CHAPTER TEN

Liquid Chromatography—Mass Spectrometry of Emerging Disinfection By-products

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1. INTRODUCTION

The disinfection of drinking water is regarded as a major triumph for public health, as the 1900s brought an end to most waterborne diseases in developed countries. However, disinfection by-products (DBPs) are formed when chemicals used to kill microorganisms react with natural organic matter (NOM) and other substances in source waters [1,2].

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Some cities have pristine, protected source waters, but most are impacted by upstream wastewater treatment plants, which can send a host of chemicals downstream that are not completely removed in wastewater treatment. These can include pharmaceuticals, estrogens, antibacterial agents, pesticides, nanomaterials, textile dyes, bisphenol A (BPA), alkylphenol ethoxylate (APEO) surfactants, and ultraviolet (UV) filters. Because some of their chemical structures contain functional groups that can react with chemical disinfectants (including chlorine, chloramines, ozone, and chlorine dioxide), DBPs can also form from these contaminants.

There is concern about DBPs because human epidemiological studies have shown bladder cancer, miscarriage, and birth defects [2–7]. Also, while only 11 DBPs are regulated in the United States [8], many scientists believe that DBPs other than those regulated may be responsible for the human health effects. These unregulated DBPs are often called "emerging DBPs," especially those that have been shown to be more toxic than those regulated [1,9,10]. Swimming pools are also treated with disinfectants, and DBPs can form in them too, with precursors coming not only from NOM but also from human inputs [11–13]. Swimming pool concerns include the potential for increased asthma and other respiratory illnesses in professional swimmers or swimming pool workers [11], as well as bladder cancer [14].

Along the way, nearly 700 DBPs have been identified, mostly using gas chromatography (GC)-mass spectrometry (MS) [1]. However, liquid chromatography (LC)-MS is increasingly being used to identify both highly polar and high-molecular-weight DBPs that have been missed in previous studies. Because GC-MS requires some volatility of the analytes for their analysis, molecular weight limitations of ~600 Da generally exist. Also, highly polar compounds are generally not volatile and do not chromatograph well by GC unless they are derivatized. LC-MS is perfectly suited to both these categories, providing a nice complement to GC-MS. Moreover, ultrahigh-performance liquid chromatography (UHPLC), which provides a much higher number of theoretical plates and better chromatographic resolution of analytes, is progressively being used over traditional LC with MS.

Quadrupole (Q)-time-of-flight (TOF) mass spectrometers and Orbitrap mass spectrometers are increasingly being used with LC, which provides high-resolution accurate mass capability to enable the identification of unknowns. Previously, magnetic sector mass spectrometers were used with GC, which enabled many unknown DBPs to be measured; now, high-resolution MS is becoming more common with LC. Moreover, a tandem MS (MS/MS) technique that is popular with triple quadrupole (QqQ) mass spectrometers, precursor ion scan, is enabling many new brominated and iodinated DBPs to be identified. Dr. Xiangru Zhang at the Hong Kong University of Science and Technology pioneered this technique for unknown DBP analysis [15], and its use is spreading to other laboratories.

This chapter will cover the advances made using LC-MS for the identification and quantification of emerging DBPs. These will include DBPs formed by the reaction of disinfectants with NOM and with wastewater contaminants.

2. LIQUID CHROMATOGRAPHY-MASS SPECTROMETRY METHODS

LC-MS methods have been developed both for quantifying important emerging DBPs and also to discover new ones. One of the most important emerging DBP methods developed for quantification, involves a highly sensitive solid-phase extraction (SPE)-LC-electrospray ionization (ESI)-MS/MS method that Dr. Xing-Fang Li's group created for measuring nine nitrosamines (NAs), including *N*-nitrosodimethylamine (NDMA), in drinking water [16]. This method expanded on the previous EPA method [17] that used GC-chemical ionization-MS/MS to measure seven NAs, enabling the detection of two additional NAs, including *N*-nitrosodiphenylamine (NDPhA), which is thermally labile and can degrade in a GC injection port. This method also enables low and sub-ng/L detection and was subsequently used to discover that NAs can increase in concentration in the distribution system, with higher levels found at longer distances from the treatment plant. A few years later, Lee et al. created an automated SPE-LC-MS/MS method that utilizes atmospheric pressure chemical ionization (APCI) and also provides low and sub-ng/L detection for nine NAs [18]. This method was subsequently used to measure NAs in treated wastewater and in rivers.

Halobenzoquinones (HBQs) were an entirely new class of DBPs discovered by creating a sensitive UHPLC-negative ESI-MS/MS method to look for them [19]. HBQs, which are predicted to be carcinogens, had not been identified previously in drinking water, but they had been postulated to form. As a result, Li's group created a new method based on available standards and achieved ng/L detection limits with a high-resolution Q-TOF-mass spectrometer. HBQs included chloro-, bromo-, and iodospecies. The ionization of these molecules was very unusual, with $(M + H)^-$ ions observed in the negative ion mode, which are formed by two-electron reduction and addition of a proton. Typically $(M-H)^-$ ions are formed in the negative ion mode, but benzoquinones have unusual redox chemistry that produces these ions in ESI.

Haloacetamides were the focus of another quantitative LC-APCI-MS/MS method created by Chu et al., who measured 13 chloro-, bromo-, and iodospecies at detection limits ranging from 7.6 to 19.7 ng/L [20]. This method was subsequently used to report the first measurements of tribromoacetamide and chloroiodoacetamide in drinking water in China. Iodinated haloacetic acids (iodo-HAAs) were the subject of another new LC-MS method by Li et al., who used large-volume direct aqueous injection with LC-ESI-MS/MS to measure four iodoacids in drinking water [21]. The use of a divert valve to divert the mobile phase from the ESI source was key to the success of this method to overcome ionization suppression caused by coeluting inorganic anions.

Precursor ion scan with LC-MS/MS has helped revolutionize the discovery of new polar brominated and iodinated emerging DBPs. While precursor ion scanning has always been available with the use of QqQ mass spectrometers, it was not until Zhang's group published these seminal papers did it start to become realized. Precursor ion scanning involves the selection of an MS/MS product ion in the third quadrupole (Q3) while scanning in Q1 for precursor ions. Because brominated DBPs will typically produce Br fragment ions (m/z 79/81) by MS-MS (in either positive or negative ionization mode), scanning for the precursor ions that gave rise to these Br fragment ions can reveal the presence of new Br compounds. A precursor ion scan for the I fragment ion (m/z 127) can similarly reveal iodinated DBPs. Zhao and Zhang initially published the first article on precursor ion scan without the use of chromatography for the detection of new brominated DBPs [15]. This work was followed by a new method utilizing ultraperformance liquid chromatography (UPLC) with MS/MS, which enabled even more Br-DBPs to be discovered, including 2,4,6-tribromophenol, 3,5-dibromo-4-hydroxybenzoic acid, 2,6-dibromo-1,4-hydroquinone and 3,3-dibromopropenoic acid, which were confirmed with authentic standards [22]. New iodo-DBPs were discovered in a subsequent study using precursor ion scanning, which revealed 17 iodo-DBPs formed by chloramination and chlorination [23].

Total organic iodine (TOI) was the subject of another LC-MS method by Zhang's group, which used selected ion recording with UPLC-ESI-MS/MS to enable improved detection of this parameter over ion chromatography (IC) [24]. TOI is an important surrogate measurement in the DBP area because it enables the total measurement of iodine species formed—not only the *known* iodo-DBPs but also the *unknowns*. Like the previous TOI method [25], this one also utilized sorption of a water sample on activated carbon, followed by combustion to form HI, which was absorbed into an aqueous solution. However, rather than using IC detection, which generally only permits around 20 μg/L detection, the UPLC-MS/MS method could achieve 2.5 μg/L quantification limits for an 80-mL water sample. Gong and Zhang created another method using UHPLC-MS/MS that could determine iodide, iodate and organic iodine [26]. Specifically, iodide and iodate were derivatized to organic iodine, which was measured using the TOI method described earlier. For this approach, iodide is reacted with monochloramine to form HOI, which is reacted with phenol to form organic iodine. Iodate is reduced with ascorbic acid to form iodide and is determined as iodide. This method was subsequently used to quantify iodide, iodate and organic iodine in tap water, seawater and urine and wastewater with recoveries of 91%—109%, 90%—108% and 91%—108%, respectively, and detection limits of 2.5 μg/L.

LC-MS methods have also been created to measure highly polar carbonyl DBPs in drinking water. However, carbonyl DBPs, such as formaldehyde, are difficult to extract from water and are also difficult to ionize with ESI or APCI-MS; as a result, derivatization has been used in these methods. For example, in a very early study, Richardson et al. utilized dinitrophenylhydrazine (DNPH) derivatization with LC-MS to identify new highly polar carbonyl DBPs in ozonated drinking water [27]. This method also allowed aldehydes to be easily distinguished from ketones from the difference in their mass spectra and chromatographic behaviour. Zwiener et al. further refined this procedure using SPE to allow quantification of carbonyl DBPs in chlorinated swimming pools, at low μg/L levels [28]. Later, Banos and Silva further improved on this procedure by sorbing DNPH on a C18 minicolumn, where derivatization and preconcentration could be performed simultaneously [29]. Derivatization with *O*-(carboxymethyl)hydroxylamine [30] or 4-dimethylamino-6-(4-methoxy-1-naphthyl)-1,3,5-triazine-2-hydrazine (DMNTH) [31] has also been used with LC-MS to successfully identify highly polar carbonyl

DBPs in drinking water. DMNTH offers an additional advantage of providing excellent sensitivity for UV and fluorescence detection, as well as LC-MS.

3. DISCOVERY OF NEW EMERGING DISINFECTION BY-PRODUCTS

As mentioned earlier, precursor ion scan has enabled much progress towards uncovering highly polar Br- and I-DBPs. Pan and Zhang used it along with UHPLC-MS/MS to uncover four new groups of aromatic halogenated DBPs in chlorinated drinking water, including dihalo-4-hydroxybenzaldehydes, dihalo-4-hydroxybenzoic acids, dihalosalicylic acids and trihalophenols [32]. It was suggested that these compounds might be important intermediate DBPs that can then continue to react to form the smaller trihalomethanes (THMs) and HAAs, which are regulated. Pan et al. used UHPLC-MS/MS with precursor ion scanning, multiple reaction monitoring (MRM), and product ion scanning to detect 19 new polar I-DBPs in simulated chlorinated drinking water, 11 of which were confirmed with authentic standards [33]. Tap water samples from China also revealed the presence of seven of these new DBPs, with levels ranging from 0.11 to 28 ng/L, along with two new nitrogen-containing phenolic I-DBPs at levels ranging from 0.12 to 24 ng/L. Zhai et al. used UHPLC-MS/MS to investigate the formation of polar brominated DBPs in chloraminated drinking water, detecting 29 aliphatic, aromatic or nitrogenous Br-DBPs in chloraminated drinking water [34]. The authors also developed a model with 33 major reactions to describe the overall kinetics.

In a particularly creative study, Pan et al. investigated the potential formation of I-DBPs in cooking with iodized table salt [35]. In their study, cooking conditions were simulated using wheat flour added to NOM-containing pure water, which was reacted with chlorine or chloramines with heat. They found many polar I-DBPs, including 3-iodo-4-hydroxybenzaldehyde, 3-iodo-4-hydroxybenzoic acid, 3-iodo-4-hydroxy-5-methylbenzoic acid, diiodoacetic acid, 3,5-diiodo-4-hydroxybenzaldehyde, 3,5-diiodo-4-hydroxylbenzoic acid, 2,6-diiodo-4-nitrophenol, 2,4-diiodo-7-nitrophenol and 2,4,6-triiodophenol, which were confirmed with standards.

In another creative study, Xiao et al. investigated the formation of halogenated DBPs in swimming pool water, as well as their permeability across skin [36]. Precursor ion scanning was used with UHPLC-MS/MS to identify halophenols and halonitrophenols as new pool DBPs. Permeability values for 2,4-dibromophenol, 2,4-dichlorophenol and 2-bromophenol ranged from 0.021 to 0.031 cm/h. Pan et al. also identified new halophenols in tap water samples from China using precursor ion scan, product ion scan and MRM, with LC-MS/MS, and found levels ranging from 9.5 to 330 ng/L [37].

Tang et al. published a groundbreaking article on an entirely new strategy for comprehensively identifying DBPs and other compounds in water using LC-MS/MS [38]. Rather than using precursor ion scan, which targets specifically brominated and iodinated DBPs, this method allows all DBPs to be detected. It also helps to overcome a limitation with data (in) dependent acquisition, which is a common MS tool that triggers MS/MS scans when peaks are detected with LC-MS. This new strategy by Tang et al. uses multiple SPE with three different phases (Oasis HLB, Bond Elut C18 and Bond Elut ENV), LC with two complementary columns (C18 and HILIC), high-resolution MS/MS and a new technique called precursor ion elimination (PIE). Through the use of multiple SPE, a broader range of compounds can be extracted; through the use of LC compounds of very different polarity, more extensive separations can be achieved for this broader range of compounds; and through high-resolution MS/MS, empirical formulae can be obtained for unknown precursor molecules and their fragment ions. Moreover, the novel PIE strategy allows for many more quality MS/MS spectra to be obtained compared with data-(in)dependent acquisition. With PIE, an initial MS/MS scan is conducted for high abundance ions, followed by a second MS/MS scan, which excludes these initial high abundance ions and focuses on lower abundance ions that would normally be missed in traditional approaches. This new strategy was demonstrated on source water and finished drinking water, and using the Human Metabolome Database, they were able to detect >600 peptides and confirm 3 disinfection reaction pathways that convert peptides into DBPs.

In another study, Wu et al. investigated antiestrogenic DBPs formed by the reaction of phenylalanine with chlorine [39]. Semipreparative LC was used to isolate fractions that showed antiestrogenic activity, and LC-MS and nuclear magnetic resonance (NMR) spectroscopy revealed the identity of a key compound exhibiting this antiestrogenic activity: 2,4-diphenylcrotonaldehyde.

The LC-MS/MS method for the nine NAs mentioned earlier has been used in many subsequent studies regarding their occurrence, formation and fate in drinking water. For example, this method was used for the most extensive study of NAs in North America [40]. In this study, 38 drinking water systems in the United States and Canada, which used a variety of treatments—chlorine, chloramines, ozone-chlorine, and chlorine-ozone—were sampled. NDMA, NDPhA, and *N*-nitrosomorpholine (NMor) were all detected, with NDMA up to 130 ng/L (in 28 systems), NDPhA up to 1.8 ng/L (in five systems), and NMor at 2.2 ng/L (in one system). In another study, Zhou et al. used this LC-MS/MS method to discover an important precursor in the formation of NDPhA in chloraminated drinking water: diphenylamine [41]. In addition, two new DBPs were also identified, phenazine and a chlorinated phenazine derivative, using LC-MS/MS.

Tobacco-specific and alkyl NAs were included with the nine NAs mentioned earlier in another new SPE-LC-MS/MS method by Qian et al. [42]. These included *N*-nitrosonornicotine (NNN), *N*-nitrosoanatabine, *N*-nitrosoanabasine (NAB), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL). Method detection limits of 0.01—2.7 ng/L and recoveries of 53%—93% were achieved for the 14 NAs. When measured in eight drinking water systems, NNAL was detected (0.5 ng/L, in one system), along with NDMA and NDPhA. This represents the first time a tobacco-specific NA has been identified as a DBP in drinking water. Formation potential tests also revealed that NDMA and NNAL precursors are present in water subject to tobacco leaching and also in wastewater-impacted drinking water. In another study by Chen et al., precursors and mechanisms of tobacco-specific NA formation in chloraminated drinking water was the focus [43]. Results revealed that NNK and NNAL were formed from nicotine, as shown in Fig. 1.

Moreover, NNN was found to form from nornicotine, and NAB from anabasine. Reaction pathways were proposed for the formation of

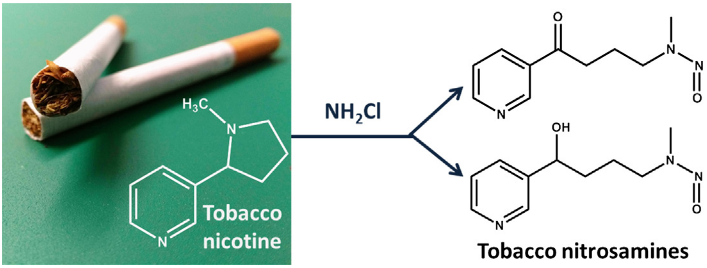

Figure 1 Formation of tobacco nitrosamines with chloramination.

these tobacco-specific NAs from the alkaloids originating from tobacco in cigarettes. Wu et al. reported the measurement of tobacco-specific NAs in chloraminated drinking water and in wastewater treatment plants using LC-MS/MS, and found that NNAL and NNK were formed [44]. However, the sum of the tobacco-specific NAs was 100 times lower than NDMA, indicating that these tobacco-specific NAs are minor contributors to the total NA levels in treated waters.

Saline wastewater effluents were the focus of another study by Ding et al., who used precursor ion scan with UHPLC-MS/MS to investigate the formation of DBPs formed when these wastewaters are chlorinated [45]. This study was conducted because Hong Kong uses seawater for toilet flushing to save the use of freshwater, and it was not known what kind of DBPs might form and impact ecosystems when this water is treated with chlorine. Fifty-four major polar Br-DBPs were identified in these samples, with six being reported for chlorinated wastewater for the first time: bromomaleic acid, 5-bromosalicylic acid, 3,5-dibromo-4-hydroxybenzaldehyde, 3,5-dibromo-4-hydroxybenzoic acid, 2,6-dibromo-4-nitrophenol and 2,4,6-tribromophenol. Compared with secondary treatment, primary treatment of saline wastewater generated fewer and lower levels of Br-DBPs.

As mentioned earlier, HBQs are a new class of DBPs uncovered recently. Several studies have been conducted to assess their formation and fate. For example, Zhao et al. reported the discovery of three new HBQs: 2,6-dichloro-3-methyl-1,4-benzoquinone, 2,3,6-trichloro-1,4-benzoquinone and 2,6-dibromo-1,4-benzoquinone using LC-MS/MS with high-resolution accurate mass [46]. Concentrations ranged from 0.5 to 165 ng/L in chlorinated drinking water. Eight HBQs, including Br-HBQs, were the focus of a large occurrence study of nine drinking water plants in the United States and Canada [47]. The compounds 2,6-dichlorobenzoquinone, 2,6-dibromobenzoquinone, 2,6-dichloro-3-methylbenzoquinone and 2,3,6-trichlorobenzoquinone were found in 16, 11, 6, and 3 of 16 samples, respectively, with concentrations ranging from 4.5 to 274.5 ng/L. Finally, Wang et al. published an excellent review on the analytical characterization, occurrence, transformation and removal of HBQs in water [48]. Challenges of HBQ analytical method development were also presented.

N-chloroacetamides were the focus of an article by Yu and Reckhow, who studied their formation and occurrence in chlorinated drinking water [49]. A new SPE-UHPLC-MS/MS (QTOF) method was created to measure the occurrence of seven *N*-chloroacetamides in drinking water, and three species were identified for the first time in drinking water: *N*-chloro-2,2-dichloroacetamide, *N*-chloro-2,2-bromochloroacetamide and *N*-chloro-2,2,-dibromoacetamide. This study suggests that previous identifications of dichloroacetamide in drinking water may have actually been *N*-chlorodichloroacetamide. This is because the nitrogen-bound chlorine in *N*-chlorodichloroacetamide can be readily reduced by commonly used quenching agents that are used to quench free chlorine. This study came after a previous study conducted by Kimura et al., in 2013, which first identified an *N*-chloroacetamide (*N*,2-dichloroacetamide) in drinking water, but used GC-MS instead of LC-MS/MS [50]. In this earlier study, a reaction pathway was also uncovered in which monochloramine reacts with chloroacetaldehyde (a common DBP) to form a carbinolamine, 2-chloro-2-(chloramino)ethanol, which can then react with monochloramine to form *N*,2-dichloroacetamide.

Trihalo-hydroxy-cyclopentene-diones were another new class of DBPs uncovered by Pan et al., who used UHPLC-MS/MS in full scan, MRM and product ion scan modes for their identification [51]. A synthesized standard was used to confirm tribromo-hydroxy-cyclopentene-dione and reaction pathways were proposed. New alkyl-benzaldehyde DBPs were reported by Fernandez-Molina and Silva, who used a new LC-MS method with a micro-SPE column impregnated with 2,4-DNPH to identify these compounds as their hydrazine derivatives [52]. Levels ranged from 0.12 to 0.83 μg/L in ozonated drinking water and chlorinated pool water.

Several studies focused on reaction mechanisms for emerging DBPs. Wang et al. used UHPLC-MS/MS to probe secondary amines as NA precursors [53]. This study investigated nine potential secondary amine precursors and confirmed four of them as NA precursors in chloraminated drinking water: dimethylamine, diethylamine, morpholine and di-*n*-butylamine. In another study from Japan, NA precursors were investigated in groundwater and river water from Tokyo [54]. NDMA precursors ranged from 4 to 84 ng NDMA equivalents/L in groundwater and 11-185 ng NDMA equivalents/L in river water, which suggests that NDMA precursors are biodegraded, sorbed or volatilized during infiltration into groundwater. NDMA precursors were found mostly in the <0.5 kDa fraction of NOM, followed by 0.5—3 kDa. Wang et al. published one of the first reports of NAs in China, measuring nine NA species using UHPLC-MS/MS, and observed increasing formation in the distribution systems, confirming this phenomenon previously reported in North America [55]. Levels of NDMA, NMor, *N*-nitrosopyrrolidine (NPYR), *N*-nitrosopiperidine (NPIP), *N*-nitrosomethylethylamine (NMEA) and *N*-nitrosodipropylamine (NDPA) reached 35.7, 12.1, 6.3, 20.9, 4.5 and 79.4 ng/L, respectively, for the four cities sampled.

The fate of emerging DBPs has been the focus of other research. For example, Wang et al. investigated the fate and stability of HBQ DBPs in controlled laboratory experiments and in real drinking water distribution systems [56]. For this work, a sensitive UHPLC-high-resolution MS/MS method using SPE was created to measure potential hydroxyl-HBQ hydrolysis products in water, which allowed sub-ng/L detection limits and 68%–96% recoveries. Results showed an increase in OH-HBQs as the parent HBQs decreased with time in treated water for both laboratory and distribution system experiments, suggesting that the OH-HBQs were the more stable forms of HBQ DBPs in water. While these OH-HBQs exhibited toxicity in a mammalian cell assay, it was lower than that exhibited by the parent HBQs. However, it is notable that the mammalian cell toxicity of both these DBP classes was substantially higher than those of DBPs currently regulated (THMs and HAAs).

The fate of HBQs in the presence of UV light was the focus of another study by Qian et al., who used LC-MS/MS to identify photolysis products [57]. Results showed that up to 90% of HBQs in pure water and tap water were transformed to other products, with 3-hydroxyl-2,6-dichloro-1,4-benzoquinone, 5-hydroxyl-2,6-dichloro-3-methyl-1,4-benzoquinone, 5-hydroxyl-2,3,6-trichloro-1,4-benzoquinone and 3-hydroxyl-2,6-dibromo-1,4-benzoquinone identified as major products from dichlorobenzoquinone, dichloromethylbenzoquinone, OH-trichlorobenzoquinone and OH-dibromobenzoquinone, respectively. These hydroxylated reaction products were further degraded to monohalobenzoquinone at UV doses >200 mJ/cm^2.

Liu et al. also investigated photolysis with UV light for the destruction of halophenol DBPs in seawater [58]. Halophenol transformation occurred by the following progressive reactions: (1) photonucleophilic substitution, with bromo- and iodophenol DBPs converted to Cl- or OH-analogues, (2) further conversion of Cl-phenol DBPs to OH-phenol analogues and (3) further decomposition of OH-phenols to aliphatic compounds. Overall, this resulted in dehalogenation and detoxification of the water.

4. PHARMACEUTICAL DISINFECTION BY-PRODUCTS

Pharmaceutical DBPs have been an intense area of research in recent years. Interest derives from the possibility of entering drinking water sources from incomplete removal in wastewater treatment, followed by reaction with disinfectants in drinking water treatment, along with transformation in wastewater treatment itself, as many wastewater treatment plants also treat with chlorine to inactivate pathogens before discharging to surface waters or reuse. As a result, pharmaceutical DBPs could present an issue for both human and ecological health. After reaction with disinfectants, sometimes the active part of the molecules is destroyed, and therefore, the initial pharmaceutical activity is diminished. However, sometimes, the portion of the molecule that encompasses the biological activity remains. Moreover, the toxicity of the molecule can increase through the formation of more toxic halogenated DBPs. Therefore, pharmaceutical DBPs are important to investigate. Some of the earliest articles in the field were authored by Dodd and Huang and collaborators, who focused on the reaction of different antibiotics with chlorine and included extensive kinetics and proposed mechanisms and pathways [59–61]. These studies included an investigation of the reaction of sulfamethoxazole, fluoroquinolone, and trimethoprim with chlorine, and LC-MS was used, along with fractionation for NMR analysis, to identify the DBPs formed.

High-resolution MS is a growing trend for identifying and studying pharmaceutical DBPs. For example, Gonzalez-Mariño et al. published an interesting study investigating the transformation of the main cannabis metabolite, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol during water chlorination using LC with high-resolution-QTOF-MS [62]. Of the DBPs identified, three resulted from electrophilic substitution of chlorine (or bromine) for hydrogen on the aromatic ring and four resulted from halogenation and hydration across the carbon–carbon double bond. The proposed transformation pathway is shown in Fig. 2. Toxicity calculations for *Daphnia magna* indicated that these DBPs will have toxicity similar to or greater than that of the parent molecule.

Chemotherapy (cytostatic) drugs have also been a recent focus, due to their high cytotoxicity and potential impact on the environment. Specifically, Barcelo's group has recently reported the identification of chlorine DBPs of vinca alkaloids and erlotinib using UHPLC-high resolution MS/MS using a Q-Orbitrap mass spectrometer [63,64]. Vinca alkaloids

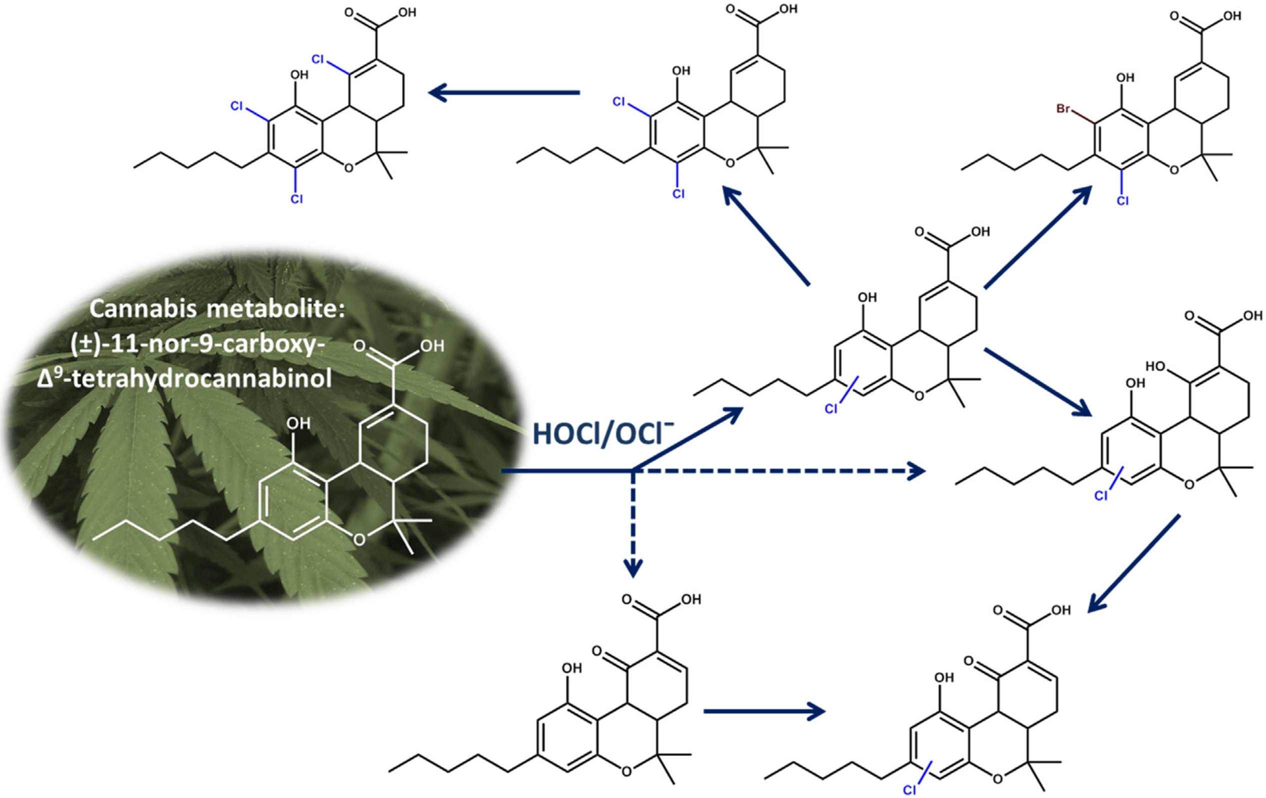

Figure 2 Formation of chlorine DBPs from a cannabis metabolite.

are plant-derived chemotherapeutic agents that are widely used as single agents or in combination with other drugs for the treatment of non—small cell lung cancer, breast cancer, bladder cancer, lymphomas, and leukaemias. Negreira et al. reported the reactivity of vincristine, vinblastine, vinorelbine and its metabolite 4-*O*-deacetyl vinorelbine with chlorine under simulated drinking water conditions and tentatively identified 65 DBPs [63]. Of these DBPs, 24 were mono-Cl compounds, eight were di-Cl compounds, and two were tri-Cl compounds. Other DBPs were formed by oxidation or hydroxylation reactions. High-resolution MS was key to empirical formula determination for these new DBPs. In the other chemotherapeutic drug DBP article, Negreira et al. reported DBPs from erlotinib, which is used for treating the most common type of lung cancer [64]. Nineteen DBPs were identified under simulated wastewater chlorination conditions, six of which contained chlorine atoms; others involved oxidation or hydroxylation reactions. Moreover, time course measurements were conducted, and an extensive transformation pathway proposed.

Iodinated X-ray contrast media (ICM) have also been extensively investigated since the first reports of iopamidol DBPs by Duirk et al. [65]. ICM are commonly used for medical imaging of soft tissues and organs and are composed of aromatic rings with three iodines and three amide side chains. Levels of ICM are among the highest found in the environment for any pharmaceutical, due to the high doses given (up to 200 g/person/day) and due to their poor removal during wastewater treatment (typically 0% removal) [65]. Initially, highly toxic low-molecular-weight iodoacids and iodo-THMs were discovered from one of these ICM—iopamidol [65], but more recent work by Wendel et al. has uncovered the initial high-molecular-weight reaction products of iopamidol (molecular weight = 777 Da), as well as an extensive reaction pathway [66]. For this work, LC-high-resolution MS/MS was used with an Orbitrap mass spectrometer, which allowed empirical formulae to be obtained for both precursor and fragment ions. Nineteen DBPs were identified using both LC-high-resolution MS/MS and preparative LC fractionation and NMR spectroscopy. A follow-up study by Wendel et al. investigated the mammalian cell cytotoxicity and genotoxicity of five of the high-molecular-weight iopamidol DBPs, which were isolated using preparative LC [67]. Four of the five DBPs exhibited a low level of cytotoxicity, while none were genotoxic. This is in contrast to the high genotoxicity of lower molecular weight DBPs of iopamidol, such as iodoacetic acid [65].

UV—chlorine reactions of the ICM, iohexol, were investigated by Wang et al., who used UHPLC-ESI-MS for analysis [68]. In these reactions, iohexol was found to be effectively removed with pseudo-first-order reaction kinetics and formed five intermediate DBPs along with terminal I-THM products. Reactions involved hydrogen abstraction from amide side chains, deiodination, hydroxyl addition, chlorine substitution and hydroxyl substitution for an amide side chain. Further, the use of chlorine with UV accelerated the degradation of iohexol.

β-Blockers and β-agonists were the focus of another article by Quintana et al., who investigated chlorine reactions of these pharmaceuticals using LC-QTOF-MS [69]. Specifically, atenolol, propranolol, and salbutamol were reacted with chlorine and bromide using a Box-Behnken experimental design. The use of high-resolution MS enabled the identification of 14 DBPs, which were formed by halogenation, hydroxylation, and dealkylation. Rodil et al. reported the identification of chlorinated DBPs from phenazone-type drugs that are used as analgesics and antipyretics: phenazone and propyphenazone [70]. LC-high resolution MS/-MS using a QTOF mass spectrometer revealed the formation of DBPs, including chloro-hydroxy-phenazone and *N*-demethyl-chloro-hydroxyl-phenazone, *N*-demethyl-hydroxy-propyphenazone and *N*-demethyl-chloro-hydroxy-propyphenazone. Moreover, results indicated that these DBPs can be formed at the household emission point and during drinking water treatment. The transformation of the β-blocker acebutolol by chlorine was investigated by Khalit and Tay, who used also used LC-high-resolution QTOF-MS [71]. Seven major DBPs were identified, which were formed by chlorination, dealkylation, hydroxylation and oxidation reactions.

High-resolution MS was used by Wood et al. to examine chlorination DBPs from the anti—human immunodeficiency virus (HIV) drug nevirapine [72]. Several DBPs were identified, both in controlled laboratory reactions and in the environment (i.e., surface waters close to wastewater treatment plants). In addition, preparative chromatography was used to isolate fractions and test them for in vitro toxicity and anti-HIV activity. While some of these DBPs were not as toxic as the parent drug, they still retained the antiviral activity.

A group of seven pharmaceuticals and personal care products and their halogenated DBPs was the focus of a study by Bulloch et al., who investigated their transformation in secondary and tertiary treated wastewater in Southern California [73]. Specifically, DBPs of salicylic acid, BPA, gemfibrozil, naproxen, diclofenac, technical 4-nonylphenol and 4-*tert*-octylphenol were investigated in wastewater treatment using LC-MS/MS and also using synthesized chlorinated and brominated standards and isotopically labelled internal standards. Concentrations of chloro/bromo-DBPs ranged from <4 to 370 ng/L (for dibromo-nonylphenol). These included seven DBPs from salicylic acid, four DBPs from 4-nonylphenol, one DBP from 4-*tert*-octylphenol, one DBP from diclofenac, two DBPs from naproxen, and two DBPs from gemfibrozil. Surprisingly, no DBPs were detected from BPA, despite its ability to form halogenated DBPs via reaction of chlorine or bromine with its aromatic ring.

In another study, Qin et al. determined kinetic models and pathways for the reaction of the antibiotic/antiprotozoal agent ronidazole with chlorine, UV and UV—chlorine [74]. Degradation intermediates were identified using UHPLC-MS and reaction pathways were proposed.

NDMA formation from the chloramination of ranitidine was the focus of an article by Le Roux et al., who used LC-MS to uncover the DBPs formed [75]. Most DBPs consisted of chlorinated and hydroxylated analogues of ranitidine, and excess NH_2Cl resulted in intermediates that formed NDMA in high yields.

Finally, methadone DBPs were the focus of a 2015 study by Hanigan et al., who investigated their formation in chloraminated surface waters and wastewaters [76]. Methadone is a drug used to mitigate heroin withdrawal symptoms and also for chronic pain. It contains a dimethylisopropylamine group that can react with NH_2Cl to form high concentrations of NDMA, at a molar yield of 23%—70% depending on the NH_2Cl dose. In this study, methadone was found to be responsible for 1%—10% of the NDMA formation potential in most raw surface waters and up to 62% of NDMA formation in wastewater.

5. HORMONE DISINFECTION BY-PRODUCTS

Hormones also have functional groups that can react in drinking water or wastewater treatment to form DBPs. In particular, the natural hormones 17β-oestradiol (E2) and estrone (E1) and the synthetic hormone ethinyloestradiol (EE2) used as a contraceptive have been shown to form DBPs. Sometimes the estrogenic activity is lowered with these reactions, and sometimes it remains the same. Early articles in 2003—2004 laid the groundwork for this field, with investigations of chlorine and ozone by-products using LC-MS. For example, Hu et al. reacted E2 with chlorine under controlled laboratory conditions and identified seven DBPs using LC-MS: 2,4-dichloro-E2, monochloro-estrone, 2,4-dichloro-estrone and four other DBPs similar to 4-[2-(2,6-dichloro-3-hydroxyphenyl)ethyl]-7α-methyloctahydroinden-5-one [77]. Estrogenic activity remained in the reaction mixtures, and some of these DBPs were synthesized and examined individually for estrogenic activity. 2,4-Dichloro-E2 and 2,4-dichloro-estrone were found to be the main drivers of estrogenic activity in the reactions for 120 and 180 min. Huber et al. investigated ozone DBPs of EE2 and found several DBPs, including cyclohexanone, 1-hydroxycyclohexanoic acid, adipic acid, and other oxygenated products [78]. At ozone doses used in drinking water treatment, only the phenolic group reacted with ozone, but at higher doses, the ethinyl group can also react. In this case, the estrogenicities of the products were significantly lower, by a factor of 200 compared with that of the parent EE2 molecule. Moriyama et al. discovered the first chlorine DBPs from EE2, identifying six DBPs, with 4-chloro-EE2 and 2,4-dichloro-EE2 as the major ones [79]. LC-MS, preparative LC, and NMR were used to identify them. EE2 reacted very quickly with chlorine, with EE2 almost completely consumed in 5 min. 4-Chloro-EE2 was found to retain the estrogenic activity similar to the parent EE2 compound, but 2,4-dichloro-EE2 had 10 times lower activity.

Ozone DBPs of E2 and E1 were investigated by Pereira et al. using UHPLC-MS/MS with a QqQ and a QTOF mass spectrometer [80]. E2 and E1 formed two main DBPs, with molecular masses of 286 and 276 Da, respectively. They were formed via electrophilic *ortho/para*-substitution on the aromatic ring and ring cleavage.

6. ULTRAVIOLET FILTER DISINFECTION BY-PRODUCTS

UV filters are used in sunscreens, cosmetics and other personal care products, such as shampoos and hair dyes, to protect against sun damage. These include organic UV filters that absorb light and inorganic UV filters that reflect and scatter light. Many organic UV filters have activated aromatic rings or other functional groups that can readily react with chlorine. Zwiener et al. identified five UV filters in public outdoor swimming pools: 2-hydroxy-4-methoxybenzophenone (BP3), ethylhexylmethoxy cinnamate, 2-ethylhexyl-2-cyano-3,3-diphenyl-2-propenoate, 2-phenyl-1H-benzimidazole-5-sulfonic acid, and 4-methylbenzylidene camphor, along with chlorination DBPs from them, including two Cl-BP3 isomers, which are formed by electrophilic substitution *ortho* and *para* to the phenolic OH group [81]. Xiao et al. used LC-high-resolution MS and NMR to identify 15 DBPs from the reaction of chlorine with BP3 in a controlled laboratory study [82]. Transformation pathways were proposed, which included electrophilic chlorination, Baeyer-Villiger—type oxidation, ester hydrolysis, decarboxylation and desulfonation. Brominated DBPs were the subject of another study by Xiao et al. who chlorinated 2-hydroxy-4-methoxy-5-sulfonylbenzophenone in the presence of bromide [83]. The reaction mechanisms involved electrophilic substitution generating mono- or dihalogenated DBPs, followed by oxidation to esters and hydrolysis to phenol derivatives.

Kalister et al. reacted the UV filter avobenzone with chlorine and used LC-high-resolution MS/MS and GC-MS to identify the DBPs formed [84]. In this case, rather than reacting with the aromatic ring, chlorine reacted with the carbon-carbon double bond of the enolic form of the diketone, forming 2-chloro-1-(4-*tert*-butylphenyl)-3-(4-methoxyphenyl)-1,3-propanedione and 2,2-dichloro-1-(4-*tert*-butylphenyl)-3-(4-methoxyphenyl)-1,3-propanedione as the main products. Finally, Liu et al. used UHPLC-QTOF-MS and NMR to determine the DBPs resulting from the reaction of chlorine with 4-hydroxylbenzophenone (4HB) and identified seven major products [85]. One of the major DBPs, 3,5-dichloro-4HB, was found to be responsible for increasing the acute toxicity after chlorination.

7. BISPHENOL A DISINFECTION BY-PRODUCTS

BPA has two phenolic rings in its structure that can readily react with chlorine. Hu et al. used LC-APCI-MS and NMR to identify DBPs in reactions of BPA with chlorine [86]. Thirteen DBPs were identified: 4-chloro-BPA, 2,6′-dichloro-BPA, 2,6-dichloro-BPA, 2,2′,6′-trichloro-BPA, 2,2′,6,6′-tetrachloro-BPA, trichlorophenol, 4-isopropyl-2′-hydroxylphenol and six types of polychlorinated phenoxyphenols. The chlorinated DBP mixture was assessed in an estrogen receptor binding assay and had higher estrogenic activity, with the ability to mimic the effect of the estrogen hormone.

8. ALKYLPHENOL ETHOXYLATE SURFACTANT DISINFECTION BY-PRODUCTS

APEOs are widely used surfactants in cleaning products and detergents, and they can react in drinking water or wastewater to form chlorinated DBPs. Their structures contain phenolic groups that are very reactive with chlorine and exhibit *ortho/para* substitution on the phenolic ring. Barcelo's group in Spain were pioneers in exploring the reactions of these surfactants with chlorine, publishing as early as 2001. In their first article, Petrovic et al. used LC-MS to identify and quantify chlorinated APEOs formed after drinking water and wastewater treatment [87]. Halogenated DBPs were found only in drinking water treatment plant samples, with Br-APEOs in prechlorinated water. However, these were effectively removed in the subsequent treatment stages of flocculation, rapid sand filtration, ozonation, granular activated carbon (GAC) filtration and final chlorination, such that they were not observed in the finished drinking water. However, they were observed in the resulting sludge at the drinking water plant, at 220 μg/kg (Br-nonylphenol), 430 μg/kg (Br-nonylphenol mono- and diethoxylates) and 1600 μg/kg (for Br-nonylphenol ethoxylates with 3–15 ethoxylate groups). Chlorinated nonylphenol ethoxylates were estimated at 660 μg/kg, and halo-octylphenol ethoxylates were also identified, but at 50 times lower levels than the nonylphenol ethoxylates.

In another study from Barcelo's group, the occurrence and removal of short-chain nonylphenol ethoxylates and their halogenated DBPs was examined in drinking water treatment [88]. Concentrations of the parent surfactants ranged from 8.3 to 22 μg/L in the source waters, and prechlorination lowered these by 25%–35%, but this reduction was partly due to formation of mostly brominated DBPs. Further treatment steps helped to eliminate these DBPs and the parent compounds, with ozonation and GAC filtration providing the largest benefit, with 87% and 73% removal, respectively.

9. PESTICIDE DISINFECTION BY-PRODUCTS

Pesticides mostly enter surface waters via runoff from agriculture, and several of them have functional groups that can form DBPs. For example, in very early work published in 1994, Mascolo et al. used LC with low- and high-resolution MS to investigate DBP formation when sulfur-containing S-triazine herbicides react with chlorine and chlorine dioxide [89].

All triazines studied (prometryne, terbutryne, ametryne and desmetryne) were found to react in the same way, producing oxidation products, but no DBPs containing halogens. A sulfoxide, sulfone and a sulfone hydrolysis product were the DBPs observed for chlorine, whereas chlorine dioxide was less reactive and formed only one DBP, the sulfoxide. The popular herbicide atrazine was studied by Nelieu et al. using an advanced oxidation treatment, ozone—hydrogen peroxide [90]. LC-MS/MS was used to identify the DBPs, which included ammeline as a major product, along with hydroxydeethylatrazine, hydroxydeisopropylatrazine and hydroxyatrazine.

The herbicides terbutryn and isoproturon were the focus of another study by Lopez et al., who also investigated reactions with chlorine and chlorine dioxide [91]. In chlorine reactions, isoproturon underwent chlorine substitution reactions and oxidation reactions with chlorine dioxide. On the other hand, terbutryn only underwent oxidation reactions (no chlorine substitution) with both chlorine and chlorine dioxide treatment. LC-MS was key to identifying the DBPs formed.

In another study by Zambonin et al., the herbicide chlortoluron was found to react with chlorine to form DBPs resulting from chlorination and hydroxylation reactions on the aromatic ring. MS^n ($n = 1-4$) was used to determine the chemical structures of these DBPs [92]. Xu et al. examined the kinetics, pathways, and DBP formation for chlortoluron [93]. GC-purge-and-trap-MS was used to identify volatile DBPs, and UHPLC-MS was used to identify nonvolatile DBPs, along with a few others, such as dichloroacetic acid and NDMA. The proposed reaction pathways included simultaneous oxidation, substitution and hydroxylation on the aromatic ring and the ureic side chains, followed by opening of the ring to form several chlorine-containing DBPs.

Finally, Lin et al. used LC-MS/MS to determine by-products of the herbicide isoxaflutole in chlorinated tap water [94]. It was found to rapidly react with chlorine, forming a benzoic acid DBP as the major product. In fact, using only 1 mg/L of chlorine (which is on the low side of the residual levels found in US drinking water distribution systems), isoxaflutole could be completely degraded, and the DBP was found to be nonphytotoxic.

10. FLAME RETARDANT DISINFECTION BY-PRODUCTS

Flame retardants are used in many commercial products, including foam cushions in chairs and sofas, computers and other electronics, plastics and children's sleepwear. While most are environmentally persistent, some can form DBPs. For example, Gao et al. reported that tetrabromobisphenol A can react with chlorine to form DBPs, including several halogenated phenols and a quinonelike product: 2,6-dibromoquinone [95]. Precursor ion scan, focused on the m/z 79 and 81 of the bromine fragment ion, was used with LC-MS/MS to uncover the brominated DBPs formed. The reaction pathway proposed included oxidation to form a phenoxy radical, and then beta-scission, followed by substitution, dimerization and oxidation. Results confirmed that chlorine can also transform phenolic compounds via electron transfer, rather than only electrophilic substitution.

11. BENZOTRIAZOLE DISINFECTION BY-PRODUCTS

Ozonation is often used in drinking water treatment to remove contaminants, as well as disinfect the water. Muller investigated the potential for DBP formation when ozone reacts with 4- and 5-methyl-1H benzotriazole in drinking water treatment [96]. LC-QTOF-MS was used in full-scale mode, along with hydrogen—deuterium (H/D) exchange and derivatization to structurally elucidate the products formed. In particular, a positive H/D exchange indicated the presence of azide hydrogen atoms and hydroxyl groups in the molecules. Several oxidation products were identified in controlled laboratory experiments, and three of these were also found in treated waters from a full-scale drinking water plant using ozone. Reaction pathways involved oxidation of methyl groups to carboxylic acid, as well as formation of aldehydes and ketones by ring cleavage. However, the triazole ring remained intact.

12. SALICYLATE DISINFECTION BY-PRODUCTS

Salicylates used in personal care products were the focus of another study, which used LC-MS to identify chlorine by-products, tentatively identified as mono- and dichlorosubstituted products, formed by electrophilic substitution on the phenolic ring [97].

13. DISINFECTION BY-PRODUCTS OF OTHER MICROPOLLUTANTS

Zahn et al. used HILIC LC with high-resolution MS to uncover a new class of organic micropollutants, halogenated methanesulfonic acids, which are believed to be formed by chlorination reactions [98]. Chlorinated and brominated methanesulfonic acids appeared to co-occur, implying a common source, and some results point towards drinking water disinfection being a major pathway for their formation, even though they were also found in environmental surface waters. The unknown precursor is yet to be identified.

14. ALGAL TOXIN DISINFECTION BY-PRODUCTS

Unlike other emerging contaminants discussed earlier, algal toxins are naturally produced. Microcystins, cylindrospermopsin, nodularins and saxitoxins have received much attention in recent years due to increased algal blooms worldwide, and they also have functional groups that can react with chlorine, chloramines, chlorine dioxide and ozone. As a result, researchers have conducted reactions with these oxidants to try to remove the algal toxins in water. For microcystins, six chlorination DBPs have been reported: dihydroxy-microcystin, monochloro-microcystin, monochloro-hydroxy-microcystin, monochloro-dihydroxy-microcystin, dichloro-dihydroxy-microcystin, and trichloro-hydroxy-microcystin. High-resolution accurate mass using an LTQ-Orbitrap mass spectrometer helped to uncover some of these [99]. An LTQ-Orbitrap mass spectrometer was also used to uncover chlorination DBPs from cylindrospermopsin, which produced 5-chloro-cylindrospermopsin, cylindrospermopsic acid and a compound with a molecular formula of $C_{13}H_{18}N_4O_7S$ [100]. Ozone can also transform microcystins through hydroxyl radical attack on the conjugated diene and cleavage of the Adda amino acid, which leads to opening of the peptide ring [101]. Finally, while chlorine dioxide can also degrade algal toxins to form nontoxic DBPs (such as dihydroxy products), reactions are quite slow (much slower than with chlorine), so that chlorine dioxide is not seen as a good treatment method for removing microcystin-LR in drinking water [102].

15. CONCLUSIONS

LC-MS is enabling a more complete picture of DBP formation, allowing highly polar and high-molecular-weight species to be identified that was not possible with GC-MS alone. As a result, both LC-MS and GC-MS techniques are complementary. Advances in LC-MS instrumentation, particularly with regard to the wider availability and sensitivity of high-resolution mass spectrometers (including QTOFs and Orbitraps), is enabling better detection and structural elucidation of unknown DBPs. Further, MS/MS scanning techniques like precursor ion scan and PIE are helping to uncover new brominated and iodinated DBPs, as well as reach beyond what data (in)dependent acquisition typically provides, allowing lower abundant peaks to be probed. As more new emerging contaminants are discovered in environmental waters, more opportunities to form DBPs from them (whether in drinking water or wastewater) will arise. To better protect human and ecological health, it is important to understand DBP formation and find ways to eliminate those that are toxic or have other adverse impacts.

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