The contribution of the antibiotic chloramphenicol and its analogues as precursors of dichloroacetamide and other disinfection byproducts in drinking water

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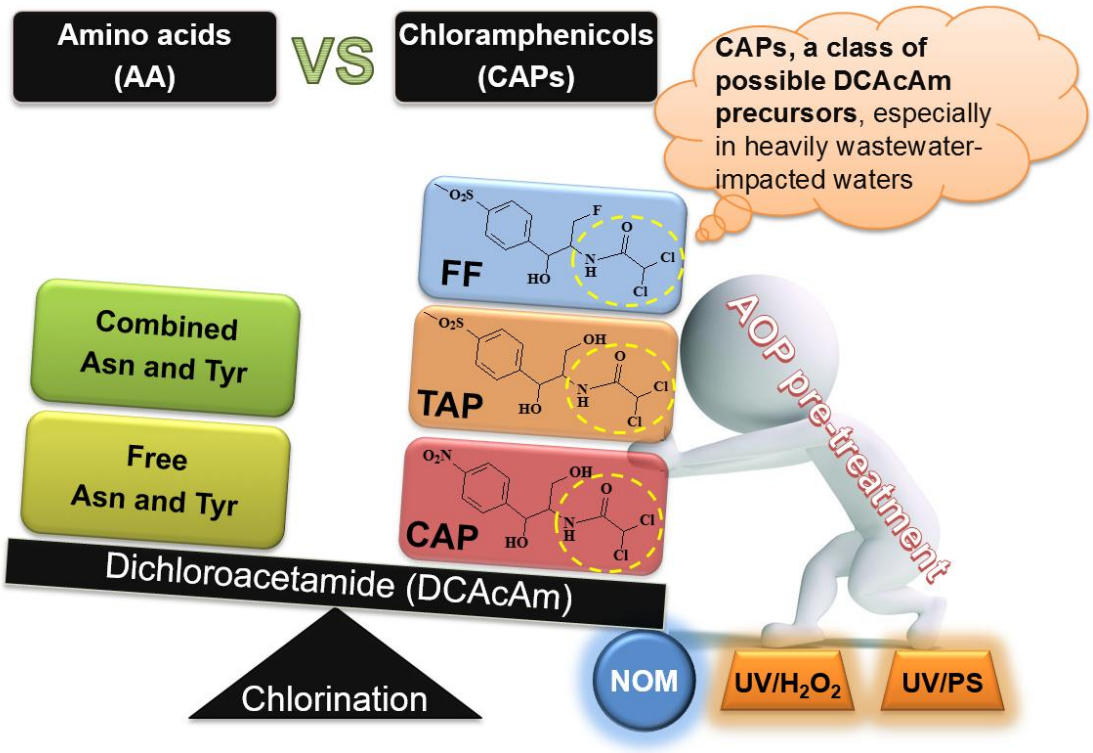

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ABSTRACT

Dichloroacetamide (DCAcAm), a disinfection byproduct, has been detected in drinking water. Previous research showed that amino acids may be DCAcAm precursors. However, other precursors may be present. This study explored the contribution of the antibiotic chloramphenicol (CAP) and two of its analogues (thiamphenicol, TAP; florfenicol, FF), referred to collectively as CAPs, which occur in wastewater-impacted source waters, to the formation of DCAcAm. Their formation yields were compared to free and combined amino acids, and they were investigated in filtered waters from drinking water treatment plants, heavily wastewater-impacted natural waters, and secondary effluents from wastewater treatment plants. CAPs had greater DCAcAm formation potential than two representative amino acid precursors. However, in drinking waters with ng/L levels of CAPs, they will not contribute as much to DCAcAm formation as the µg/L levels of amino acids. Also, the effect of advanced oxidation processes (AOPs) on DCAcAm formation from CAPs in real water samples during subsequent chlorination was evaluated. Pre-oxidation of CAPs with AOPs reduced the formation of DCAcAm during post-chlorination. The results of this study suggest that CAPs should be considered as possible precursors of DCAcAm, especially in heavily wastewater-impacted waters.

Introduction

Haloacetamides (HAcAms) are an emerging class of halogenated nitrogenous disinfection byproducts (N-DBPs), which have been widely detected at low µg/L levels in drinking water.[1-4] They have been reported to be highly cytotoxic and genotoxic in mammalian cell assays compared to other known DBPs (142× more cytotoxic and 12× more genotoxic than regulated haloacetic acids [HAAs]).[5,6] This elevated toxicity for monochloroacetamide (MCAcAm), dichloroacetamide (DCAcAm), and trichloroacetamide (TCAcAm) was also observed in recent studies based on metabonomics.[7-10] DCAcAm is the most abundant HAcAm species formed in waters that are low in bromide,[1,6,10] and it has been commonly used as a representative HAcAm in previous DBP formation studies.[2,11-16] Understanding DCAcAm formation provides valuable information towards controlling the formation of HAcAms more broadly. Furthermore, previous studies have demonstrated that dissolved organic nitrogen (DON) in source waters, originating from microbial metabolism, algal blooms, and municipal wastewater, contributed to DCAcAm formation during chlorination,[12-16] where the nitrogen in the DCAcAm molecule principally originated from biomolecule precursors (e.g., amino acids). Free and combined amino acids have been detected in drinking water at µg/L levels.[11,17] Also, studies have indicated that DCAcAm can form by multiple reactions, such as the hydrolysis of dichloroacetonitrile (DCAN),[12] but also from other pathways that are independent of DCAN.[13] However, the most important precursors are still unclear.

Antibiotic contamination of water supplies has become a world-wide environmental problem and antibiotics are now widespread in many aquatic environments[18] due to their intensive use in the treatment of bacterial infections in humans, animals, and for

agricultural purposes[19,20] Chloramphenicols (CAPs), including chloramphenicol (CAP), thiamphenicol (TAP), and florfenicol (FF), are one class of broad-spectrum antibiotics in widespread use. Due to their potential deleterious effects on human health, TAP and FF are more commonly used as alternatives to CAP for animal treatment. However, CAP is still widely used in livestock aquaculture as feed additives to control outbreaks of disease[21]. Previous studies have indicated that CAPs are stable and difficult to be metabolized after intake[22] and are ineffectively removed by wastewater treatment plants (WWTP) that apply conventional treatment processes.[23,24] Therefore, CAPs eventually reach surface waters that may be used as inputs to drinking water treatment plants.[25,26] In China, CAP concentrations in two source waters, Pearl River[27] and Huangpu River[28], were reported at 11-266 ng/L and 4-28 ng/L, respectively. Also, CAP in Nanming River reached up to 19 μg/L due to the input of municipal sewage[29]. Moreover, TAP and FF were detected at 3-12 ng/L and 8-20 ng/L in Huangpu River[28] and up to 110 and 90 ng/L in Yangtze estuary[30], respectively. CAP, TAP, and FF concentrations reached up to 47, 6, and 65 μg/L in municipal sewage.[29]

A DCAcAm side chain in CAPs[31] may be easily attacked by oxidants to form DCAcAm, as shown in Figure S1 in the Supporting Information (SI). Therefore, the major objective of the study was to evaluate the relative contribution of CAPs to DCAcAm formation by comparing them against other precursors of DCAcAm, in both laboratory-grade water and real water samples. Additionally, advanced oxidation processes (AOPs) are reported to be a promising alternative to treat pollutants in drinking water that cannot be easily treated by conventional processes. Most AOPs involve the *in situ* generation of highly reactive

84 species, such as hydroxyl and sulfate radicals, which are able to oxidize a wide range of
85 chemicals. Therefore, in this study, the impact of two common AOPs (ultraviolet
86 light/hydrogen peroxide [UV/H_2O_2] and UV/persulfate [UV/PS]) on the formation of
87 DCAcAm during subsequent chlorination of real waters spiked with CAPs was also
88 investigated.
89
90 ## MATERIALS AND METHODS
91 **Reagents and Solutions.** MCAcAm, DCAcAm, TCAcAm was obtained from Alfa
92 Aesar (Karlsruhe, Germany), and all bromine-containing HAcAms were purchased from
93 Orchid Cellmark (New Westminster, BC, Canada), except for monobromoacetamide
94 (MBAcAm). Three CAPs (CAP, TAP, and FF), MBAcAm, tyrosine (Tyr), ^{15}N-labeled Tyr,
95 asparagine (Asn), and ^{15}N-labeled Asn were purchased from Sigma–Aldrich (Oakville, ON,
96 Canada). A sodium hypochlorite solution (active chlorine >5%, Sinopharm Chemical
97 Reagent Co., Ltd., China) was used to prepare free chlorine stock solutions. Ultrapure
98 water was produced with a Millipore Milli-Q Gradient water purification system (Billerica,
99 MA, USA). Other materials were at least analytical grade and obtained from Sinopharm
100 Chemical Reagent Co., Ltd (Shanghai, China), unless otherwise noted.
101 **Experimental Procedures.** All experiments were conducted at room temperature (23
102 ± 1°C) and under headspace-free conditions in 500-mL brown glass volumetric flasks.
103 (1) Chlorination using laboratory-grade water. For chlorination experiments using
104 laboratory-grade water (ultrapure water), a typical experiment involved applying a chlorine
105 dose (0.1, 0.25, 0.5, 1.0 mM) to a precursor compound solution (0.05 mM) for a
106 designated reaction time (3, 12, 24 h). In addition, to compare the relative contribution of

DCAcAm from CAP to other representative DCAcAm precursors, chlorination experiments were conducted by adding a certain chlorine dose (0.5 mM) to a mixed solution containing unlabeled CAP (0.05 mM) and ^{15}N-labeled Asn (or ^{15}N-labeled Tyr) (0.05 mM) for a designated reaction time (3, 12, 24 h). Compound solutions were buffered at pH 7.3 ± 0.3 with 10 mM phosphate buffer.

(2) Chlorination using authentic water matrices. For chlorination experiments using authentic water matrices, three CAPs at the designated concentrations (30, 60, 300, 600, 900, 1200 nM) were spiked (up to these levels) with a mixture of CAP, TAP, and FF (each CAP accounted for a third of the total concentration of the three spiked CAPs) into three water samples (A, B, C in Table S1) in 500-mL brown glass volumetric flasks, which were collected after coagulation, sedimentation, and filtration from three Chinese drinking water treatment plants (DWTPs). The raw waters of DWTPs 'A' and 'B' had a high and low specific UV absorbance at 254 nm ($SUVA_{254}$), respectively. In addition, DWTP 'C', characterized by high DON, was also selected for the study. These DWTPs were selected because of expected differences in their natural organic matter (NOM) characteristics, which allowed evaluation of the effect of NOM on DCAcAm formation from CAPs. Additionally, considering CAPs have higher concentrations in heavily wastewater-impacted watersheds, two heavily wastewater-impacted natural waters (D and E in Table S1) and two secondary effluents (F and G in Table S1) from wastewater treatment plants (WWTPs) were also collected. Waters D, E, F, and G were also spiked with a mixture of CAP, TAP, and FF up to 300, 600, 900, and 1200 nM (each CAP accounted for a third of the total concentration of the three spiked CAPs; Water G was not

129 spiked at 300 nM because the actual concentration of the three CAPs was close to 300
130 nM). The characteristics of these selected waters are summarized in Table S1. The
131 concentrations of the three CAPs shown in Table S1 are their background levels in waters.
132 These samples (A-G) were filtered with 0.45 μm membranes (mixed cellulose esters,
133 Merck Millipore Corp., German) to remove particles. Analyses of these waters did not
134 show any detectable HAcAm background levels. To examine the formation of DCAcAm in
135 these selected samples, sufficient chlorine was dosed into the glass volumetric flasks to
136 provide the desired 24-h chlorine residual of 1.0 ± 0.5 mg-Cl_2/L in a single dose, based in
137 part on the Uniform Formation Conditions method developed by Summers et al.[32]. The
138 chlorine dose was sufficient to breakout the raw-water ammonia and to meet the desired
139 residual. The sample pH was adjusted to 7.3 ± 0.3 by addition of H_2SO_4 or NaOH in
140 phosphate buffered samples, because higher HAcAm formation potential could be
141 achieved at this pH level.[33] At the end of the experiment, the chlorine residual was
142 quenched with a stoichiometric amount of ascorbic acid and was analyzed as soon as
143 possible[3,4].

144 (3) Molecular weight (MW) cut-offs of NOM. To examine the role of NOM on DCAcAm
145 formation from CAPs, the selected three filtered waters (A, B, and C in Table S1) were
146 fractionated using two ultrafiltration (UF) membranes (YM100 and YM1, Merck Millipore
147 Corp., Germany) with MW cut-offs of 100k and 1k Da, respectively. The fractionation
148 experiment was conducted in a 400-mL stirred cell (Amicon 8400, Merck Millipore Corp.,
149 Germany) under a constant nitrogen gas pressure of 0.1 MPa. Prior to the experiments,
150 ultrapure water was filtered through the membranes to remove any possible leached

151 organic matter until the DOC of the effluent was less than 0.1 mg-C/L. After UF separation,
152 the filtrates with MW ranges of <100k and <1k Da were analyzed for their organic content
153 (e.g., DOC, DON) and tested for DCAcAm formation during chlorination. It was expected
154 that the background CAPs went through the two UF membranes due to the lower MW
155 (<400 Da) of the three CAPs. After the UF separation, the filtrates were spiked with CAPs
156 up to 30, 60, 300, 600, 900, and 1200 nM (each CAP accounted for a third of the total
157 concentration of the three spiked CAPs). Details on the UF procedure are available
158 elsewhere[34] and in SI Figure S2.

159 (4) UV/H_2O_2 and UV/PS pre-oxidation. To examine the effect of UV/H_2O_2 or UV/PS
160 pre-oxidation on the formation of DCAcAm in authentic waters containing CAPs (unspiked
161 or spiked with a mixture of CAP, TAP, and FF at 100 nM each) during post-chlorination, a
162 UV collimated beam apparatus, consisting of a low-pressure mercury lamp above
163 quiescently-stirred Petri dishes was used.[35] Water samples were irradiated for calculated
164 durations to achieve six different incident UV doses ranging from 0 to 585 mJ/cm^2. The
165 oxidation was initiated once the Petri dishes were moved under the UV lamps, by adding
166 H_2O_2 or PS (0.5 mM) into the Petri dishes. After UV/H_2O_2 or UV/PS treatment, sufficient
167 chlorine was immediately added into the stirred dish to provide the desired 24-h chlorine
168 residual of 1 ± 0.5 mg-Cl_2/L in a single dose. The sample was stirred for 15 s and
169 transferred into a headspace-free 500-mL brown glass volumetric flask, which was kept in
170 the dark. Details are available elsewhere,[36,37] and are included in the SI (Figure S3). All
171 samples were prepared in triplicate and the error bars in the figures represent the
172 standard deviations from triplicate measurements.

Analytical Methods. DCAcAm and some bromine-containing HAcAms were analyzed by combining solid-phase extraction (SPE), high-pressure liquid chromatography (HPLC), and triple quadrupole mass spectrometry (tqMS) with atmospheric pressure chemical ionization, using selective reaction monitoring in the positive mode. The detection limit and quantification limit for DCAcAm were 12 ng/L (approx. 0.1 nM) and 36 ng/L (0.3 nM). The details of the analyses of DCAcAm, other N-DBPs (haloacetonitriles [HANs] and halonitromethanes [HNMs]), the three CAPs, bromide, iodide, DOC, DON, and $SUVA_{254}$ are presented elsewhere[3,12,28] and in the Supporting Information.

Because no standards for ^{15}N-labeled DCAcAm were commercially available, the ^{15}N-labeled DCAcAm was analyzed indirectly by measuring the changing of the DCAcAm (^{14}N-DCAcAm) parent ion from 128 to 129 m/z. The analytical method was validated by performing the chlorination of unlabeled Asn (also Tyr) and ^{15}N-labeled Asn (also ^{15}N-labeled Tyr) under the same conditions. The formed concentration of unlabeled DCAcAm from unlabeled Asn was identical with ^{15}N-labeled DCAcAm from ^{15}N-labeled Asn, indicating that the tqMS responses were similar for unlabeled DCAcAm and ^{15}N-DCAcAm. This indirect determination method for ^{15}N-labeled DCAcAm[13] and other N-DBPs[38,39] has been proven successful in other studies.

RESULTS AND DISCUSSION

DCAcAm Formation from Individual Compounds. Tyr can react with chlorine to form many N-DBPs,[40,41] including DCAcAm, with a DCAN intermediate. Also, Asn can form DCAcAm during chlorination without a DCAN intermediate.[14] Besides free Tyr and

Asn, boc-Tyr and boc-Asn were also selected as N-protected amino acids (i.e., protection with a tert-butoxycarbonyl group) mimicking peptide bonds, because free amino acids constitute only ~5% of total amino acids in most waters.[17]

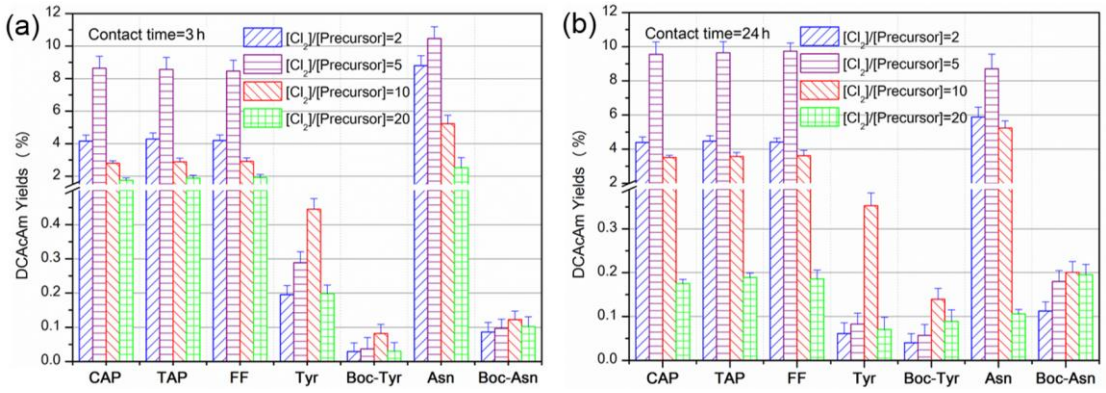

Figure 1. DCAcAm formation from the chlorination of seven model precursors at different contact times (a vs b) and different Cl_2/precursor molar ratios (each precursor compound concentration = 0.05 mM). The HAcAm yield was the molar ratio of the formed HAcAm to the initial concentration of precursor (DCAcAm yields = [DCAcAm]/[precursor]×100%).

As shown in Figure 1, regardless of short or long contact time at different chlorine doses, boc-Tyr and boc-Asn exhibited the lowest DCAcAm yields, probably because the protection of the amino group in boc-Tyr and boc-Asn restrained the formation of organic chloramines by initial substitution, which is the first step in the formation of N-DBPs,[42] as shown in SI Scheme S1.[14,36,37] There was a substantial difference in DCAcAm yield between Asn and Boc-Asn, whereas the difference in yield between Tyr and Boc-Tyr was not that large, as the yield from Tyr in its free form was relatively low compared to the other model compounds. Notably, in natural waters, there is substantially more of the combined amino acid than the free form, which will change the relative significance of each in terms of DCAcAm yield (e.g., combined Tyr may contribute more DCAcAm than free Tyr, whereas free Asn may contribute more than combined Asn, based on the

approximate average concentration (N content) ratio of free amino acids and total amino acids of 1:60[17], and the highest formation yields of the four selected amino acid precursors).

Regardless of contact time, free Tyr exhibited higher yields at $[Cl_2]$/[Precursor] = 10 than at $[Cl_2]$/[Precursor] = 2, 5, and 20, which is consistent with a previous study.[41] However, the three CAPs and free Asn all had their highest DCAcAm yields at $[Cl_2]$/[Precursor] = 5. Insufficient chlorine cannot promote DCAcAm formation[41], and over-abundant chlorine will catalyze the hydrolysis of the formed DCAcAm.[43] There is a higher chlorine demand for free Tyr (approx. 13 mol Cl_2/mol Tyr)[41] than for free Asn (6 mol Cl_2/mol Asn), due to the reactivity of the Tyr phenoxy group.[44] Therefore, Tyr and Asn reach an optimal chlorine dose to form DCAcAm at $[Cl_2]$/[Precursor] = 10 and 5, respectively. As is the case for Asn, the three CAPs also reached an optimal chlorine dose to form DCAcAm at $[Cl_2]$/[Precursor] = 5, and had similar DCAcAm yields, probably due to their similar molecular structures (Figure S1). As shown in Figure S4, at a $[Cl_2]$/[Precursor] = 2, the initial chlorine of 0.1 mM (7.1 mg/L) was rapidly consumed by CAP to under 1.0 mg/L after the first 3 h, and the residual chlorine was barely detected at a 0.02 mg/L detection limit after 12 or 24 h, which was insufficient chlorine to oxidize CAP to form more DCAcAm (Figure 1a vs Figure 1b at $[Cl_2]$/[Precursor] = 2). At $[Cl_2]$/[Precursor] = 10 and 20, the residual chlorines were both greater than 21 mg/L (0.3 mM) after 24 h (Figure S4). The excess chlorine accelerated the hydrolysis rate of DCAcAm,[43] which was likely higher than the simultaneous rate of formation of DCAcAm. At $[Cl_2]$/[Precursor] = 5, there was more residual after 3 h than for $[Cl_2]$/[Precursor] = 2, but there was similar residual after 12

or 24 h. The optimal ratio was likely somewhere between 5 and 10 (most likely closer to 5). Notably, in plants that pre-chlorinate and post-chloraminate, they may form DCAcAm during the pre-disinfection step but may not destroy it during distribution. However, DCAcAm can undergo base-catalyzed hydrolysis in the distribution system if the pH is sufficiently high (pH > 8)[43].

After 3 h of chlorination reaction time (Figure 1a), Asn showed the highest DCAcAm yields followed by the three CAPs and, to a much lesser extent, Tyr, boc-Tyr, and boc-Asn. Moreover, the three CAPs presented similar or somewhat higher DCAcAm yields than Asn after chlorination for 24 h. However, to better compare the relative contribution of these compounds as precursors of DCAcAm, we examined the formation of DCAcAm from the chlorination of a mixture of CAP and Asn.

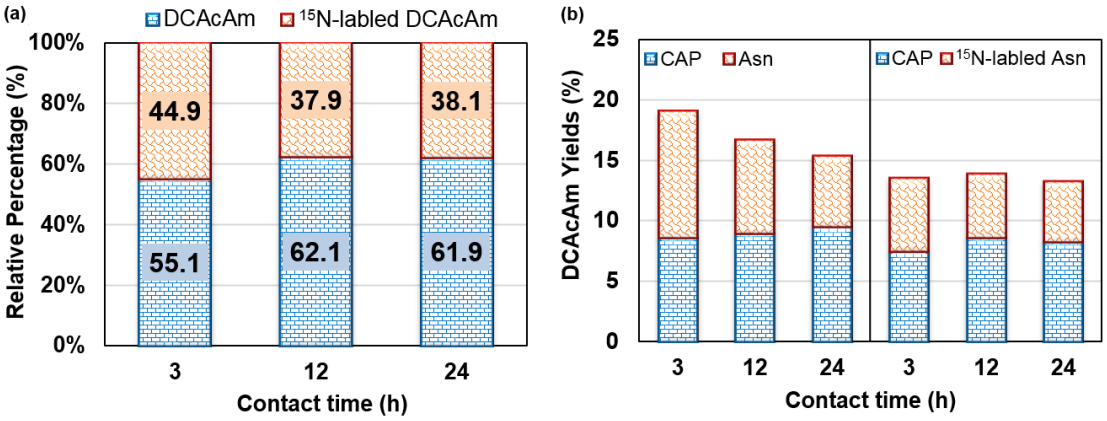

Figure 2. DCAcAm formation from chlorination of the mixture of CAP and ^{15}N-labeled Asn at different contact times ([Cl_2]/[CAP+^{15}N-labeled Asn] = 5, [CAP] = [^{15}N-labeled Asn] = 0.05 mM). Figure 2a presents the relative percentage of DCAcAm yields for CAP and ^{15}N-labeled Asn; Figure 2b presents DCAcAm yields from un-mixed CAP and Asn (Left set of bars in Figure 2b, taken directly from Figure 1) and mixed CAP and ^{15}N-labeled Asn (Right set of bars in Figure 2b).

DCAcAm Formation from the Mixture of CAP and ^{15}N-labeled Asn. Figure 2a

displays the relative proportion of formed DCAcAm from the chlorination of mixed CAP and ^{15}N-labeled Asn. As shown in Figure 1a, DCAcAm yield from the chlorination of Asn alone in all selected [Cl_2]/[Precursor] ratios were higher than the yields from CAP when the contact time was 3 h, whereas CAP formed similar or somewhat more DCAcAm than free Asn after 24 h (Figure 1b). However, CAP formed more DCAcAm than free ^{15}N-labeled Asn after 3, 12 or 24 h in the mixture (Figure 2a).

Moreover, as shown in Figure 2b, the sum of DCAcAm yields from un-mixed CAP and Asn (the left set of bars in Figure 2b, taken directly from Figure 1) were all higher than from the mixture of CAP and ^{15}N-labeled Asn (the right set of bars in Figure 2b) at all contact times. Notably, the chlorine doses in these two sets of tests were different ([Cl_2]/[Precursor] = 5 in the left set of bars and while this same ratio was used in the right set of bars, i.e., [Cl_2]/[CAP + ^{15}N-labeled Asn] = 5, for each model compound the ratio for each specific precursor was 10, i.e., [Cl_2]/[CAP] = [Cl_2]/[^{15}N-labeled Asn] = 10). Chlorine can easily attack the asymmetric position in the CAP molecule (C2 in Figure S1), the formation pathway of DCAcAm from CAP is simpler to understand than from Asn (Scheme S1). In addition, we examined the formation of DCAcAm from the mixture of CAP and ^{15}N-labeled Tyr at [Cl_2]/[Precursor] = 5 and 10 (Figure S5), considering that CAP and Tyr obtained their highest DCAcAm yields at [Cl_2]/[Precursor] = 5 and 10, respectively. As shown in Figure S5, relative yields of 97-98% and 68-75% of DCAcAm were formed from CAP at [Cl_2]/[Precursor] = 5 and 10, respectively.

In summary, these results indicate that CAP has greater DCAcAm formation potential than two representative amino acid precursors—Asn and Tyr under the same precursor

279 concentration conditions in 24 h. However, free Asn, free Tyr, and their combined forms
280 are likely present at higher concentrations than that of the CAPs in many drinking water
281 supplies, where significant levels of CAPs would only be expected in heavily
282 wastewater-impacted watersheds. Also, at full-scale DWTPs, the $[Cl_2]$/[Precursor] ratio will
283 be relatively high, where typically mg/L amounts of Cl_2 are applied to waters with µg/L
284 levels of amino acids and ng/L levels of CAPs. Therefore, there is still a need to
285 investigate the formation of DCAcAm from the chlorination of CAPs in real waters in the
286 presence of NOM using more practical chlorination condition, which is the next step in the
287 study.

288 **DCAcAm Formation from Real Waters Unspiked and Spiked with CAPs.** DWTP
289 'C' water had the highest DON level of the three filtered waters (which likely included
290 amino acids) from three selected DWTPs, and it formed the highest DCAcAm
291 concentration (30.3 nM) compared to DWTP 'A' and 'B' waters (10.4 and 12.7 nM,
292 respectively) when no CAPs were spiked into the waters (the intercepts for the three
293 best-fit lines in Figure 3b are the DCAcAm concentrations formed from the chlorination of
294 waters A, B, and C without CAPs spiked in). Figure 3a demonstrates that the three CAPs
295 spiked (up to 60 nM) into real water matrices had very similar yields of DCAcAm in the
296 same water matrix, probably because they have similar molecular structures (Figure S1),
297 which agrees with the observations from the experiments in laboratory-grade water.
298 Moreover, Figures 3a and 3b show that the overall formation of DCAcAm was due to a
299 combination of CAPs and naturally present precursors (e.g., NOM, amino acids). Figure
300 3b presents the formation of DCAcAm after 24 h from the chlorination of A, B, and C (with

and without bromide spiking) waters spiked with the a mixture of CAP, TAP, and FF up to 30, 60, 300, 600, 900, and 1200 nM (each CAP accounted for a third of the total concentration of the three spiked CAPs). This figure shows a good linear relationship between the DCAcAm concentration formed for all three waters and the spiked CAP concentrations after 24 h of chlorination. Although DWTP 'C' water had the highest DCAcAm formation when CAPs were not spiked in, when the three CAPs were spiked in, the slope of the best-fit line (0.047) of the formed DCAcAm from DWTP 'C' water was lower than in DWTP 'A' and 'B' waters (slopes = 0.081 and 0.063, respectively). The slopes of the best-fit lines in Figure 3b can be considered as approximating the formation yields (8.1%, 6.3%, and 4.7%) of DCAcAm from the CAPs in these three real water matrices (A, B, and C, respectively). These were lower than the yields (approximately 10%) of DCAcAm in laboratory-grade water at $[Cl_2]/[CAPs] = 5$ (chlorine residual = 1.0 ± 0.5 mg-Cl_2/L, in Figure 3) in Figure 1.

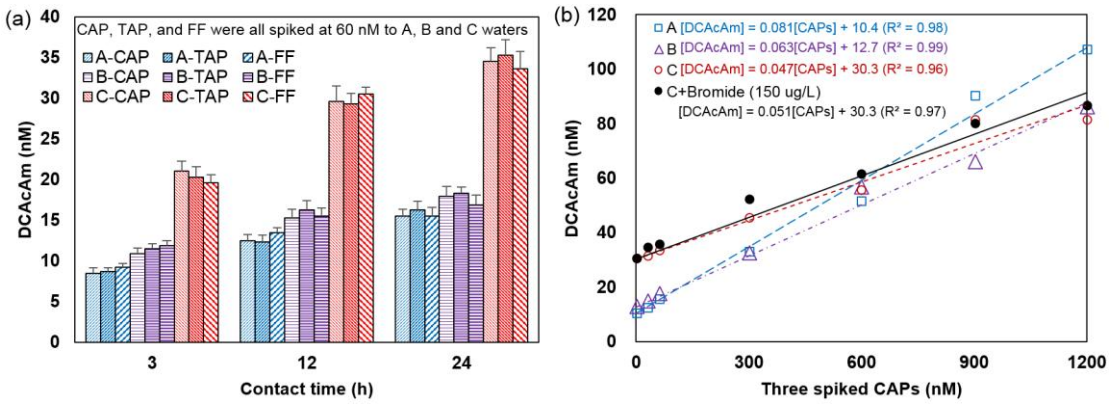

Figure 3. DCAcAm formation after chlorinating filtered waters (A, B, and C) spiked with CAPs at pH 7.3 ± 0.3 for 24 h. Figure 3a presents the impact of contact time on the formation of DCAcAm. Figure 3b presents the impact of CAP concentration on the formation of DCAcAm. In Figure 3b, A, B, and C waters were spiked with a mixture of CAP, TAP, and FF up to 30, 60, 300, 600, 900, and 1200 nM (each CAP accounted for a third of the total concentration of the three spiked CAPs).

The different DCAcAm formation yields in Figure 3b were likely influenced by the different water matrix components, such as bromide and NOM. DWTP 'C' water had the lowest formation slope (0.047) and had the lowest bromide level (21 μg/L). The presence of bromide should result in the formation of bromine-containing analogues of DCAcAm, which were not measured in this study. In order to examine the effect of bromide on DCAcAm formation from CAPs, 150 μg/L bromide was spiked into water C, which was similar to the natural bromide levels in the DWTP 'A' and 'B' waters (130-139 μg/L). From Figure 3b, the slope (0.051) of the formed DCAcAm from DWTP 'C' water spiked with bromide was similar to the slope (0.047) of DWTP 'C' water not spiked with bromide, but was significantly lower than the slopes for DWTP 'A' and 'B' waters (0.081 and 0.061, respectively). This suggests that bromide had less of a contribution to the differences in the observed DCAcAm formation profiles. It should be also noted that bromochloroacetamide was the most abundant species among all six bromine-containing HAcAms formed in all selected authentic waters, and only a little BCAcAm was detected in DWTP 'C' water. When bromide (150 μg/L) was spiked into the DWTP 'C' water, the total concentrations of bromine-containing HAcAms increased from 135 ng/L to 925 ng/L (e.g., from 135 and 0 ng/L to 379 and 134 ng/L for bromochloro- and dibromo- acetamide, respectively), which is consistent with a recent study which reported the formation of all nine chlorine- and bromine- containing HAcAms from 7 authentic waters having a range of SUVA, DOC/DON and bromide levels[33,36]. Also, iodide at μg/L levels was considered to not be relevant because a small number of iodide could be oxidized to iodate during

chlorination.[45-47] Therefore, the differences in DCAcAm yields were hypothesized to be probably due to some aspect of the NOM, which is similar to what was suggested by previous studies that found NOM may interact with pharmaceuticals and inhibit the reaction to form N-nitrosodimethylamine[48], meanwhile NOM itself can form NDMA.[49,50].

From Table S1, the three waters had similar DOC levels and the SUVA values of two of the waters, which included water C, were similar. Certain specific NOM fractions or moieties might be more relevant than would be indicated by simple bulk measurements of water quality, such as DOC and SUVA. To confirm that NOM plays an important role in the different formation yields of DCAcAm from the chlorination of different waters, the filtrates within the MW ranges of <100k Da and <1k Da for the three waters were obtained by fractionating them with a UF membrane with MW cut-offs of 100k and 1k Da. This scheme allowed us to evaluate the impact of low-MW NOM (<1k Da), as well as a combination of low- and high-MW NOM (<100k Da). The DOC, DON, and SUVA of the <100k Da fractions had similar values as the un-fractionated waters, whereas the <1k Da fractions had much less, DOC, DON, and SUVA (Table S2). The selected three waters were all collected after coagulation, sedimentation, and filtration from the three DWTPs, where particulates, colloids, and macromolecules were effectively removed by that point in the treatment train (conventional treatment preferentially removes high-MW and humic NOM). The levels of the inorganic compounds (e.g. bromide, ammonia) in the un-fractionated and fractionated waters did not show substantial differences, as they should have readily passed through the filters.

The formation of DCAcAm from the chlorination of the three selected waters that were

365 fractionated by the UF membrane with MW cut-offs of 1k Da is shown in Figure S6. Just
366 like the un-fractionated waters, Figure S6 also showed a good linear relationship between
367 the formed DCAcAm concentration for all three fractionated waters and the spiked CAP
368 concentrations after 24 h chlorination. Note, the intercepts in Figure S6 were lower than
369 what was observed for the un-fractionated waters (Figure 3b), indicating that a portion
370 (53%, 55%, and 46% for DWTP 'A', 'B', and 'C' waters, respectively) of the DCAcAm
371 precursors were of higher MW. In addition, the slopes (0.091, 0.083, and 0.081 for DWTP
372 'A', 'B', and 'C' waters, respectively) and the formation yields (9.1%, 8.3%, and 8.1% for A,
373 B, and C waters, respectively) of the formed DCAcAm from the three fractionated waters
374 (<1k Da) were more similar than those from the three un-fractionated waters (Figure 3b
375 versus Figure S6), and they were in close agreement with the findings from the
376 experiments in laboratory-grade water summarized in Figure 1. This indicates that some
377 NOM in the MW range >1k Da not removed at the DWTPs likely played a role in causing
378 the different DCAcAm formation yields in the selected three waters.

379 The formation of DCAcAm from the chlorination of heavily wastewater-impacted
380 natural waters (D and E) and treated wastewaters (secondary effluent, F and G),
381 containing significant Levels of CAPs (Table S1), was also investigated. Figure 4a
382 presents the formation of DCAcAm after 24 h from the chlorination of D, E, F, and G
383 waters spiked with a mixture of CAP, TAP, and FF up to 300, 600, 900, and 1200 nM (each
384 CAP accounted for a third of the total concentration of the three spiked CAPs). However,
385 water G was not spiked at 300 nM because the actual concentration of the three CAPs
386 was close to 300 nM). The first point, surrounded by a dotted line in Figure 4a, is the

DCAcAm concentration formed from the chlorination of the selected waters without spiked CAPs, which only contained the background levels of CAPs. Like the filtered waters (A, B, and C) in Figure 3a, Figure 4a also shows a good linear relationship between the DCAcAm concentration formed for all four waters and the spiked CAP concentrations after 24 h of chlorination. The slopes of the best-fit line (0.074 and 0.063) of the formed DCAcAm from two natural waters (D and E) were higher than in 'F' and 'G' treated wastewaters (slopes = 0.048 and 0.052, respectively). As discussed earlier, this is probably due to the presence of NOM with different characteristics.

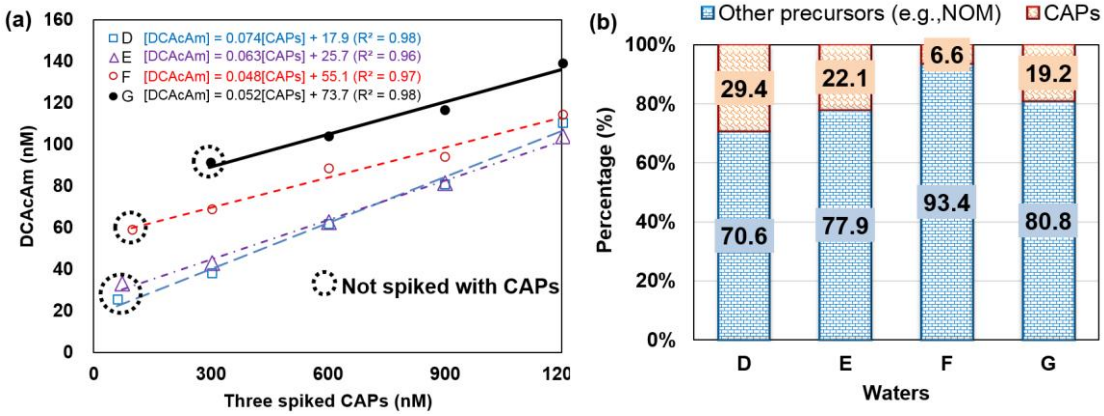

Figure 4. DCAcAm formation after chlorinating natural waters (D and E) and treated wastewaters (F and G) spiked with CAPs at pH 7.3± 0.3 for 24 h. Figure 4a presents the impact of CAP concentration on the formation of DCAcAm from the chlorination of spiked D, E, F, and G waters. Figure 4b presents the relative percentage of DCAcAm yields for CAPs and other precursors in these selected waters without spiked CAPs (Table S3).

Most importantly, according to the linear relationship in Figure 4a, we can determine the intercept (17.9, 25.7, 55.1, and 73.7 nM) for the four best-fit lines, which is the approximate DCAcAm concentration formed from the chlorination of the selected waters in the absence of CAPs. Therefore, the relative contribution of CAPs and other precursors (e.g., NOM, amino acids) on DCAcAm formation in these waters could be calculated, as

shown in Figure 4b. From Figure 4b, the background levels of CAPs in the four selected waters (Table S1) contributed 6.6–29% to the formation of DCAcAm during 24-h chlorination. This indicates that CAPs are an important class of DCAcAm precursors in heavily wastewater-impacted waters.

Effect of AOP Pre-Treatment on the Formation of DCAcAm and Other HAcAms upon Subsequent Chlorination of Real Waters with and without Spiked CAPs. Previous studies found that UV/H_2O_2 and UV/PS pre-oxidation, using UV (585 mJ/cm^2), H_2O_2 (0.5 mM), and PS (0.5 mM) doses typically employed for trace contaminant removal, achieved good performance in controlling the formation of HAcAms in the selected DWTP 'A', 'B', and 'C' waters during post-chlorination (e.g., DCAcAm in Figures 5).[36,37] However, the formation of DCAcAm after UV/H_2O_2 or UV/PS pre-oxidation and subsequent chlorination of real waters containing CAPs was unknown at the outset of this study. Three chlorinated HAcAms (MCAcAm, DCAcAm, and TCAcAm), and six brominated HAcAms were measured to compare their formation from the AOP and chlorination of the waters unspiked and spiked with the mixed CAPs (CAP, TAP, and FF) up to 100 nM each, except for Water G (Figure 5). Water G was not spiked because the actual concentration of the sum of the concentrations of the three CAPs was close to 300 nM.

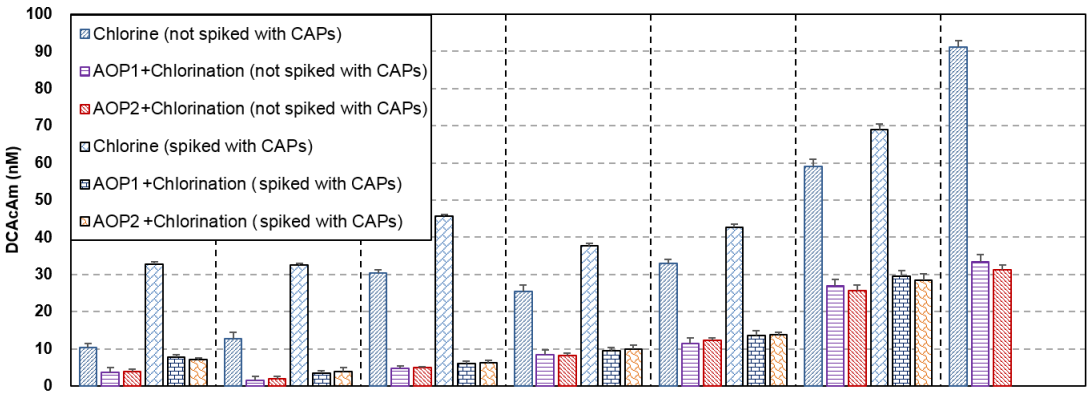

Figure 5. DCAcAm formation during chlorination with or without AOP pre-treatment (**AOP1**: UV/H_2O_2 oxidation, **AOP2**: UV/PS oxidation; water G was not spiked because the actual concentration of CAP exceeded 100 nM and the sum of the concentrations of the three CAPs was close to 300 nM in this water.

As shown in Figure 5a (also shown in Figure 4a), the spiked CAPs significantly increased the formation of DCAcAm from the chlorination of the selected waters (A-F) spiked with CAPs.

The formation yields of DCAcAm after AOP pre-treatment and subsequent chlorination were lower than that during chlorination alone (Figure 5A). This indicates that UV/H_2O_2 and UV/PS pre-oxidation can effectively reduce the total formation of DCAcAm from the chlorination of the NOM and amino acid precursors and the CAPs in the selected waters. Other selected HAcAms (MCAcAm, TCAcAm, six brominated HAcAms) did not present an increasing trend after chlorination (or AOP coupled with chlorination) when the concentrations of CAPs were increased.

Implications. Pharmaceuticals have become important emerging contaminants, due to their presence in environmental waters worldwide, and concerns about possible estrogenic and other adverse effects (e.g., antibiotic resistance of microbes), both to wildlife and humans.[2,51,52] The possibility for formation of N-DBPs from pharmaceuticals during chlor(am)ination disinfection has become another significant concern for delivered drinking water quality because of their potent cytotoxicity, genotoxicity, and potential carcinogenicity[53]. This study found that three CAPs (CAP, TAP, and FF), which commonly occurred in source waters[23-30], presented a greater formation potential of DCAcAm than two representative amino acid precursors, regardless of whether these amino acids were in their free or combined form.

As mentioned earlier, CAP in Nanming River reached up to 19 µg/L due to the impact of municipal sewage discharges.[29] Let us suppose this natural water was used as a source water for DWTPs and all of the CAPs passed through the conventional treatment process to the chlorination stage of treatment. Once chlorine is added to the filtered waters containing 19 µg/L (58.8 nM) of CAP, the concentration of DCAcAm from CAP will reach 350 ng/L (using the lowest formation yield [4.7% for C water] in the selected filtered waters) and possibly as high as 600 ng/L (using the highest formation yield [8.1% for A water] in the selected filtered waters). Thus, CAPs can account for some of the DCAcAm formation in drinking water (which can be at low µg/L levels). Moreover, it was found that CAP, TAP, and FF concentrations reached up to 47, 5.7, and 65 µg/L (145, 16, and 252 nM) in municipal sewage.[29] Due to the inefficiency of conventional treatment in WWTPs for removing CAPs,[23,24] the total formation potential of DCAcAm from the three CAPs (CAP, TAP, and FF) could potentially reach 2,160 ng/L (using the lower formation yield [4.8% for F water] in the selected secondary effluent waters) and as high as 2,340 ng/L (using the highest formation yield [5.2% for G water] in the selected secondary effluent waters) in the chlorinated effluent of the WWTP. Although HAcAms (mostly DCAcAm) only account for 0.5% by mass of the identifiable DBPs in most drinking waters,[1,54] they could represent a higher proportion in chlorinated waters containing CAPs, especially those that are substantially wastewater-impacted.

UV/H_2O_2 and UV/PS pre-oxidation, using UV (585 mJ/cm^2), H_2O_2 (0.5 mM), and PS (0.5 mM) doses typically employed for trace contaminant removal, showed good performance in controlling the formation of DCAcAm during post-chlorination of waters

containing CAPs. Additionally, considering that CAPs are aromatic compounds, chlorine might be substituted on the benzene ring (at the ortho-positions of the carbon that connects to carbon C1 in Figure S1), leading to the formation of chlorinated aromatic DBPs.[55,56] It is necessary to further examine the formation of chlorinated aromatic DBPs during chlorination with and whitout AOP pre-treatment, because aromatic DBPs generally exhibit substantially higher developmental toxicity and growth inhibition than halogenated aliphatic DBPs.[57,58] The ability of pre-treatment processes to reduce CAPs and other HAcAm precursor concentrations prior to chlorination should be evaluated as a means of minimizing HAcAm formation.

ASSOCIATED CONTENT

Supporting Information

Further information on analytical methods, experimental apparatus, sample fractionation, and proposed formation pathway of N-DBPs from three model compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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