMs in drinking water (when concentration was less than 6.03 ppb or more than 14.08 ppb) (Kuo et al., 2009). Some other surveys showed that TTHMs concentration had a strong positive correlation to the death risk of bladder cancer (Chang et al., 2007), and had a weak positive correlation to the death risk of kidney and esophageal cancer (Liao et al., 2012; Tsai et al., 2013). The epidemiological study of main DBPs in drinking water of China is shown in Appendix A Table S6.

5. Control and management of DBPs

Killing pathogens and eliminating DBPs in disinfected water are two important tasks in water treatment. To achieve the two goals, many techniques have been developed to control DBPs concentration in water through reduction of precursors, optimization of disinfection operation and removal of DBPs.

5.1. Reduce precursors

NOM and anthropogenic chemicals in water are the main precursors of DBPs, so the removal of precursors is the most effective strategy for DBPs control (Bond et al., 2011). It is possible for water utilities to lower the content of DBPs precursors by adopting some technologies such as enhanced coagulation (CW), adsorption, membrane filtration, photocatalysis, pre-oxidation and so on (Bond et al., 2011). However, the physicochemical properties of precursors are quite different due to their complex components, which would heavily influence the choice of treatment techniques and removal efficiency of DBPs. Taking CW as an example, it has great ability to remove high molecular weight (MW), hydrophobic and anionic precursors, while it is limited in removing hydrophilic and low molecular weight precursors. The study of Han et al. (2015) showed that the concentration of THMs decreased from 59 to 39 μg/L by removing hydrophobic acids (HoA) fraction using CW, whereas the removal efficiency was very low for the precursors whose MW < 5 kDa.

Adsorption is one of the effective techniques for removing many kinds of pollutants. And activated carbon is commonly used due to its large surface area. Granular activated carbon (GAC) is usually utilized between CW-filtration/sedimentation and post-disinfection units. It has been found that placing GAC after chlorination was beneficial to eliminate aromatic halogenated DBPs precursors (Jiang et al., 2017). When GAC was placed after chlorination, the removals of THM4, HAA5, HAA9 and TOX were 96.9%, 78.2%, 88.6% and 63.2%, respectively. However, when GAC was placed before chorination, the removals were 29.6%, 30.7%, 31.2% and 37.6%, respectively (Jiang et al., 2017). Compared to GAC, powdered activated carbon (PAC) has bigger surface area, which can be applied at various stages of water treatment. Wang et al. (2017a)) found that PAC adsorption significantly improved the removal efficiency of THMs precursor (from 10.5% to 70%) and N-DBPs precursor (from 45% to 93%) compared with the single CW. However, Gao et al. (2016)) found that the addition of PAC in membrane bioreactor (MBR) relatively increased the formation of Br-THMs by 200% and increased THMs formation reactivity by 42% during the subsequent chlorination.

Pre-oxidation is a frequently applied technique to degrade some reductive, large molecular compounds in water. Ferrate Fe(VI), ozone, persulfate, permanganate processes, and advanced oxidation processes such as UV/H_2O_2, and UV/persulfate are usually applied in water treatment practices to remove DBPs precursors (Chu et al., 2014; Chu et al., 2015a; Chu et al., 2016a; Chu et al., 2016b; Chu et al., 2017; Hu et al., 2018; Yang et al., 2015b; Zhang et al., 2016; Zhou et al., 2015). Studies have shown that I-THMs formation decreased drastically with increasing ferrate dosage, I-THMs were not found at >2 mg/L of ferrate (Zhang et al., 2016a). In general, pre-oxidation such as pre-O_3 had a positive contribution on reduction of chloroform (CF) formation potentials (FPs) (Hu et al., 2018). However, ozone is a strong oxidant, it can efficiently convert the high-MW fractions (20–1000 kDa) of extracellular organic matter (EOM) and intracellular organic matter (IOM) into low-MW fractions (0.3–10 kDa), which would increase DBPs yields during disinfection process (Zhou et al., 2015). Moreover, the low-MW fractions are more difficult to remove than high-MW fractions with conventional treatment. Another issue in ozonation treatment is the formation of bromates and related health risk, 40%–60% of Br^- in the raw water would be transformed into BrO_3^- during ozonation treatment at a high O_3 dose (Zhang et al., 2017b; Mao et al., 2018).

Since the pollution situation in ambient water is quite complex, a single technique is usually hard to remove DBPs precursors completely, while the combined techniques would exert more advantages. For example, membrane filtration is a

promising technique for removing NOM and anthropogenic chemicals, whereas membrane fouling and inefficient removal of low-MW fractions are its serious obstacles. Therefore, PAC and resin pretreatment were combined to prevent membrane fouling and lengthen membrane operation life (Huang et al., 2015). GAC was combined with CW to remove ROC, the removal efficiency of DOC, UV_{254}, and TDS in the ROC increased from 16.9%, 18.9% and 39.7% to 91.8%, 96% and 76.5%, respectively (Sun et al., 2016). Combination of CW and ultrafiltration (UF) improved the DOC removal from 20% to 59%, DBPs formation potentials were decreased by 30.8% and 16.9% comparing with separate UF and CW (Wang et al., 2016a). CW-adsorption treatment showed a higher reduction capacity (57%) for NDMA formation potential compared with CW (28%) and adsorption (50%) alone (Wang et al., 2017c). O_3 can convert large-MW contaminants into smaller-MW fractions and make them difficult to remove with CW, while O_3/GAC combination could efficiently remove NA precursors and the maximum of NDMA formation potential (TNAFPmax) decreased from 194 to 94 ng/L (Bei et al., 2016). Permanganate oxidation and powdered activated carbon adsorption (PM-PAC) treatment process before CW–sedimentation–filtration significantly enhanced the removal of DOC, DON, NH_4^+-N, and algae from 52.9% to 69.5%, 31.6% to 61.3%, 71.3% to 92.5% and 83.6% to 97.5%, respectively (Chu et al., 2015a). UV irradiation combined with ozonation (UV/O_3) inhibited the regeneration of NDMA from NO_2^- and dimethylamine (DMA). The yields of DMA and NO_2^- were 2.25 and 3.22 mg/L during UV irradiation, while they were 0.92 and 0.45 mg/L in UV/O_3 treatment (Xu et al., 2009). Unfortunately, bromate concentration during the UV/O_3 process was 17.1–77.6 μg/L, which was 2.1–2.9 times higher than that in ozonation treatment (Zhao et al., 2013).

With the increasing eutrophication in China, algae blooms frequently occur in water body, and the IOM is important DBPs precursors. The moderate pre-chlorination was practically applied to enhance the CW removal of algae cells and reduce IOM release. The removal of algae by $KMnO_4$-Fe(II) process increased from 71 to 96% when chlorine dose increased from 0 to 0.5 mg/L(Qi et al., 2016). Ion exchange, especially magnetic ion exchange (MIEX®) resins have been widely adopted for removal of ionic precursors, e.g., bromide ions (Ding et al., 2012). The removal rate of bromide ions was up to 80% during NDMP treatment, thus Br-DBPs formation in the subsequent disinfection was decreased (Wang et al., 2014). Capacitive deionization (CDI) is a low-cost and continent process for removing a variety of cations and anions such as bromide (Xu et al., 2008) and weakly charged organic matter (Liu et al., 2016a; Wang et al., 2015a). Xu et al. (2008) reported that the ion selectivity of CDI treatment on brackish produced water, the removal order was I > Br > Ca > alkalinity > Mg > Na > Cl, bromide removal efficiency was 50% in CDI treatment.

5.2. Optimize disinfection techniques

Except for the properties of precursors, the operational conditions of disinfection have great effects on DBPs formation. Therefore, it is possible to reduce DBPs formation by optimizing disinfection conditions, such as contact time, disinfectants and their dosage and so on.

Although chlorine has been widely used as a disinfectant in the past decades, the formation of DBPs during chlorination disinfection resulted in the search for alternative disinfectants, such as chlorine dioxide (ClO_2) (Fan et al., 2011; Zhou et al., 2016), chloramine, ozone, permanganate and so on. The reactivity of chloramine is lower than that of chlorine, so it was expected to generate less DBPs during the chloramination process. During the chloramination of acetaminophen, the yields of TCM, DCAN, DCAcAm, and TCAcAm were 0.004%, 0.005%, 0.39%, 0.035%, less than those during chlorination 2.25%, 0.54%, 0.63%, 0.2%, respectively (Ding et al., 2018). However, some other studies showed that chloramination would generate more HAcAms than chlorination. The concentrations of HAcAms formed during chloramination and chlorination process were 4.0–88.5 nmol/L, and <30 nmol/L, respectively (Huang et al., 2017c). Also, NH_2Cl would provide nitrogen for formation of TCNM. Moreover, chloramination would enhance the formation of I-DBPs (Wang et al., 2016b), the levels of IAA and IF in WTPs with chloramination (15 and 11 μg/L, respectively) were higher than those with chlorination (about 2 and 0 μg/L, respectively) (Wei et al., 2013a). Dose of disinfectant had obvious effects on DBPs formation, lower chlorine dose would decrease the formation of DBPs. It was found that there was no significant correlation between the formation of THMs and HAAs with the increasing chlorine dosages up to the breakpoint, but the formation increased sharply beyond the breakpoint dosing level (Du et al., 2017a; Yang et al., 2005). Nevertheless, reduction of disinfectant dose is limited since it has to meet the basic requirement for killing pathogens and keeping residual chlorine level in distribution system. As shown in Fig. 9, a concept of multiple-step chlorination process was provided. Compared with conventional one-step chlorination, the two-step chlorination and three-step chlorination of a primary saline sewage effluent decreased DBPs formation by 16.7% and 23.4% with the same total chlorine dosage (Li et al., 2017a; Li et al., 2017b).

Except for chemical disinfection methods, physical or physicochemical methods draw more interests recently. Huo et al. developed a copper oxide nanowire (CuONW)-modified 3-D copper foam electrode and achieved superior disinfection performance with 1 V of operation voltage. Within 7 sec of treatment period, the energy consumption was 25 J/L, DBPs formation potential was decreased because of the low concentration of chlorine (Huo et al., 2016). Ultrasound (US) is regarded as a good option for disinfection enhancement methods when combined with ClO_2, it would increase the production of ClO_2^- and ClO_3^- from 1.37 to 4.71 mg/L and from 0.168 to 2.57 mg/L, respectively (Zhou et al., 2016). UV irradiation combined with chlorination or chloramination is a possible alternative disinfection scheme, in which UV irradiation is expected to kill pathogens so that a lower chlorine/chloramine dose can be used as the secondary disinfectant. However, comparing with chlorination treatment, additional UV irradiation obviously increased formation of TCM (up to 2.12 times), DCAA (up to 1.67 times) and CNCl (up to 2.26 times) (Liu et al., 2006). Increasing UV intensity during sequential oxidation by Cl_2, NH_2Cl or ClO_2 would promote the release of iodide ions and enhance the formation of I-DBPs (from 0 to 0.660 μmol/L) during iopamidol degradation (Tian et al., 2014).
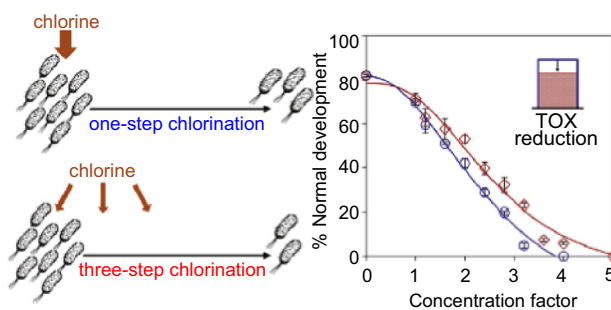
Fig. 9 – Developmental toxicity of the primary sewage effluent samples with one-step chlorination (◯) and three-step chlorination (◇) with a total chlorine dose of 4.0 mg/L as Cl₂ and a total contact time of 30 min (Li et al., 2017a).

5.3. Reduce the generated DBPs

For DBPs formed in disinfected water, it is necessary to remove them by using many chemical, physical or biological methods, such as boiling, UF, nanofiltration (NF), reverse osmosis (RO), advanced oxidation process (AOP), adsorption, ion exchange, electrodialysis and so on. Among them, heating was an effective household "detoxification" process for removing DBPs in water and reducing human exposure through tap water ingestion. Boiling was an effective household "detoxification" process for removing some DBPs in water and reducing human exposure through tap water ingestion. Li et al. (2013b) found that THMs were removed over 92.3% after boiling for 3 min. Pan et al. also found that after boiling for 5 min, the overall level of halogenated DBPs was reduced by 62.3%. Among them, the removal percentages of Br-DBPs and Cl-DBPs were 62.8% and 61.1%, respectively.

Membrane filtration can effectively intercept some pollutants. RO, UF and NF have been widely used for the removal of trace DBPs in water. RO/NF can reject more than 90% of HAAs due to the combined effects of size exclusion and charge repulsion (Yang et al., 2017a). However, the high energy consumption and concentrated water limit the massively use of membrane in DBPs removal.

Since most DBPs are halogenated organic compounds, dehalogenation of DBPs in redox reactions is a possible pathway to remove DBPs. The sulfite/UV_{254} process (Li et al., 2012) could eliminate 100% of MACC by dechlorination within 15 min, while the UV irradiation almost could not degrade yet. Some bimetallic catalysts (Cu/Fe and Pd/Fe) achieved 100% reductive dehalogenation of bromoform and TBAA within 60 min (Zha et al., 2016). TCAA could occur dechlorination rapidly via a carboxyl anion radical (CO_2^-) mechanism in $UV254$-TiO_2 catalysis system with the presence of formate (FM) and dissolved oxygen (Liu et al., 2016c).

Adsorption is a useful technique not only used in the control of DBPs precursors, but also in the removal of DBPs directly. Especially, some new materials (e.g., nanocomposites) were developed to achieve effective removal of DBPs. Zero-valent iron has been used intensively for removal of a variety of pollutants, such as chlorohydrocarbon, nitrobenzenes, chlorinated phenols, polychlorinated biphenyls, heavy metals and anions from water due to its large surface area, great surface reactivity and low price (Fu et al., 2014; Liang

et al., 2014; Liu et al., 2007). Xiao et al. (2015)) developed zero valent iron/activated carbon nanocomposite (NZVI/AC), which could remove 90% of THMs via synergetic effect. Graphene is regarded as an ideal support material for loading inorganic nanoparticles because of its huge surface area, a graphene/Fe⁰ nanocomposite (G-nZVI) was prepared to remove almost 100% of TCNM (Chen et al., 2016a). Macroporous Cl-type strong base anion exchange resin (D201-Cl) was used as a low-cost and efficient sorbent to remove bromate from drinking water (Chen et al., 2014). Quartz sand (QS) is also a low-cost material used to remove organic pollutants in drinking water (Liu et al., 2011). For example, QS and ultrasound technique were combined to remove 12 regulated DBPs in drinking water, whose removal efficiency was more than 20% (Yang et al., 2014a).

In order to reduce the generation of DBPs in water, it is necessary to develop and optimize treatment techniques for reducing precursors, improving disinfection efficiency and removing DBPs. Moreover, it is quite important to protect water source from pollution. It was reported that leaf organic matter (OM) (from allochthonous plant) and algal OM (from authonous algae) were potential precursors of C-DBPs and N-DBPs, respectively (Sun et al., 2018). The study of Hong et al. (2013) showed that the sediment could release substantial amount of NOM to water and further transform to THMs and HAAs during disinfection treatment. The invasion of wastewater would lead more production of DBPs due to the precursors in wastewater (Xue et al., 2017). And, some inorganic ions (bromide, iodine and nitrite) sourced from sea water intrusion or wastewater input would become precursors and increase the formation of Br-DBPs, I-DBPs and N-DBPs (Yang et al., 2017a; Hong et al., 2015; Hong et al., 2016). The study of Hong et al. (2015) showed that nitrite and bromide had significant positive effects on the formation of HNMs during chloramination. And both T-THMs and T-HANs were positively correlated with bromide (Hong et al., 2016). Besides, the presence of iodide ions increased the produce of I-DBPs during the chlorination of BP-4 (Yang et al., 2017b).

6. DBPs studies in future

Although more than 700 DBPs have been reported in the literature, more than 50% of the total organic halogen (TOX)

formed during chlorination of drinking water is unknown yet. Similarly, more than 50% of the assimilable organic carbon (AOC) formed during ozonation of drinking water has not been identified. The identification of unknown DBPs can hardly perform without the help of powerful detection instruments and optimized methods. Therefore, in the future, the first emergent task is to develop effective separation and sample pretreatment methods, sensitive and rapid methods for DBPs analysis. Second, the components in China's water source are quite complex, hundreds and thousands of natural and anthropogenic chemicals have been found, which would be the potential precursors of DBPs. Revealing the transformation mechanisms of various precursors become a hard but important work. Third, the DBPs exposure including internal and external exposure and adverse toxicological consequences are very complex, it needs to be disclosed by long-term systematic toxicological study, even epidemiological survey. Fourth, the control and management countermeasures on DBPs are still weak in China, some practically effective degradation techniques for DBPs and precursors should be developed and extended widely, and the framework of efficient assessment and management measures should be proposed as soon as possible. Fifth, the toxicity effects are the most important characteristic of DBPs, so toxicity-directed method can string together all DBPs related studies including identification of DBPs with high risk, their formation mechanisms, choice and assessment of elimination techniques, and management. The toxicity-directed DBPs studies would be an innovative and efficient method (Chen et al., 2018). All in all, the study on DBPs is multi-disciplinary, involving chemistry, toxicology, epidemiology, engineering and technology. The close communication and cooperation between the scientists and engineers from different disciplines must be an effective way for preventing the outbreak of water-borne diseases, and reducing the potential health risk of DBPs.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jes.2019.02.003.

REFERENCES

APHA, 1998. Standard Methods for the Examination of Water and Wastewater. twentieth ed. American Public Health Association, New York, p. 1287.

Baeyer, A., Villiger, V., 1899. Einwirkung des Caro'schen Reagens auf Ketone. Ber. Dtsch. Chem. Ges. 32 (3), 3625–3633.

Bei, E., Shu, Y., Li, S., Liao, X., Wang, J., Zhang, X., Chen, C., Krasner, S., 2016. Occurrence of nitrosamines and their precursors in

drinking water systems around mainland China. Water Res. 98, 168–175.

Bellar, T., Lichtenberg, J., Kroner, R., 1974. The occurrence of organohalides in chlorinated drinking waters. J. Am. Water Works Ass. 66, 703–706.

Bond, T., Goslan, E., Parsons, S., Jefferson, B., 2011. Treatment of disinfection by-product precursors. Environ. Technol. 32 (1), 1–25.

Boyce, S., Hornig, J., 1983. Reaction pathways of trihalomethane formation from the halogenation of dihydroxyaromatic model compounds for humic acid. Environ. Sci. Technol. 17, 202–211.

Cao, W., Zeng, Q., Luo, Y., Chen, H., Miao, Y., Li, L., Cheng, Y., Li, M., Wang, F., You, L., Wang, Y., Yang, P., Lu, W., 2016. Blood biomarkers of late pregnancy exposure to trihalomethanes in drinking water and fetal growth measures and gestational age in a Chinese cohort. Environ. Health Perspect. 124 (4), 536–541.

Chang, C., Ho, S., Wang, L., Yang, C., 2007. Bladder cancer in Taiwan: relationship to Trihalomethane concentrations present in drinking-water supplies. J. Toxicol. Environ. Health 70 (20), 1752–1757.

Chang, H., Tung, H., Chao, C., Wang, G., 2010. Occurrence of haloacetic acids (HAAs) and trihalomethanes (THMs) in drinking water of Taiwan. Environ. Monit. Assess. 162, 237–250.

Chen, R., et al., 2014. Sorption of trace levels of bromate by macroporous strong base anion exchange resin: influencing factors, equilibrium isotherms and thermodynamic studies. Desalination 344, 306–312.

Chen, H., Cao, Y., Wei, E., Gong, T., Xian, Q., 2016a. Facile synthesis of graphene nano zero-valent iron composites and their efficient removal of trichloronitromethane from drinking water. Chemosphere 146, 32–39.

Chen, H., Yin, J., Zhu, M., Cao, C., Gong, T., Xian, Q., 2016b. Cold on-column injection coupled with gas chromatography/mass spectrometry for determining halonitromethanes in drinking water. Anal. Meth. 8 (2), 362–370.

Chen, T., Xu, Y., Liu, Z., Zhu, S., Shi, W., Cui, F., 2016c. Evaluation of drinking water treatment combined filter backwash water recycling technology based on comet and micronucleus assay. J. Environ. Sci. 42, 61–70.

Chen, M., Wei, D., Du, Y., 2018. Toxicity-directed identification of disinfection by-products with high risk. Sci. Sin. Chim. https://doi.org/10.1360/N032018-00094 (In Chin).

Chu, W., Gao, N., Yin, D., Krasner, S.W., Mitch, W., 2014. Impact of UV/H$_2$O$_2$ pre-oxidation on the formation of Haloacetamides and other nitrogenous disinfection byproducts during chlorination. Environ. Sci. Technol. 48 (20), 12190–12198.

Chu, W., Li, D., Gao, N., Yin, D., Zhang, Y., Zhu, Y., 2015a. Comparison of free amino acids and short oligopeptides for the formation of trihalomethanes and haloacetonitriles during chlorination: effect of peptide bond and pre-oxidation. Chem. Eng. J. 281, 623–631.

Chu, W., Li, X., Gao, N., Deng, Y., Yin, D., Li, D., Chu, T., 2015b. Peptide bonds affect the formation of haloacetamides, an emerging class of N-DBPs in drinking water: free amino acids versus oligopeptides. Sci. Rep. 5, 14412.

Chu, W., Chu, T., Bond, T., Du, E., Guo, Y., Gao, N., 2016a. Impact of persulfate and ultraviolet light activated persulfate pre-oxidation on the formation of trihalomethanes, haloacetonitriles and halonitromethanes from the chlor(am)ination of three antibiotic chloramphenicols. Water Res. 93, 48–55.

Chu, W., Li, D., Deng, Y., Gao, N., Zhang, Y., Zhu, Y., 2016b. Effects of UV/PS and UV/H2O2 pre-oxidations on the formation of trihalomethanes and haloacetonitriles during chlorination and chloramination of free amino acids and short oligopeptides. Chem. Eng. J. 301, 65–72.

Chu, W., Yao, D., Deng, Y., Sui, M., Gao, N., 2017. Production of trihalornethanes, haloacetaldehydes and haloacetonitriles during chlorination of microcystin-LR and impacts of pre-oxidation on their formation. J. Hazard. Mater. 327, 153–160.

Deng, Y., Wei, J., E, X., Wang, W., et al., 2008. Study for distribution byproducts in drinking water from six cities in China. J. Hyg. Res. 37 (2), 207–210 (In Chin).

Deng, Y., Zhang, Y., Zhang, R., Wu, B., Ding, L., Xu, K., Ren, H., 2014. Mice in vivo toxicity studies for monohaloacetamides emerging disinfection byproducts based on metabolomic methods. Environ. Sci. Technol. 48 (14), 8212–8218.

Deng, Y., Zhang, Y., Lu, Y., Lu, K., Bai, H., Ren, H., 2017. Metabolomics evaluation of the in vivo toxicity of bromoacetonitriles: one class of high-risk nitrogenous disinfection byproducts. Sci. Total Environ. 579, 107–114.

Ding, L., Deng, H.P., Wu, C., Han, X., 2012. Affecting factors, equilibrium, kinetics and thermodynamics of bromide removal from aqueous solutions by MIEX resin. Chem. Eng. J. 181, 360–370.

Ding, H., Meng, L., Zhang, H., Yu, J., An, W., Hu, J., Yang, M., 2013. Occurrence, profiling and prioritization of halogenated disinfection by-products in drinking water of China. Environ. Sci. Process Impacts 15 (7), 1424–1429.

Ding, S., Chu, W., Bond, T., Wang, Q., Gao, N., Xu, B., Du, E., 2018. Formation and estimated toxicity of trihalomethanes, haloacetonitriles, and haloacetamides from the chlor(am)ination of acetaminophen. J. Hazard. Mater. 341, 112–119.

Dong, L., Wang, H., Cai, H., Li, T., 2016. Investigation on nitrogenous disinfection by-products in drinking water in six cities, China. J. Environ. Health 33 (3), 232–235 (In Chin).

Du, H., Li, J., Moe, B., Mcguigan, C., Li, X., 2014. A real-time cell-electronic sensing method for comparative analysis of toxicity of water contaminants. Anal. Methods 6 (7), 2053–2058.

Du, Y., Lv, X., Wu, Q., Zhang, D., Zhou, Y., Peng, L., Hu, H., 2017a. Formation and control of disinfection byproducts and toxicity during reclaimed water chlorination: a review. J. Environ. Sci. 58, 51–63.

Du, Y., Wu, Q., Lu, Y., Hu, H., Yang, Y., Liu, R., Liu, F., 2017b. Increase of cytotoxicity during wastewater chlorination: impact factors and surrogates. J. Hazard. Mater. 324, 681–690.

Fan, M., Qiao, J., Wang, W., Shao, J., 2011. Study on water disinfection by - products during 2004 to 2010. J. Med. Pest Control 27 (3), 200–204.

Fenech, M., 2000. The in vitro micronucleus technique. Mutat. Res. Fundam. Mol. Mech. Mutagen. 455 (1–2), 81–95.

Fu, F., Dionysiou, D., Liu, H., 2014. The use of zero-valent iron for groundwater remediation and wastewater treatment: a review. J. Hazard. Mater. 267, 194–205.

Gan, W., Guo, W., Mo, J., He, Y., Liu, Y., Liu, W., Liang, Y., Yang, X., 2013. The occurrence of disinfection by-products in municipal drinking water in China's Pearl River Delta and a multipathway cancer risk assessment. Sci. Tol. Environ. 447, 108–115.

Gao, Y., Ma, D., Yue, Q., Gao, B., Huang, X., 2016. Effect of powdered activated carbon (PAC) on MBR performance and effluent trihalomethane formation: at the initial stage of PAC addition. Bioresour. Technol. 216, 838–844.

Guan, C., Jiang, J., Pang, S., Luo, C., Yang, Y., Ma, J., Yu, J., Zhao, X., 2018. Effect of iodide on transformation of phenolic compounds by nonradical activation of peroxydisulfate in the presence of carbon nanotube: kinetics, impacting factors, and formation of iodinated aromatic products. Chemosphere 208, 559–568.

Han, Q., Yan, H., Zhang, F., Xue, N., Wang, Y., Chu, Y., Gao, B., 2015. Trihalomethanes (THMs) precursor fractions removal by coagulation and adsorption for bio-treated municipal wastewater: molecular weight, hydrophobicity/hydrophily and fluorescence. J. Hazard. Mater. 297, 119–126.

Hong, H., Huang, F., Wang, F., Ding, L., Lin, H., Liang, Y., 2013. Properties of sediment NOM collected from a drinking water reservoir in South China, and its association with THMs and HAAs formation. J. Hydrol. 476, 274–279.

Hong, H., Qian, L., Xiong, Y., Xiao, Z., Lin, H., Yu, H., 2015. Use of multiple regression models to evaluate the formation of halonitromethane via chlorination/chloramination of water from Tai Lake and the Qiantang River, China. Chemosphere 119, 540–546.

Hong, H., Song, Q., Mazumder, A., Luo, Q., Chen, J., Lin, H., Yu, H., Shen, L., Liang, Y., 2016. Using regression models to evaluate the formation of trihalomethanes and haloacetonitriles via chlorination of source water with low SUVA values in the Yangtze River Delta region, China. Environ. Geochem. Health 38, 1303–1312.

Hu, Y., Tan, L., Zhang, S., Zuo, Y., Han, X., Liu, N., Lu, W., Liu, A., 2017. Detection of genotoxic effects of drinking water disinfection by-products using *Vicia faba* bioassay. Environ. Sci. Pollut. Res. Int. 24 (2), 1509–1517.

Hu, J., Chu, W., Sui, M., Xu, B., Gao, N., Ding, S., 2018. Comparison of drinking water treatment processes combinations for the minimization of subsequent disinfection by-products formation during chlorination and chloramination. Chem. Eng. J. 335, 352–361.

Huang, J., Fan, Q., Kou, G., Liu, C., 1987. The investigation of trihalomethanes in waterworks plant in China. Environ. Chem. 6 (4), 80–86 (In Chin).

Huang, F., Ruan, M., Yan, J., Hong, H., Lin, H., Xiong, Y., 2013. An improved method for determining HNMs in drinking water. Water Sci. Technol: Water Supply 13 (5), 1257–1264.

Huang, W., et al., 2015. Effects of macro-porous anion exchange and coagulation treatment on organic removal and membrane fouling reduction in water treatment. Desalination 355, 204–216.

Huang, G., Jiang, P., Li, X., 2017a. Mass spectrometry identification of N-chlorinated dipeptides in drinking water. Anal. Chem. 89, 4204–4209.

Huang, H., Zhu, H., Gan, W., Chen, X., Yang, X., 2017b. Occurrence of nitrogenous and carbonaceous disinfection byproducts in drinking water distributed in Shenzhen, China. Chemosphere 188, 257–264.

Huang, H., Chen, B., Zhu, Z., 2017c. Formation and speciation of haloacetamides and haloacetonitriles for chlorination, chloramination, and chlorination followed by chloramination. Chemosphere 166, 126–134.

Huo, Z., Xie, X., Yu, T., Lu, Y., Feng, C., Hu, H., 2016. Nanowire-modified three-dimensional electrode enabling low-voltage electroporation for water disinfection. Environ. Sci. Technol. 50 (14), 7641–7649.

Jiang, J., Zhang, X., Zhu, X., Li, Y., 2017. Removal of intermediate aromatic halogenated DBPs by activated carbon adsorption: a new approach to controlling halogenated DBPs in chlorinated drinking water. Environ. Sci. Technol. 51 (6), 3435–3444.

Kuo, H., Tiao, M., Wu, T., Yang, C., 2009. Trihalomethanes in drinking water and the risk of death from colon cancer in Taiwan. J.Toxicol. Environ. Health 72 (20), 1217–1222.

Kürti, L., Czakó, B., 2005. Strategic Applications of Named Reactions in Organic Synthesis. Elsevier Academic Press, Burlington; San Diego; London, p. 28.

Li, S., Liang, X., Yang, Y., Gao, Y., Lu, L., 2007. Gas chromatography for determining HAAs in drinking water. South China J. Prev. Med. 33 (2), 75–95 (In Chin.).

Li, X., Ma, J., Liu, G., Fang, J., Yue, S., Guan, Y., Chen, L., Liu, X., 2012. Efficient reductive dechlorination of monochloroacetic acid by sulfite/UV process. Environ. Sci. Technol. 46 (13), 7342–7349.

Li, L., Wei, D., Wei, G., Du, Y., 2013a. Transformation of cefazolin during chlorination process: products, mechanism and genotoxicity assessment. J. Hazard. Mater. 262, 48–54.

Li, X., Liu, R., Lan, Y., Yu, S., Wen, X., Chen, L., Zhang, Y., 2013b. Study on chlorinated disinfection byproducts and the relevant health risk in tap water of J City. Environ. Sci. 34 (9), 3474–3479 (In Chin.).

Li, C., Wang, D., Li, N., Luo, Q., Xu, X., Wang, Z., 2016a. Identifying unknown by-products in drinking water using comprehensive

two-dimensional gas chromatography–quadrupole mass spectrometry and in silico toxicity assessment. Chemosphere 163, 535–543.

Li, M., Wei, D., Du, Y., 2016b. Genotoxicity of quinolone antibiotics in chlorination disinfection treatment: formation and QSAR simulation. Environ. Sci. Pollut. Res. Int. 23 (20), 20637–20645.

Li, Y., Zhang, X., Yang, M., et al., 2017a. Three-step effluent chlorination increases disinfection efficiency and reduces DBP formation and toxicity. Chemosphere 168, 1302–1308.

Li, Y., Yang, M., Zhang, X., Jiang, J., Liu, J., Yau, C., Graham, N., Li, X., 2017b. Two-step chlorination: a new approach to disinfection of a primary sewage effluent. Water Res. 108, 339–347.

Liang, L., Sun, W., Guan, X., Huang, Y., Choi, W., Bao, H., Li, L., Jiang, Z., 2014. Weak magnetic field significantly enhances selenite removal kinetics by zero valent iron. Water Res. 49, 371–380.

Liao, Y., Chen, C., Chang, C., Peng, C., Chiu, H., Wu, T., Yang, C., 2012. Trihalomethanes in drinking water and the risk of death from kidney Cancer: does hardness in drinking water matter? J. Toxicol Environ. Health 75 (6), 340–350.

Liu, W., Cheung, L., Yang, X., Shang, C., 2006. THM, HAA and CNCl formation from UV irradiation and chlor(am)ination of selected organic waters. Water Res. 40, 2033–2043.

Liu, Y., Phenrat, T., Lowry, G., 2007. Effect of TCE concentration and dissolved groundwater solutes on NZVI-promoted TCE Dechlorination and H2 evolution. Environ. Sci. Technol. 41 (22), 7881–7887.

Liu, J., Wang, X., Fan, B., 2011. Characteristics of PAHs adsorption on inorganic particles and activated sludge in domestic wastewater treatment. Bioresour. Technol. 102 (9), 5305–5311.

Liu, D., Wang, X., Xie, Y., Tang, H., 2016a. Effect of capacitive deionization on disinfection by-product precursors. Sci. Total Environ. 568, 19–25.

Liu, W., Wei, D., Liu, Q., Du, Y., 2016b. Transformation pathways and acute toxicity variation of 4-hydroxyl benzophenone in chlorination disinfection process. Chemosphere 2016 (154), 491–498.

Liu, X., Zhong, J., Fang, L., Wang, L., Ye, M., Shao, Y., Li, J., Zhang, T., 2016c. Trichloroacetic acid reduction by an advanced reduction process based on carboxyl anion radical. Chem. Eng. J. 303, 56–63.

Liu, S., Li, Z., Dong, H., Goodman, B., Qiang, Z., 2017. Formation of iodo-trihalomethanes, iodo-acetic acids, and iodo-acetamides during chloramination of iodide-containing waters: factors influencing formation and reaction pathways. J. Hazard. Mater. 321, 28–36.

Lu, T., Su, C., Tang, F., Chen, C., Yen, C., Fang, K., et al., 2015. Chloroacetic acid triggers apoptosis in neuronal cells via a reactive oxygen species-induced endoplasmic reticulum stress signaling pathway. Chem. Biol. Interact. 225, 1–12.

Mao, Y.Q., et al., 2018. Effects of conventional ozonation and electro-peroxone pretreatment of surface water on disinfection by-product formation during subsequent chlorination. Water Res. 130, 322–332.

Page, N., Saffiotti, U., 1976. Report on Carcinogenesis Bioassay of Chloroform. National Cancer Institute, Bethesda, MD.

Pan, S., An, W., Li, H., Su, M., Zhang, J., Yang, M., 2014a. Cancer risk assessment on trihalomethanes and haloacetic acids in drinking water of China using disability-adjusted life years. J. Hazard. Mater. 280, 288–294.

Pan, Y., Zhang, X., Wagner, E., Osiol, J., Plewa, M., 2014b. Boiling of simulated tap water: effect on polar brominated disinfection byproducts, halogen speciation, and cytotoxicity. Environ. Sci. Technol. 48 (1), 149–156.

Pan, Y., Li, W., Li, A., Zhou, Q., Shi, P., Wang, Y., 2016. A new group of disinfection byproducts in drinking water: Trihalo-hydroxy-cyclopentene-diones. Environ. Sci. Technol. 50, 7344–7352.

Qi, J., Lan, H., Liu, H., Liu, R., Miao, S., Qu, J., 2016. Simultaneous surface-adsorbed organic matter desorption and cell integrity maintenance by moderate prechlorination to enhance Microcystis aeruginosa removal in KMnO4-Fe(II) process. Water Res. 105, 551–558.

Richardson, S., 1998. Drinking water disinfection by-products. In: Meyers, R. (Ed.), The Encyclopedia of Environmental Analysis and Remediation. 3. Wiley, New York, pp. 1398–1421.

Rook, J., 1974. Formation of haloforms during chlorination of natural waters. Water Treat. Exam. 23, 234–243.

Serrano, M., Montesinos, I., Cardador, M.J., Silva, M., Gallego, M., 2015. Seasonal evaluation of the presence of 46 disinfection by-products throughout a drinking water treatment plant. Sci. Total Environ. 517, 246–258.

Sun, Y., Yang, Z., Ye, T., Shi, N., Tian, Y., 2016. Evaluation of the treatment of reverse osmosis concentrates from municipal wastewater reclamation by coagulation and granular activated carbon adsorption. Environ. Sci. Pollut. Res. 23 (13), 13543–13553.

Sun, H., Song, X., Ye, T., Hu, J., Hong, H., Chen, J., Lin, H., Yu, H., 2018. Formation of disinfection by-products during chlorination of organic matter from phoenix tree leaves and Chlorella vulgaris. Environ. Pollut. https://doi.org/10.1016/j.envpol.2018.10.021.

Tian, F., Xu, B., Lin, Y., Hu, C., Zhang, T., Gao, N., 2014. Photodegradation kinetics of iopamidol by UV irradiation and enhanced formation of iodinated disinfection by-products in sequential oxidation processes. Water Res. 58, 198–208.

Tsai, S., Chiu, H., Yang, C., 2013. Trihalomethanes in drinking water and the risk of death from esophageal Cancer: does hardness in drinking water matter? J. Toxicol. Environ. Health 76 (2), 120–130.

USEPA, 2005. Guidelines for carcinogen risk assessment. Risk Assessment Forum U.S. Environmental Protection Agency Washington, DC.

Wang, L., Hu, H., Wang, C., 2007a. Effect of ammonia nitrogen and dissolved organic matter fractions on the genotoxicity of wastewater effluent during chlorine disinfection. Environ. Sci. Technol. 41 (1), 160–165.

Wang, W., Ye, B., Yang, L., Li, Y., Wang, Y., 2007b. Risk assessment on disinfection by-products of drinking water of different water sources and disinfection processes. Environ. Int. 33 (2), 219–225.

Wang, H., Chen, Z., Zhang, X., 2011. Study on analysis method of halomethanes by liquid-liquid extraction and gas chromatography in drinking water. J. Harbin Univ. Comm. 27 (3), 297–300 (In Chin.).

Wang, Q., et al., 2014. The performance of quaternized magnetic microspheres on control of disinfection by-products and toxicity in drinking water. Chem. Eng. J. 254, 230–236.

Wang, C., Song, H., Zhang, Q., Wang, B., Li, A., 2015a. Parameter optimization based on capacitive deionization for highly efficient desalination of domestic wastewater biotreated effluent and the fouled electrode regeneration. Desalination 365, 407–415.

Wang, H., Zhu, Y., Hu, C., Hu, X., 2015b. Treatment of NOM fractions of reservoir sediments: effect of UV and chlorination on formation of DBPs. Sep. Purif. Technol. 154, 228–235.

Wang, F., Gao, B., Ma, D., Yue, Q., Li, R., Wang, Q., 2016a. Reduction of disinfection by-product precursors in reservoir water by coagulation and ultrafiltration. Environ. Sci. Pollut. Res. Int. 23 (22), 22914–22923.

Wang, X., Wang, J., Zhang, Y., Shi, Q., Zhang, H., Zhang, Y., Yang, M., 2016b. Characterization of unknown iodinated disinfection byproducts during chlorination/chloramination using ultra-high resolution mass spectrometry. Sci. Total Environ. 554-555, 83–88.

Wang, F., Gao, B., Yue, Q., Bu, F., Shen, X., 2017a. Effects of ozonation, powdered activated carbon adsorption, and

coagulation on the removal of disinfection by-product precursors in reservoir water. Environ. Sci. Pollut. Res. 24 (21), 17945–17954.

Wang, H., Qin, M., Dong, L., Lv, J., Wang, X., 2017b. Genotoxicity of a low-dose nitrosamine mixture as drinking water disinfection byproducts in NIH3T3 cells. Int. J. Med. Sci. 14 (10), 961–969.

Wang, M., Meng, Y., Ma, D., Wang, Y., Li, F., Xu, X., Xia, C., Gao, B., 2017c. Integration of coagulation and adsorption for removal of N-nitrosodimethylamine (NDMA) precursors from biologically treated municipal wastewater. Environ. Sci. Pollut. Res. 24 (13), 12426–12436.

Wei, X., Chen, X., Wang, X., Zheng, W., Zhang, D., Tian, D., Jiang, S., Ong, C., He, G., Qu, W., 2013a. Occurrence of regulated and emerging iodinated DBPs in the Shanghai drinking water. PLoS One 8 (3), 59677.

Wei, X., Wang, S., Zheng, W., Wang, X., Liu, X., Jiang, S., Pi, J., Zheng, Y., He, G., Qu, W., 2013b. Drinking water disinfection byproduct iodoacetic acid induces tumorigenic transformation of NIH3T3 cells. Environ. Sci. Technol. 47 (11), 5913–5920.

World Health Organization, 2006. Guidelines for Safe Recreational Water Environments. Swim. Pools Similar Environ. 2. WHO Press, Geneva.

Wu, Q., Tang, X., Huang, H., Li, Y., Hu, H., Ding, Y., Shao, Y., 2014. Antiestrogenic activity and related disinfection by-product formation induced by bromide during chlorine disinfection of sewage secondary effluent. J. Hazard. Mater. 273, 280–286.

Xiao, M., Wei, D., Yin, J., Wei, G., Du, Y., 2013. Transformation mechanism of benzophenone-4 in free chlorine promoted chlorination disinfection. Water Res. 47, 6223–6233.

Xiao, M., Wei, D., Li, L., Liu, Q., Zhao, H., Du, Y., 2014. Formation pathways of brominated products from benzophenone-4 chlorination in the presence of bromide ions. J. Environ. Sci. 26 (12), 2387–2396.

Xiao, J., Gao, B., Yue, Q., Gao, Y., Li, Q., 2015. Removal of trihalomethanes from reclaimed-water by original and modified nanoscale zero-valent iron: characterization, kinetics and mechanism. Chem. Eng. J. 262, 1226–1236.

Xie, S., Li, Y., Tan, Y., Zheng, D., Liu, A., Xie, H., Lu, W., 2011. Urinary trichloroacetic acid levels and semen quality: a hospital-based cross-sectional study in Wuhan. China. Environ. Res. 111 (2), 295–300.

Xu, P., Drewes, J., Heil, D., Wang, G., 2008. Treatment of brackish produced water using carbon aerogel-based capacitive deionization technology. Water Res. 42 (10), 2605–2617.

Xu, B., Chen, Z., Qi, F., Ma, J., Wu, F., 2009. Inhibiting the regeneration of N-nitrosodimethylamine in drinking water by UV photolysis combined with ozonation. J. Hazard. Mater. 168 (1), 108–114.

Xue, S., Jin, W., Zhang, Z., Liu, H., 2017. Reductions of dissolved organic matter and disinfection by-product precursors in full-scale wastewater treatment plants in winter. Chemosphere 179, 395–404.

Yang, X.P., Cai, H.D., 1986. Trichloromethane and mutagen in drinking water. Environ. Sci. 7 (3), 6–9 (In Chin.).

Yang, M., Zhang, X., 2013. Comparative developmental toxicity of new aromatic halogenated DBPs in a chlorinated saline sewage effluent to the marine polychaete Platynereis dumerilii. Environ. Sci. Technol. 47 (19), 10868–10876.

Yang, X., Shang, C., Huang, J.C., 2005. DBP formation in breakpoint chlorination of wastewater. Water Res. 39 (19), 4755–4767.

Yang, F., Zhang, J., Chu, W., Yin, D., Templeton, M., 2014a. Haloacetamides versus halomethanes formation and toxicity in chloraminated drinking water. J. Hazard. Mater. 274, 156–163.

Yang, W., Dong, L., Luo, Z., Cui, X., Liu, J., Liu, Z., Huo, M., 2014b. Application of ultrasound and quartz sand for the removal of disinfection byproducts from drinking water. Chemosphere 101, 34–40.

Yang, M., Liu, J., Zhang, X., Richardson, S.D., 2015a. Comparative toxicity of chlorinated saline and freshwater wastewater effluents to marine organisms. Environ. Sci. Technol. 49 (24), 14475–14483.

Yang, X., Gan, W., Zhang, X., Huang, H., Sharma, V.K., 2015b. Effect of pH on the formation of disinfection byproducts in ferrate(VI) pre-oxidation and subsequent chlorination. Sep. Purif. Technol. 156, 980–986.

Yang, Y., Lu, Y., Wu, Q.Y., Hu, H.Y., Chen, Y.H., Liu, W.L., 2015c. Evidence of ATP assay as an appropriate alternative of MTT assay for cytotoxicity of secondary effluents from WWTPs. Ecotoxicol. Environ. Saf. 122, 490–496.

Yang, L., She, Q., Wan, M., Wang, R., Chang, V., Tang, C., 2017a. Removal of haloacetic acids from swimming pool water by reverse osmosis and nanofiltration. Water Res. 116, 116–125.

Yang, F., Wei, D., Xiao, M., Sun, X., Guo, Q., Liu, Y., Du, Y., 2017b. The chlorination transformation characteristics of benzophenone-4 in the presence of iodide ions. J. Environ. Sci. 58, 93–101.

Zha, X., Ma, L., Liu, Y., 2016. Reductive dehalogenation of brominated disinfection byproducts by iron based bimetallic systems. RSC Adv. 6 (20), 16323–16330.

Zhang, H., Zhang, Y., Shi, Q., Hu, J., Chu, M., Yu, J., Yang, M., 2012a. Study on transformation of natural organic matter in source water during chlorination and its chlorinated products using ultrahigh resolution mass spectrometry. Environ. Sci. Technol. 46, 4396–4402.

Zhang, H., Zhang, Y., Shi, Q., Ren, S., Yu, J., Ji, F., Luo, W., Yang, M., 2012b. Characterization of low molecular weight dissolved natural organic matter along the treatment trait of a waterworks using Fourier transform ion cyclotron resonance mass spectrometry. Water Res. 46, 5197–5204.

Zhang, L., Xu, L., Zeng, Q., Zhang, S., Xie, H., Liu, A., Lu, W., 2012c. Comparison of DNA damage in human-derived hepatoma line (HepG2) exposed to the fifteen drinking water disinfection byproducts using the single cell gel electrophoresis assay. Mutat. Res. 741 (1–2), 89–94.

Zhang, H., Zhang, Y., Shi, Q., Zheng, H., Yang, M., 2014. Characterization of unknown brominated disinfection byproducts during chlorination using ultrahigh resolution mass spectrometry. Environ. Sci. Technol. 48, 3112–3119.

Zhang, X., Yang, H., Wang, X., Karanfil, T., Xie, Y., 2015a. Trihalomethane hydrolysis in drinking water at elevated temperatures. Water Res. 2015 (78), 18–27.

Zhang, Y., Zhao, F., Deng, Y., Zhao, Y., Ren, H., 2015b. Metagenomic and metabolomic analysis of the toxic effects of trichloroacetamide-induced gut microbiome and urine metabolome perturbations in mice. J. Proteome Res. 14 (4), 1752–1761.

Zhang, M., Xu, B., Wang, Z., Zhang, T., Gao, N., 2016. Formation of iodinated trihalomethanes after ferrate pre-oxidation during chlorination and chloramination of iodide-containing water. J. Taiwan Inst. Chem. Eng. 60, 453–459.

Zhang, B., Xian, Q., Lu, J., Gong, T., Li, A., Feng, J., 2017a. DBPs formation and genotoxicity during chlorination of pyrimidines and purines bases. Chem. Eng. J. 307, 884–890.

Zhang, Y., Chu, W., Yao, D., Yin, D., 2017b. Control of aliphatic halogenated DBP precursors with multiple drinking water treatment processes: formation potential and integrated toxicity. J. Environ. Sci. 58, 322–330.

Zhang, H., Chang, S., Wang, L., Wang, W., 2018. Estimating and comparing the cancer risks from THMs and low-level arsenic in drinking water based on disability-adjusted life years. Water Res. 145, 83–93.

Zhao, G., Lu, X., Zhou, Y., Gu, Q., 2013. Simultaneous humic acid removal and bromate control by O3 and UV/O3 processes. Chem. Eng. J. 232, 74–80.

Zhou, W., Lou, L., Zhu, L., Li, Z., Zhu, L., 2012a. Formation and cytotoxicity of a new disinfection by-product (DBP) phenazine by chloramination of water containing diphenylamine. J. Environ. Sci. 24 (7), 1217–1224.

Zhou, W., Xu, L., Xie, S., Li, Y., Li, L., Zeng, Q., Du, Y., Lu, W., 2012b. Decreased birth weight in relation to maternal urinary trichloroacetic acid levels. Sci. Total Environ. 416, 105–110.

Zhou, S., Zhu, S., Shao, Y., Gao, N., 2015. Characteristics of C-N-DBPs formation from algal organic matter: role of molecular weight fractions and impacts of pre-ozonation. Water Res. 72, 381–390.

Zhou, X., Zhao, J., Li, Z., Lan, J., Li, Y., Yang, X., Wang, D., 2016. Influence of ultrasound enhancement on chlorine dioxide consumption and disinfection by-products formation for secondary effluents disinfection. Ultrason. Sonochem. 28, 376–381.

Zhou, X., Zheng, L., Chen, S., Du, H., Raphael, B.M.G., Song, Q., Wu, F., Chen, J., Lin, H., Hong, H., 2019. Factors influencing DBPs occurrence in tap water of Jinhua Region in Zhejiang Province, China. Ecotoxicol. Environ. Saf. 171, 813–822.

Zong, W., Sun, F., Sun, X., 2013. Evaluation on the generative mechanism and biological toxicity of microcystin-LR disinfection by-products formed by chlorination. J. Hazard. Mater. 252-253, 293–299.

Zuo, Y., Hu, Y., Lu, W., Cao, J., Wang, F., Han, X., Lu, W., Liu, A., 2017. Toxicity of 2,6-dichloro-1,4-benzoquinone and five regulated drinking water disinfection by-products for the Caenorhabditis elegans nematode. J. Hazard. Mater. 321, 456–463.