Organic Haloamines in Chlorine-Based Disinfected Water Systems: A Critical Review

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Abstract

This paper is a critical review of current knowledge of organic chloramines in water systems, including their formation, stability, toxicity, analytical methods for detection, and their impact on drinking water treatment and quality. The term organic chloramines may refer to any halogenated organic compounds measured as part of combined chlorine (the difference between the measured free and total chlorine concentrations), and may include *N*-chloramines, *N*-chloramino acids, *N*-chloraldimines and *N*-chloramides. Organic chloramines can form when dissolved organic nitrogen or dissolved organic carbon react with either free chlorine or inorganic chloramines. They are potentially harmful to humans and may exist as an intermediates for other disinfection by-products. However, little information is available on the formation or occurrence of organic chloramines in water due to a number of challenges. One of the biggest challenges for the identification and quantification of organic chloramines in water systems is the lack of appropriate analytical methods. In addition, many of the organic chloramines that form during disinfection are unstable, which results in difficulties in sampling and detection. To-date research has focused on the study of organic monochloramines. However, given that breakpoint chlorination is commonly undertaken in water treatment systems, the formation of organic dichloramines should also be considered. Organic chloramines can be formed from many different precursors and pathways. Therefore, studying the occurrence of their precursors in water systems would enable better prediction and management of their formation.

Keywords: amino acids, disinfection by-products, organic chloramines, *N*-chloramine, drinking water quality, organic bromamines, organic iodamines

Contents

1. Introduction

Water disinfection is a crucial step in the production of safe drinking water, whereby pathogenic microorganisms are removed or deactivated by either physical or chemical means. Some disinfection processes also provide a disinfectant residual to prevent microbial regrowth during water distribution, where the presence of a disinfectant residual is more important for large distribution systems with long retention times or when the replacement of distribution system pipes is infrequent (more than 50 years) (Rosario-Ortiz et al., 2016). Chlorination and chloramination are the most widely used disinfection practices in the world because they are effective, inexpensive, and provide disinfectant residual within the distribution system. However, while chlorine and chloramine are effective in deactivating pathogens, they also react readily with inorganic and dissolved organic matter present in the

69 water to form unintended disinfection by-products (DBPs) (McMahen et al., 2016; Reckhow
70 et al., 1990).
71 Since the discovery of DBPs in chlorinated drinking water in the early 1970s, extensive
72 research has been undertaken to understand the formation of DBPs and their management
73 (Richardson, 2003). While more than 600 DBPs have now been identified, minimal
74 information on occurrence and toxicology is available for most DBPs. Furthermore, the
75 fraction of DBPs that have been quantified in drinking water typically accounts for less than
76 40% of total organic halogen (Krasner et al., 2006). One group of DBPs that have not been
77 extensively studied are nitrogenous disinfection by-products (N-DBPs). However, interest in
78 N-DBPs has grown recently with studies showing that some N-DBPs are more genotoxic and
79 cytotoxic than the currently regulated DBPs by several orders of magnitude (Muellner et al.,
80 2007; Plewa et al., 2004; 2008). In particular, haloacetamides, halonitriles, heterocyclic
81 amines and organic halamines were identified to be of highest interest from a potential
82 toxicity perspective (Bull et al., 2011). Within these classes of DBPs, the toxicity has been
83 reported to increase from the chlorine analogue to the bromine analogue and then to the
84 iodine analogue, with the iodine analogue being the most toxic (Plewa et al., 2010).
85 Organic chloramines (more accurately referred to as organic *N*-chloramines) are
86 compounds that contain at least one chlorine atom directly bonded to an amine nitrogen atom
87 in an organic molecule. In the water industry, the term 'organic chloramines' typically refers
88 to any organic halogen compounds measured as combined chlorine, the difference between
89 the measured free and total chlorine concentration (**Fig. 1**). However this fraction can include
90 a number of different chlorinated species. In this review, we refer to 'organic chloramines' as
91 a collective term for *N*-chloramines, *N*-chloramino acids, *N*-chloraldimines and *N*-
92 chloramides, where *N*-chloramines and *N*-chloramino acids are organic chloramines formed
93 from amines or from amino acids, respectively. The structures and precursors of these four
94 classes are presented in **Table 1**.
95 In this review we critically analyse the current knowledge of organic chloramines in
96 water systems including their formation, stability and toxicity of organic chloramines,
97 analytical methods for detection, and their impact on drinking water treatment and quality.
98 While most of the literature available to-date has focussed on organic chloramines,
99 information on organic bromamines and iodamines is also included, where available.
100

2. Formation and degradation of organic chloramines

Organic chloramines can form when dissolved organic nitrogen (DON) or dissolved organic carbon (DOC) react with either free chlorine (Hunter and Faust, 1967) or inorganic chloramines (Isaac and Morris, 1983; Snyder, 1982). The reaction is much quicker with chlorine than with chloramines. For example, chlorination of natural organic matter (NOM) isolates produced maximum concentrations of organic chloramines within 10 minutes, but maximum concentrations after chloramination were reached after 120 hours (Lee and Westerhoff, 2009). The formation of organic chloramines after both chlorination and chloramination was found to increase with increasing DON/DOC ratio (Lee and Westerhoff, 2009). In another study by Zhang et al. (2016), organic chloramine formation from algal organic matter reached its maximum concentration contributing to 79.1% of total chlorine measured 8 hours after chlorination, while reaching maximum concentration contributing to 22.1% of total chlorine 24 hours after chloramination. The study by Zhang et al. (2016), also show that the concentration of organic chloramines during chlorination was the highest at the start and to decrease over time, while the concentration of organic chloramines slowly increase over time.

The formation of organic chloramines is favoured at high pH (Saunier, 1979), while the reaction kinetics vary for different nitrogen precursors (**Table 2**). For example, the rates of reaction of free chlorine with amino acids and organic amines are between 2 and 80 times faster than the rate of reaction of free chlorine with ammonia (Hunter and Faust, 1967; Yoon and Jensen, 1993). In contrast, amides react very slowly with chlorine (Hureiki et al., 1994), typically nine order of magnitudes slower than the reaction with ammonia (**Table 2**). Once formed, organic chloramines are less likely to undergo hydrolysis ($k < 10^{-5}$ s^{-1}) (Yoon and Jensen, 1993) than inorganic chloramines ($k = 2.1 \times 10^{-5}$ s^{-1}) (Morris and Isaac, 1983). This suggests that organic chloramines are more stable in water than inorganic chloramines.

The formation of organic monochloramines and/or organic dichloramines from chlorination or chloramination is controlled by the chlorine to nitrogen ratio and also by the presence of secondary functional groups in the organic compound that may also react with the chlorine-based oxidant (How et al., 2016b, 2017; Shang et al., 2000). Of note, breakpoint chlorination can only be achieved after the formation of organic dichloramines, as the complete chlorine demand of the organic compounds present must be satisfied before residual free chlorine will be present in the water system.

Organic bromamines, the bromine analogues of organic chloramines, are formed when organic matter, such as amines or amino acids, reacts with hypobromous acid (Antelo et al., 1993; 1986) or inorganic bromamines (Simon et al., 2015). Simon et al. (2015) found that the bromination of amino acids (k = 132 to 704 L/mol·s) was about 400 times faster than the chloramination of amino acids (k = 0.71 to 2.13 L/mol·s). Similar to inorganic bromamines, organic bromamines are less stable than their chlorine analogues (Antelo et al., 1993; 1986). To date there have been no reports of the formation or degradation of organic iodamines in water systems.

After formation, organic chloramines can degrade to numerous disinfection by-products including aldehydes and nitriles (Nweke and Scully, 1989). Many factors can affect the stability of organic chloramines. For example, an increase in acidity of the amine nitrogen reduces organic chloramine stability (Pitman et al., 1969). The presence of an α-hydrogen can promote the degradation of organic chloramines through dehydrohalogenation (Hui and Debiemme-Chouvy, 2013), while UV irradiation may also accelerate organic chloramine degradation (Zhang et al., 2016). The formation and degradation of specific classes of organic chloramines are discussed in the following sections.

2.1 *N*-Chloramines

Primary and secondary amines react rapidly with free chlorine to form *N*-chloramines (Abia et al. 1998). The rate constants for the reaction with chlorine range between 10^7 and 10^8 L/mol·s for primary and secondary amines (**Table 2**). Tertiary amines react with free chlorine to form *N*-chlorinated quaternary ammonium salts, rather than *N*-chloramines, with much lower rate constants (10^3 - 10^4 L/mol·s) (Abia et al. 1998). Common primary and secondary amines, like methylamine, dimethylamine, diethylamine and ethylamine, and some heterocyclic amines (piperidine and pyrrolidine) have been found in drinking waters (Scully and Bempong, 1982; Wang et al., 2011). Primary and secondary amines, histamine, ethanolamine, propylamine and pyrrolidine, have been previously identified in human urine (Perry et al., 1962) and may be present in wastewaters. When drinking water or wastewater is chlorinated, these amines can form *N*-chloramines. While alkanolamines such as ethanolamine have both hydroxyl and amine functional groups, the hydroxyl functional group has negligible reactivity with chlorine (Prütz, 1996) and thus they can be considered to react to form *N*-chloralkanolamines.

Considering self-decay by hydrolysis only, *N*-chloramines have been found to be more stable than inorganic chloramines (How et al., 2016b; Scully and Bempong, 1982) (**Table 3**). For example, the half-lives of *N*-chloropiperidine and *N*-chlorodiethylamine were both more than 2 days (Scully and Bempong, 1982), while inorganic monochloramine have half-lives of around 9 hours(Isaac and Morris, 1983). *N*-Chloramines degrade more quickly when the pH is greater than 10 or less than 7 due to acid/base catalysis (Antelo et al., 1996).

The mechanism of *N*-chloramine degradation involves β-elimination of HCl to form an imine that hydrolyses rapidly to an aldehyde or a ketone (**Fig. 2**) (Antelo et al., 1996). The degradation mechanism for *N*-chloralkanolamines is an E1 reaction (two-step elimination reaction mechanism) which involves the formation of a nitrenium ion and subsequent loss of the α-carbon substituent, but ultimately results in the same by-products as an *N*-chloramine (**Fig. 2**) (Antelo et al., 1996).

2.2 *N*-Chloramino acids

The *N*-chloramino acids are the most widely studied organic chloramines, because they form from the reaction of free chlorine and amino acids. Amino acids are considered the main constituent of DON (Ellis and Soper, 1954; Yoon and Jensen, 1993), and may be present in natural waters as 'free' amino acids, or as 'combined' amino acids in the form of peptides and proteins. Amino acids have been found to contribute up to 75% of DON (Westerhoff and Mash, 2002), especially in waters impacted by algae or sewage effluent. Studies have also shown that free amino acids are poorly removed during biological filtration (Prevost, 1998), and the concentration of free amino acids might even increase after sand filtration (LeCloirec et al., 1986), hence it is likely that free amino acids will be present in waters during disinfection. The reported reaction pathways of free amino acids with chlorine are presented in **Fig. 3**. The free amino acids would first react with the chlorine to form *N*-monochloramino acids which would then be chlorinated at a slower rate to form *N,N*-dichloramino acids (How et al., 2017) (**Table 2**),. Similar to free amino acids, combined amino acids such as peptides have also been found to react with free chlorine through a stepwise reaction forming *N*-monochloropeptides, and then *N,N*-dichloropeptides. It has also been suggested than *N,N*-dichloropeptides can be formed from the chlorine transfer from N-Cl compounds (Bergt et al., 2004; Domigan et al., 1995), i.e. chloramination from an *N*-monochloropeptide. Once formed, *N*-monochloropeptides have been found to be stable for more than 48 hours (Huang et al., 2017; Jensen et al., 1999) (**Table 3**), while *N,N*-dichloropeptides have been found to be

198 stable from 5 hours to more than 24 hours (Fox et al., 1997; Huang et al., 2017; Keefe et al.,
199 1997) (**Table 3**).

200 The rate constants of formation of *N*-chloroamino acids from chlorinations of
201 carbonaceous free amino acids range between 10^7 and 10^8 L/mol·s (**Table 2**), which is slower
202 than the rate constants of formation of *N*-chloroamino acids from sulfur-containing amino
203 acids (10^8 and 10^9 L/mol·s). While the reaction between sulfur-containing amino acids and
204 chlorine is much faster than with carbonaceous amino acid, sulfur-containing amino acids
205 only form *N*-chloramino acids at higher chlorine to amino acid ratios, due the higher
206 reactivity of the sulfur to chlorine (Shang et al., 2000).

207 The half-lives of *N*-monochloramino acids are summarized in Table 3, and have been
208 found to vary from 0.01 hours to greater than 96 hours (Armesto et al., 1996; Hand et al.,
209 1983; How et al., 2016b; Li et al., 2011a). As illustrated by the rate constants in **Table 3**,
210 most *N*-monochloramino acids are less stable than *N*-monochloramines, with the *N*-
211 monochloramino acids exhibiting half-lives of less than 90 min ($k < 1.3 \times 10^{-4}$ s^{-1}) (How et
212 al., 2016b) (**Table 3**). Amino acids with a more basic amine nitrogen may be expected to be
213 more stable, given the suggestion by Pitman et al. (1969) that, in general, a more basic amine
214 would form a more stable organic chloramine. However there is no trend between the pK_a of
215 the amine nitrogen and the stability of the *N*-monochloramino acids (**Table 3**). The stability
216 of *N*-chloramino acids (e.g. of alanine) is highly influenced by the presence and reactivity of
217 the α-hydrogen (α to the acid group); more reactive α-hydrogens result in less stable *N*-
218 chloramino acids (Hui and Debiemme-Chouvy, 2013). *N*-Chloramino acids with two
219 substituents at the α position to the acid functional group (e.g. α-aminoisobutyric acid) have
220 been reported to be the least stable (Hand et al., 1983). Among *N*-chloramino acids with the
221 same number of substituents, a larger substituent is also reported to reduce stability (Hand et
222 al., 1983), e.g. α-aminoisobutyric acid is less stable than proline. The type of acid group in an
223 amino acid was also found to impact the stability of the *N*-chloramino acids, and amino
224 sulfonic acids reportedly form more stable *N*-chloramino acids than amino carboxylic acids
225 (Gottardi and Nagl, 2010). In contrast, pH appears to have little impact on the stability of *N*-
226 chloramino acids, since no significant change in the rate of decomposition of *N*-chloramino
227 acids has been observed with changing pH (Hui and Debiemme-Chouvy, 2013).

228 *N,N*-Dichloramino acids are less stable than their analogous *N*-monochloramino acids
229 (Coker et al., 2008), possibly due to the increased likelihood of dehalogenation. The stability
230 of the *N,N*-dichloramino acids is also reported to be influenced by the substituent(s) on the α-
231 carbon, similar to the trend observed for *N*-monochloramino acids (Coker et al., 2008).

2.3 *N*-Chloramides

N-Chloramides form from the chlorination or chloramination of amides, or as a minor product from the chloramination of aldehydes. The rates of formation of *N*-chloramides from chlorination and chloramination of amides are reported to be very slow (Deborde and von Gunten, 2008; Jensen et al., 1999; Thomm and Wayman, 1969), with formation rate constants ranging from 1.70×10^{-3} to 0.075 L/mol·s at pH 7-8 and temperature 20-25 ºC, typical of conditions expected during water disinfection (**Table 2**). Alternatively, *N*-chloramides can be formed from the chloramination of aldehydes (Kimura et al., 2013). As illustrated in **Fig. 4**, an aldehyde can react with inorganic monochloramine to form an *N*-chloralkanolamine, which can either react with inorganic monochloramine to form an *N*-chloramide or undergo dehydration to form a *N*-chloraldimine. This alternative pathway for the formation of *N*-chloramide is much faster than chlorination of most amides, with the rate constant for chloramination of acetaldehyde being 24.3 L/mol·s at 25 ºC. However, in the competitive reactions from the aldehydes, the formation of the *N*-chloraldimine is reported to be preferred (Kimura et al., 2015), as the dehydration of the *N*-chloralkanolamine is more favourable than the oxidation of the *N*-chloralkanolamine by inorganic monochloramine.

The formation of *N*-chloramides through the chlorination of haloacetonitriles, followed by hydrolysis of the *N*-chloramides into the haloacetic acids, was proposed by Yu and Reckhow (2015). The formation rate constants of *N*-chloramides from the chlorination of the corresponding haloacetonitriles (**Table 2**) were generally one to four magnitude faster than from the chlorination or chloramination of haloacetamides, or from the chloramination of aldehydes (Kimura et al., 2015). In addition, it was also shown that for haloacetonitriles, the greater the extent of halide substitution, the higher the rate of reaction between the haloacetonitrile and chlorine (**Table 2**). As haloacetonitriles are commonly found in treated waters (Bond et al., 2015), the formation of *N*-chloramides from haloacetonitriles could be a significant source of organic chloramines in treated waters.

Although no experimental data on the stability of *N*-chloramides is available, they are predicted to be less stable than *N*-chloramines based on their hydrolysis constants; the hydrolysis constant of *N*-chloramides is 10^{-9} L/mol·s while *N*-chloramine is 10^{-12} L/mol·s (Qian and Sun, 2003). But *N*-chloramides are more stable than the *N*-chloramino acids, which has a hydrolysis constant of 10^{-5} L/mol·s (Yoon and Jensen, 1993).

2.4 *N*-Chloraldimines

N-Chloraldimines can be formed by either the decarboxylation and dehydrohalogenation of *N,N*-dichloramino acids (**Fig. 3**) or by the chloramination of aldehydes (**Figs. 3 and 4**) (Kimura et al., 2015; Nweke and Scully, 1989; Pedersen et al., 1999), and therefore result from the presence of amino acids. *N*-Chloraldimines are often considered as intermediates in the formation of nitriles (**Figs. 3 and 4**). The formation of *N*-chloraldimines from aldehydes is reported to first involve a rapid, but reversible, reaction with inorganic monochloramine to form an *N*-chloralkanolamine, which then undergoes slow dehydration to the *N*-chloraldimine (Pedersen et al., 1999). Rate constants for the chloramination of acetaldehyde and chloroacetaldehyde are reported in **Table 2**. The rate of dehydration is the rate limiting step (Pedersen et al., 1999), and the rate constant for this step ranges from 1.24 to 277 L/mol·s, depending on the aldehyde species, temperature, and pH (Kimura et al., 2015; Pedersen et al., 1999). Overall, the formation of *N*-chloraldimines from chloramination of aldehydes is reported to be slow. The rate constant for the formation of the *N*-chloraldimine from chloramination of acetaldehyde was found to be 9.8×10^{-3} L/mol·s at pH 6.5 by Scully et al. (1997) and 23.2 L/mol·s at pH 7.8 by Kimura et al. (2015). The rate constant of the reaction between inorganic monochloramine and acetaldehyde has been found to increase with both increasing pH (7.8 to 9.8), due to base catalysis (Kimura et al., 2015), and decreasing pH (6.5 to 5.0) due to acid catalysis (Scully et al., 1997).

Despite being considered as intermediates, *N*-chloraldimines have been found to be very stable (half-lives of more than 60 minutes) in the absence of ammonia (Nweke and Scully, 1989). In a study by Brosillon et al. (2009), *N*-chloroisobutyraldimine, *N*-chloro-3-methylbutan-1-imine and *N*-chloro-2-methylbutan-1-imine were found in a drinking water distribution network after more than 20 hours of chlorine contact time. Interestingly, *N*-chloraldimines could contribute to off-flavours in drinking water. The odour threshold concentrations of *N*-chloroisobutyraldimine and *N*-chloro-3-methylbutan-1-imine were found to be 0.2 and 0.25 µg/L, respectively (Freuze et al., 2005). Thus, among the four classes of organic chloramines discussed, *N*-chloraldimines could be considered to be of the highest interest for drinking water, due to their stability, their odorous properties and the abundance of their amino acid precursors.

3. Analytical methods

A variety of analytical methods have been used for the detection of organic chloramines in water, either as a bulk parameter (i.e., all organic chloramines) or as individual compounds (**Table 4**). Organic chloramines behave identically to inorganic chloramines (monochloramine, dichloramine, trichloramine) in most available analytical methods for determining concentrations of inorganic chloramines in aqueous solutions, including standard colorimetric methods (iodometric titration and the DPD (*N,N*-diethyl-*p*-phenylenediamine) method) and UV-based methods (Smallwood et al., 1994). Indeed, none of the standard methods for the analysis of chloramines can distinguish between organic and inorganic chloramines (Black & Veatch Corporation, 2010; Donnermair and Blatchley, 2003; Lee et al., 2007; Tao et al., 2008). This may lead to an overestimation of the true concentration of inorganic chloramines in samples containing large amounts of nitrogen-containing organic matter (Scully et al., 1996).

3.1 Impact of organic chloramines on the determination of free chlorine and inorganic chloramine using the DPD method

At high concentrations, organic chloramines may be measured as free chlorine residual using the DPD method (Jensen and Johnson, 1990), and combined chlorine concentrations higher than 0.5 mg/L are considered to interfere in the measurement of free chlorine by this method (Eaton, 2005). This interference may result in an overestimation of free chlorine concentration. How et al. (2016a) has also shown that high concentrations of organic chloramines (> 4 mg/L as Cl) result in high variability in free chlorine measurements, and that the addition of thioacetamide immediately after the DPD reagent to stop the reaction between the DPD reagent and the oxidant did not reduce this variability. However, sodium arsenite has been found to quench free chlorine and inorganic chloramines without quenching most of the organic chloramines, which then allows for their quantification by the DPD method (Zhang et al., 2015). Although a pre-column derivatisation follow by liquid chromatography and fluorescence detection has been used to distinguish between inorganic chloramines and organic chloramines, this method cannot differentiate between monochloramine and dichloramine (Scully et al., 1984). To date, the only analytical technique that has been able to explicitly differentiate between free chlorine, individual inorganic chloramines and organic chloramines (as a bulk parameter) is membrane introduction mass spectrometry (MIMS) (Ferriol et al., 1991; Shang et al., 2000). However,

even MIMS relies on the assumption that no other oxidative species (such as bromamine) is present in the water samples because the concentration of organic chloramines was still calculated indirectly by subtracting the concentration of free chlorine and individual inorganic chloramines from the total chlorine (oxidant) concentration.

3.2 Detection methods for organic chloramines

The DPD method has been used to determine if all free chlorine has reacted (Li et al., 2011a; Scully and Bempong, 1982), and to monitor the formation and degradation of organic chloramines (Laingam et al., 2012; Li et al., 2011a), by monitoring the change in concentration of combined chlorine in the samples over time with the assumptions of 1) all combined chlorine measured is organic chloramines and 2) the concentration of organic chloramines does not interfere with the measurement of free chlorine (i.e. < 0.5 mg/L). Direct UV detection has been also used for the analysis of pure solutions of individual organic chloramines and bromamines (Antelo et al., 1999; Antelo et al., 1995; Olszanecki and Marcinkiewicz, 2004). The maximum absorbance of organic chloramines is around 250 nm with molar extinction coefficients ranging from 350 to 380 L/mol·cm, while the maximum absorbance of organic bromamines is around 290 nm with molar extinction coefficients between 430 to 470 L/mol·cm (Antelo et al., 1993).

Typically, *N*-chloramino acids and *N*-chloramines in ultrapure water have been analysed using liquid chromatography (LC) coupled with detection using 1) a mass spectrometer (MS) (How et al., 2016b; Li et al., 2011a; Li et al., 2010; Takats et al., 2001; Yang et al., 2010); 2) derivatisation with UV-Vis or fluorescence detection (Furness-Green et al., 1998; Scully et al., 1984); 3) post-column electrochemical detection (Bedner et al., 2002) and 4) adsorption-pyrolysis method for pure *N*-chloramino acids samples where the *N*-chloramino acids were measured as total organic chlorine (Li et al., 2011b). Derivatisation of *N*-chloramines and *N*-chloramino acids followed by UV-Vis or fluorescence detection has been used for screening *N*-chloramines and *N*-chloramino acids in water, while mass spectrometry is more suitable for analysis of individual species (Li et al., 2011a). MIMS has also been used for the detection of *N*-chloramines formed from 2-aminobutane and 1,3-diaminoproane (Kotiaho et al., 1991).

Generally, detection of *N*-chloraldimines has used gas chromatography coupled with a mass spectrometer (GC-MS), with either liquid injection or headspace sample introduction. This is consistent with the higher volatility of *N*-chloraldimines compared to *N*-chloramino

362 acids. *N*-chloroisobutaldimine, *N*-chloro-3-methylbutan-1-imine, *N*-chloro-2-methylbutan-1-
363 imine and *N*-chlorophenylacetaldimine were detected by Conyers et al. (1993) from
364 chlorination formation potential experiments using wastewater using GC-MS direct
365 headspace injection followed by GC-MS analysis. In another study by Brosillon et al. (2009),
366 *N*-chloroisobutaldimine, *N*-chloro-3-methylbutan-1-imine, *N*-chloro-2-methylbutan-1-imine
367 and *N*-chlorophenylacetaldimine were detected in drinking water using purge and trap GC-
368 MS. *N*-chloroacetamide was detected by direct injection of samples followed by double
369 focusing mass spectrometry (Kimura et al., 2015) by while *N*-chloro-2,2-chloroacetamidewas
370 detected by LC-MS in negative mode (Yu and Reckhow, 2017). Recently, Huang et al.
371 (2017) reported the identification of *N*-chloropeptides in drinking water using solid phase
372 extraction followed by LC-MS analysis.
373
374 **3.3 Challenges for the analysis of organic chloramines in real water**
375 Despite the existence of published methods for all classes of organic chloramines reviewed in
376 this study, most analytical methods have not been used for analysis of real water samples.
377 Further improvements in the analytical procedure for the extraction and isolation of organic
378 chloramines is required to reduce the impact of matrix effects. In addition, detection methods
379 with higher sensitivity are required for the analysis of organic chloramines at the
380 concentrations found in real water samples. As seen from **Table 3**, many organic chloramines
381 are unstable, especially the *N*-chloramino acids, and therefore rapid extraction methods (i.e.,
382 < 45 min) are required. The sample preparation methods used for the extraction of organic
383 chloramines to date are listed in **Table 5**. The derivatisation of some organic chloramines
384 using 5-dimethylaminonaphthalene-1-sulfonic acid ($DANSO_2H$) produces highly fluorescent
385 derivatives, allowing them to be measured using a LC coupled with a fluorescence detector.
386 However, the derivatisation process is complex and long (Scully et al., 1984), has low
387 recovery of <26% (Jersey et al., 1990) and significant matrix interferences (Jersey et al.,
388 1990; Scully et al., 1984; Tao et al., 2008) and therefore practical use of the derivatisation for
389 organic chloramine analysis is limited.
390 An additional challenge for the analysis of organic chloramines is the effect of oxidant
391 quenching, a common procedure for water samples that contain free chlorine or other
392 oxidants. Quenching of the oxidant residual is typically undertaken to prevent further
393 formation of DBPs during the holding time between sample collection and analysis (Kristiana
394 et al., 2014). Most of the commonly used quenching agents in water analysis (e.g. ascorbic

acid, sodium sulphite and sodium thiosulfate) are reducing agents, and therefore 'quench' the disinfectant (the oxidant) through a redox reaction (Kristiana et al., 2014). Some organic chloramines are also oxidants, and thus quenching transforms these organic chloramines into other by-products. For example, addition of a quenching agent (sodium thiosulfate) has been found to cause the reduction of *N*-chloroacetamide to acetamide (Kimura et al., 2015). The conversion of organic chloramines into other by-products via quenching therefore alters the concentrations and distribution of DBPs in the sample (Kimura et al., 2015) and results in the false negative detection of organic chloramines. Therefore, the use of quenching agents should be avoided when possible. Sodium arsenite and 50% formic acid have been used to quench free chlorine and inorganic chloramines, without quenching most of the organic chloramines which then allows for their detection or quantification (Huang et al., 2017; Zhang et al., 2015). On the other hand, without the use of quenching agents, oxidants such as residual chlorine or inorganic monochloramines, and even the organic chloramines themselves, may damage the analytical column in both LC and GC, GC injector and the MS source if GC-MS is use after constant exposure to the oxidant. Thus the decision to use quenching agents should be made on a case by case basis, depending on the analytes of interest, and considering the potential information obtained and the potential damage to LC or GC column and other components of the analytical instrument.

Finally, there are no reported analytical standards for purchase, and this limits the number of organic chloramines that can be identified and accurately quantified. The relatively short half-lives of some organic chloramines mean that analytical standards also have short shelf-life, and standards must be made in-house and used immediately after verification. This means that verification of methods through standard traceability studies and use of certified reference materials is generally not possible. Only two limits of detection for organic chloramines have been reported. The limit of detection of *N*-chloropiperidine being around 1 μM LC-post column derivatisation and fluorescence detection , while the limit of detection of *N*-chlorophenylalanine was 50 μM using LC-UV (λ = 254 nm) (Freuze et al., 2004).

4. Toxicology of organic chloramines

Although water-related toxicological studies of organic chloramines are limited, several biomedical studies describing the potential adverse health effects of organic chloramines have been published. In the human body, inflammation is reported to cause generation of

428 HOCl from activated phagocytes, which can then react with amino acids, peptides, or
429 proteins (Hawkins and Davies, 1999; Hawkins et al., 2003). The formation of organic
430 chloramines from such reactions can result in tissue damage (Hawkins and Davies, 1999;
431 Hawkins et al., 2003) and/or RNA and DNA damage (Hawkins and Davies, 2002), which can
432 ultimately contribute to aging and cancers (Ames, 1989; Hoeijmakers, 2009). The principal
433 mechanism for the toxicity of organic chloramines is not well understood. Grisham et al.
434 (1984) hypothesised that organic chloramines convert to toxic forms when in contact with
435 cells, while Cemeli et al. (2006) attributed measured cytotoxicity and genotoxicity to cellular
436 oxidative stress. Studies have shown that organic chloramines produced from the reaction of
437 HOCl and plasma proteins give rise to aminyl radicals (Hawkins and Davies, 1999) which
438 result in radical-induced damage to DNA (Sortino et al., 1999). Oxidative damage was
439 reported in collagen treated with organic chloramines (Davies et al., 1993). It has previously
440 been found that an electrophilic nitrogen from aromatic amines was responsible for
441 alkylamination of DNA (Miller, 1978) and this mechanism may also be relevant here as the
442 nitrogen in organic chloramines is also electrophilic (Calvo et al., 2007; Scully and Bempong,
443 1982).
444 Specific studies of carcinogenicity have indicated that *N*-chloramino acids can cause
445 protein-DNA cross-links (Kulcharyk and Heinecke, 2001), inhibit DNA repair (Pero et al.,
446 1996), and affect the kinetics of the cell cycle, including cellular apoptosis (Englert and
447 Shacter, 2002; Hosako et al., 2004), all of which are commonly observed carcinogenic
448 effects.
449 While there have been no *in vivo* toxicity studies conducted for organic chloramines to
450 date, a number of *in vitro* studies have demonstrated that several organic chloramines
451 (precursors listed in **Table 6**) are mutagenic towards bacteria (Nakamura et al., 1993; Scully
452 and Bempong, 1982; Süssmuth, 1982; Thomas et al., 1987), and cytostatic or cytotoxic to
453 Chinese hamster ovary cells (Bempong and Scully, 1980). In a recent *in vitro* study by
454 Laingam et al. (2012), significant cytotoxicity and genotoxicity were observed for WIL2-NS
455 cells (human lymphoblastoid) that were treated with *in situ*-formed *N*-chloroethanolamine, *N*-
456 chloroglycine, *N*-chlorohistamine or *N*-chlorolysine at micromolar concentrations that are
457 relevant for drinking water systems. All four of these organic chloramines have also
458 demonstrated mutagenic effects in bacterial assays (Nakamura et al., 1993; Süssmuth, 1982;
459 Thomas et al., 1987). Two studies of the effect of *N*-chloroacetamide on Chinese hamster
460 ovary cells found that *N*-monochloroacetamide was cytotoxic but not genotoxic (Kimura et

al., 2015), while *N,2*-dichloroacetamide was both cytotoxic and genotoxic, and more potent than *N*-monochloroacetamide (Kimura et al., 2015).

Direct comparison of the toxicity of organic chloramines with other DBPs is difficult due to differences in experimental methodology, including the cells tested and the length of exposure. As highlighted by Escher et al. (2014), only a few bioassays have standardised protocols. However, it may be possible to undertake relative comparison between toxicity tests conducted using similar cell types. **Table 7** shows our estimates of the LC_{50} concentration and genotoxic potency (GP, being the concentration that results in mutation in 50% of cells) of *N*-chloramino acids using the cell viability and mirconuclei data reported by Laingam et al. (2012). Both linear and exponential regression analysis were undertaken due to the low number of data points available. Typically, dose-response curves are sigmoidal in shape, and thus it is expected that modelling with a linear curve would overestimate LC50, while an exponential curve would underestimate LC50. The correlation coefficient (R^2) for the regression analysis ranged from 0.930 to 0.994 (linear) or 0.978 to 0.994 (exponential) for cytotoxicity, and 0.947 to 0.950 (linear) or 0.907 to 0.997 (exponential) for genotoxicity. For cytotoxicity, there were very similar values derived from both linear and exponential regression, while the genotoxicity varied by a about one order of magnitude. The values from the linear regression analysis were used to compare the cytotoxicity and genotoxicity of the *N*-chloramino acids to mammalian cells, to that of other organic chloramines, regulated trihalomethanes and haloacetic acids, and haloacetamides (**Table 7)**. This comparison suggests that organic chloramines are generally more cytotoxic and genotoxic than the regulated DBPs and haloacetamides. When considering halogenated species, the organic chloramines had higher cytotoxicity and genotoxicity than the chlorinated trihalomethanes and haloacetic acids, but similar cytotoxicity and genotoxicity to the brominated trihalomethanes and haloacetic acids (**Table 7**). While LC_{50} and GP values were similar for the *N*-chloramino acids and the haloacetamides (**Table 7**), the *N*-chloramino acids are likely to be more cytotoxic than the haloacetamides, because the cell exposure time in the *N*-chloramino acid bioassays (3 hours) (Laingam et al., 2012) was much shorter than that used in the haloacetamide bioassays (72 hours) (Kimura et al., 2015). Further testing would be required to determine the effect of exposure time on cell response between different bioassays.

There have been no studies of the toxicity of organic bromamines or iodamines, however organic bromamines would be expected to exert similar biological effects to organic chloramines (Olszanecki and Marcinkiewicz, 2004). Given the trends observed for other DBP

classes where the bromine and iodine analogues are more toxic than the chlorine analogues (Plewa et al., 2010), it is likely that organic bromamines and iodamines are more toxic than organic chloramines.

5. Occurrence of organic chloramines and impact on water treatment and quality

5.1 Occurrence of organic chloramines

Based on the formation studies discussed above, the classes of organic chloramines that are most likely to be present in the water system after chlorination are the *N*-chloramines and *N*-chloramino acids.

Despite the fact that *N*-chloramines are relatively stable, there are currently no reports of their occurrence, either in drinking water or wastewater systems. This makes it difficult to assess the impact of *N*-chloramines on human health and the environment. All current published literature of *N*-chloramine occurrence or formation is from laboratory studies using either pure solutions or formation using collected raw water and wastewater. The lack of information of *N*-chloramine occurrence in real water systems is potentially due to a lack of suitable analytical methods for their detection. There is also little information available on the occurrence and concentration of organic amines in water systems. Given that concentrations of DON in water systems are often less than 2.5 mg/L (Westerhoff and Mash, 2002), and that amines are likely to be a minor contributor to the DON, analytical methods with limit of detections in the low μg/L range would be required to detect organic amines in water systems.

Although free amino acids readily form *N*-chloramino acids, free amino acids represent only a very small fraction of total amino acids, typically about 1% in natural waters (Chinn and Barrett, 2000; Dotson and Westerhoff, 2009; Thurman, 1985) and 7% to 29% in wastewater (Confer et al., 1995). The low abundance of free amino acids may explain the lack of occurrence data on *N*-chloramino acids in water systems. If formed, the expected concentration of *N*-chloramino acids would be very low. Most amino acids exist in the total amino acid fraction, as combined amino acids in peptides and proteins. However, to date, no occurrence studies of *N*-chloropeptides have been reported. Another factor contributing to the lack of occurrence data on *N*-chloramino acids in water systems is the instability of most *N*-chloramino acids, such that most will degrade quickly into other by-products, such as aldehydes or nitriles.

5.2 Implications for water treatment

The presence of organic nitrogen such as amino acids in drinking water increases chlorine demand (Black & Veatch Corporation, 2010). Furthermore, as described in Section 3, none of the standard methods for chloramine analysis can distinguish between organic and inorganic chloramines (Black & Veatch Corporation, 2010; Donnermair and Blatchley, 2003; Tao et al., 2008), and combined chlorine concentrations higher than 0.5 mg/L interfere in the measurement of free chlorine (Eaton, 2005). Thus, the presence of organic chloramines can lead to overestimation of the disinfectant concentration, especially within the first 8 hrs of distribution for chlorinated systems or the first 24 hrs of distribution for chloraminated systems (Zhang et al., 2016). This is of particular health significance because organic chloramines have been reported to have a much lower germicidal efficiency than both chlorine and inorganic monochloramine (Black & Veatch Corporation, 2010; Donnermair and Blatchley, 2003; Scully et al., 1996; Wolfe et al., 1985). For example, the maximum inactivation rate of *E.coli* was 0.09 L/mg·min for *N*-monochloramino acids, compared to 2.56 L/mg·min for free chlorine and 0.72 L/mg·min for inorganic monochloramine (Donnermair and Blatchley, 2003). The formation of organic chloramines from free chlorine can continue over a long period of time, resulting in a gradual decline in disinfection efficiency in the distribution system (Black & Veatch Corporation, 2010).

5.3 *In vivo* and *in situ* formation of organic chloramines and other DBPs

In many distribution systems, a free chlorine residual is required to prevent bacterial regrowth. *In vivo* formation of organic chloramines is possible when residual chlorine that remains in consumed drinking water reacts with amines in the saliva and stomachs of consumers. A study by Scully (1990) identified *N*-chloroglycine, either *N*-chloroleucine or *N*-chloroisoleucine, and *N*-chlorophenylalanine, in chlorinated rat stomach contents.

The presence of organic chloramines in distribution systems can also result in the *in situ* formation of other DBPs. For example, stable organic chloramines like *N*-chloroglycine (Hand et al., 1983) act as an intermediate for the formation of cyanogen chloride, dichloroacetontirile and trichloronitromethane (Yang et al., 2010; Yang et al., 2012). The presence of organic chloramines can also artificially enhance the measured concentration of other DBPs, due to the conversion of organic chloramines into other DBPs after quenching (Kimura et al., 2015). Organic chloramines (*N*-chloromethylamine and *N*-

chlorodimethylamine) have similar reactivity towards phenol and dihydroxybenzenes as inorganic chloramines (i.e. NH_2Cl) (Heeb et al., 2017). These reactive moieties, present in NOM, are known to be precursors of DBPs, and thus organic chloramines have similar potential as inorganic chloramines to form DBPs. However, simulation studies under practical water treatment and disinfection conditions have indicated that the formation of DBPs is mainly controlled by HOCl, rather than inorganic and organic chloramine species (Heeb et al., 2017).

6. Conclusions and Recommendations

Organic chloramines are potentially cytotoxic and genotoxic to humans, while some species, like *N*-chloraldimines, may cause aesthetic issues in drinking water and treated wastewater. The formation of organic chloramines during water disinfection can also reduce the germicidal efficiency, and lead to overestimation of inorganic monochloramine concentration. However, currently there is limited information on the occurrence of organic chloramines in water systems, due to the lack of analytical methods of sufficient sensitivity along with the destruction of organic chloramines during current quenching procedures. Furthermore, a lack of traceable analytical standards has made both identification and quantification of many organic chloramines challenging. Many of the organic chloramines formed during disinfection are too unstable for current sample preparation methods. Future analytical method development should focus on the most stable organic chloramines formed during water disinfection, as they are more likely to be detected and more likely to reach the consumer.

To date, research has focussed on the formation of organic monochloramines rather than organic dichloramines. However, it is a common disinfection strategy to achieve breakpoint chlorination during disinfection, and higher chlorine to precursor ratios are more likely to result in the formation of organic dichloramines. Therefore, further study of the formation and degradation of organic dichloramines is important to fully understand the occurrence of organic chloramines in drinking water systems. In addition, toxicity studies should focus on the organic dichloramines rather than organic monochloramine. In addition, more than 600 peptides have being identified in drinking water samples (Tang et al., 2016), however only five *N*-chloropeptides have being identified (Huang et al., 2017). This suggests that a large group of unidentified *N*-chloropeptides may be present in water. Therefore, further studies are

593 required to identify and quantify these *N*-chloropeptides in drinking water, to help assess their
594 risk to public health.

595 The formation of organic chloramines can only occur in the presence of suitable N-
596 containing precursors (e.g. amino acids) and therefore improved understanding of the
597 occurrence and concentration of precursors in water systems would help to predict the
598 formation of organic chloramines. Given the challenges identified in analysing organic
599 chloramines, analysis of precursors may provide another avenue to assess the health risks
600 associated with organic chloramines in drinking waters and to evaluate the efficacy of current
601 and future water treatment processes.

602 Given the challenges identified for the analysis of both organic chloramines and their
603 precursors, an alternative method to assess and understand the impact of organic chloramines
604 in water systems may be the development of reaction models using data from those organic
605 chloramines that have been studied to date. Such models could be used to predict the
606 formation of organic chloramines and simulate how organic chloramines may interact with
607 other chemicals present in drinking water. Ideally, these models would be able to provide
608 information on the reactions that lead to organic chloramine degradation, potential reactions
609 with other precursors, and the DBPs that form.

610

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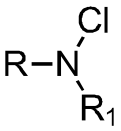
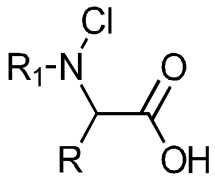
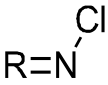
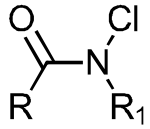
962 Tables

963 **Table 1** Structures of different organic chloramine species

	***N*-Chloramines** R,R_1: Alkyl, aromatic, halogen or hydrogen Precursors: Amines		***N*-Chloramino acids** R: Alkyl, aromatic or hydrogen R^1: Alkyl, halogen or hydrogen Precursors: Amino carboxylic acids and amino sulfonic acids
	***N*-Chloraldimines** R: Alkyl or hydrogen Precursors: Imines and amino acids		***N*-Chloramides** R,R^1: Alkyl, halogen or hydrogen Precursors: Amides and imides

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965 **Table 2** Reported chlorination and chloramination reaction rates for selected organic and
966 inorganic precursors.
967

Precursor	pK_a	k (L/mol·s)(25°C)	References
Chlorination Reaction Rates			
Inorganic nitrogen compounds			
Ammonia	9.25	3.07×10^6	Qiang and Adams (2004)
		4.2×10^6	Morris and Isaac (1983)
		2.9×10^6	Margerum et al. (1979)
Monochloramine		1.5×10^2	Margerum et al. (1979)
		3.5×10^2	Morris and Isaac (1983)
Organic nitrogen compounds			
Primary amines			
Methylamine	10.66	1.9×10^8	Margerum et al. (1979)
		3.6×10^8	Deborde and von Gunten (2008)
Ethylamine	10.81	1.98×10^8	Abia et al. (1998)
Secondary amines			
Dimethylamine	10.72	6.05×10^7	Abia et al. (1998)
		3.3×10^8	Deborde and von Gunten (2008)
		5×10^7	Deborde and von Gunten (2008)
Diethylamine	11.02	3.71×10^7	Abia et al. (1998)
		1.4×10^7	Deborde and von Gunten (2008)
		1.4×10^8	Deborde and von Gunten (2008)
Tertiary amine			
Trimethylamine	9.75	5×10^4	Abia et al. (1998)
(*N*-Me)-piperidine	10.08	8×10^4	Abia et al. (1998)
Amides			
N-Methylformamide		1.70×10^{-3}	Thomm and Wayman (1969)
N-Methylacetamide		1.70×10^{-3}	Thomm and Wayman (1969) Deborde and von Gunten (2008)
		1.40×10^{-3}	
Urea		0.075	Deborde and von Gunten (2008)
N-acetylalanine		1.58×10^{-3}	Jensen et al. (1999)
Amino acids			
Glycine	9.78	1.13×10^8	Armesto et al. (1993)
		5×10^7	Armesto et al. (1994)
Alanine	9.87	3.4×10^7	Armesto et al. (1993)
		5.4×10^7	Armesto et al. (1994)
		5.4×10^7	Margerum et al. (1979)

β-Alanine	10.06	8.9×10^7	Margerum et al. (1979)
Valine	9.74	7.4×10^4	Pattison and Davies (2001)
		5.4×10^4	How et al. (2017)
N-monochlorovaline		4.9×10^2	How et al. (2017)
Sulfur-containing amino acids			
Cysteine	8.15 and 10.29	1.2×10^9	Armesto et al. (2000)
		3.3×10^8	Pattison and Davies (2001)
Methionine	9.05	9×10^8	Armesto et al. (2000)
Haloacetonitrile			
Monochloroacetonitrile		Not significant	Yu and Reckhow (2015)
Dichloroacetonitrile		0.19	Yu and Reckhow (2015)
Trichloroacetonitrile		11	Yu and Reckhow (2015)
Bromochloroacetonitrile		9.0×10^{-2}	Yu and Reckhow (2015)
Bromodichloroacetonitrile		1.4	Yu and Reckhow (2015)
Monobromoacetonitrile		Not significant	Yu and Reckhow (2015)
Dibromoacetonitrile		4.2×10^{-2}	Yu and Reckhow (2015)
Chloramination Reaction Rates			
N-chloroalkanolamines			
1-(chloroamino)ethanol		2.67×10^4 $L^2/mol^2 \cdot s$	Kimura et al. (2015)
2-chloro-1-(chloroamino)ethanol		3.03×10^4 $L^2/mol^2 \cdot s$	Kimura et al. (2013)
Aldehyde			
Acetaldehyde		24.3	Scully et al. (1997) Kimura et al. (2015)
Chloroactetaldehyde		1.87×10^3 L/mol	Kimura et al. (2013)

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Table 3 Rate of decomposition of various organic monochloramines k ($\times 10^{-4}$)(s^{-1}) **and their half-lives (hours).** *Values in brackets are the degradation constants for the *N,N*-dichloramine species.

Precursor	Rate*	Half-life*	References
Amino acids			
α-Aminoisobutyric acid	129	0.01	Hand et al. (1983)
1-Amino- 1-carboxycyclohexane	900	0.002	Hand et al. (1983)
Alanine	2.8	0.7	Armesto et al. (1996)
	1.9 (>385)	1.0 (<0.005)	Coker et al. (2008)
	1.8	1.1	How et al. (2016)
Asparagine	11 (>385)	0.2 (<0.005)	Coker et al. (2008)
	6.7	0.3	How et al. (2016)
Aspartic acid	8.1 (>385)	0.2 (<0.005)	Coker et al. (2008)
	15	0.1	How et al. (2016)
Glutamine	3.2 (39)	0.6 (<0.05)	Coker et al. (2008)
	14	0.1	How et al. (2016)
Glutamic acid	3.1 (>385)	0.6 (<0.005)	Coker et al. (2008)
	3.1	0.6	How et al. (2016)
Glycine	0.04	48	Hand et al. (1983)
	<1.0 (8.9)	>1.9 (0.2)	Coker et al. (2008)
	0.02	96	How et al. (2016)
Histidine	2.0	1.0	How et al. (2016)
Isoleucine	1.97	1.0	Armesto et al. (1996)
	1.3	1.5	How et al. (2016)
Leucine	3.2	0.6	Armesto et al. (1996)
	2.5	0.8	How et al. (2016)
Lysine	0.42	4.6	How et al. (2016)
Phenylalanine	1.6	1.2	How et al. (2016)
Proline	8.8	0.2	Hand et al. (1983)
	56	0.03	How et al. (2016)
Serine	2.1	0.9	How et al. (2016)
Taurine	<1.0 (<1.0)	>1.9 (>1.9)	Coker et al. (2008)
	0.02	96	How et al. (2016)
Threonine	2	0.96	Hand et al. (1983)
	1.2	1.6	How et al. (2016)
Valine	2	1.0	Armesto et al. (1996)
	1.0	1.9	How et al. (2016)
Amines			
Diethylamine	0.04	48	Scully and Bempong (1982)
	0.60	3.2	How et al. (2016)
Dimethylamine	0.04	48	Scully and Bempong (1982)
	0.39	4.9	How et al. (2016)
Ethanolamine	0.05	39	How et al. (2016)
Piperidine	0.02	96	Scully and Bempong (1982)
***N*-Chloraldimines**			

N-Chloroisobutyraldimine	0.06	32	McCormick et al. (1993)
N-Chlorophenylacetaldimine	0.06 0.04	32 48	Conyers and Scully (1993) Freuze et al. (2004)
***N*-Chloropeptide**			
Acetylalanine	<0.04	>48	Jensen et al. (1999)
Alanylphenylalanine	<0.008 (<0.008, 0.5)	>240 (>240, 4.1)	Huang et al. (2017) Fox et al. (1997)
Alanyltyrosine	<0.008 (<0.008)	>240 (>240)	Huang et al. (2017)
Glycylphenylalanine	<0.008 (0.39,0.3)	>10 (5, 6.4)	Huang et al. (2017) Keefe et al. (1997)
Glycyltyrosine	<0.008 (<0.008)	>240 (>240)	Huang et al. (2017)

975 **Table 4** Analytical methods for the detection of various organic chloramine species

Species	Analytical method	References
Bulk (all organic chloramines)	1. Subtraction of free chlorine from total chlorine in the DPD method (assumption of no inorganic chloramines)	APHA (2005)
	2. Subtraction of inorganic chloramines from combined chlorine: DPD method for combined chlorine and membrane introduction mass spectrometry for inorganic chloramines	Shang et al. (2000)
	3. Pre-column derivatisation into dansyl derivatives using $DANSO_2H$. LC-RP separation with fluorescence detection	Scully et al. (1984)
N-Chloramines	1. Pre-column derivatisation into dansyl derivatives using $DANSO_2H$. LC-RP separation with fluorescence detection	Scully et al. (1984)
	2. Infusion with APCI or ESI-MS/MS in positive mode	Takats et al. (2001)
N-Chloramino acids	1. Derivatisation into dansyl derivatives using $DANSO_2H$ a. HPLC-RP separation with fluorescence detection b. GC-MS with CI	Scully et al. (1984) Scully (1990)
	2. LC-RP-ESI-MS in both negative and positive mode	Li et al. (2011a)
	3. LC-RP/HILIC with post-column reaction and detection using UV detection, organic chloramine treated with iodine to form triiodide	Furness-Green et al. (1998)
	4. LC-RP-ESI-MS in negative mode	Yang et al. (2010) Li et al. (2010)
	5. LC-RP-ESI-HRMS in positive mode	How et al. (2016)
	6. Adsorption-pyrolysis (measured as TOX)	Li et al. (2011b)
	7. Direct UV measurement at λ=250 nm or 255 nm	Antelo et al. (1995) Antelo et al. (1999) How et al. (2015)
N-Chloramides/ *N*-Chlorimides/*N*-chlorohaloacetamides	1. LC-RP-ESI-MS in positive mode	Li et al. (2011)
	2. Double focus mass spectrometry	Kimura et al. (2015)
	3. LC-RP-ESI-MS in negative mode	Yu and Reckhow (2016)
N-Chloraldimines	1. GC-MS in EI or CI	Conyers et al. (1993)
	2. GC-MS	Brosillon et al. (2009)
N-chloropetides	1. LC-RP-ESI-MS in positive mode	Huang et al. (2017)

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978 **Table 5** Extraction methods developed for organic chloramines

Extraction method	**Target**	**Reference**
Reverse phase solid-phase extraction	*N*-Chloramines (after derivatisation), *N*-chloramino acids (after derivatisation), *N*-chlorimides, *N*-chloraldimines, *N*-chloropeptides	Scully et al. (1984) Scully (1990) Li et al. (2011) Freuze et al. (2004) Huang et al. (2017)
Mixed reverse phase & strong anion exchange solid-phase extraction	*N*-chlorohaloacetamides	Yu and Reckhow (2016)
Liquid-liquid extraction using trichloromethane	*N*-Chloraldimines	Conyers et al. (1993) Scully (1997)
Headspace	*N*-Chloraldimines	
1. Direct headspace extraction		Conyers et al. 1993
2. Purge and trap		Brosillon et al. 2009

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982 **Table 6** Organic chloramines that result in mutagenicity towards bacteria

Organic chloramines	References
Amino acids	
N-Chloroarginine, *N*-chlorocysteine, *N*-chloroglycine, *N*-chlorohistidine, *N*-chlorohydroxyproline, *N*-chlorolysine, *N*-chloromethionine, *N*-chlorophenylalanine, *N*-chloroproline, *N*-chloroserine, *N*-chlorothreonine, tyrosine	Nakamura et al. 1993 Süssmuth 1982
Amines	
N-Chlorodiethylamine, *N*-chloroethanolamine, *N*-chlorohistamine, *N*-chloropiperidine, *N*-chloroputrescine	Scully and Bempong 1982 Thomas et al. 1987

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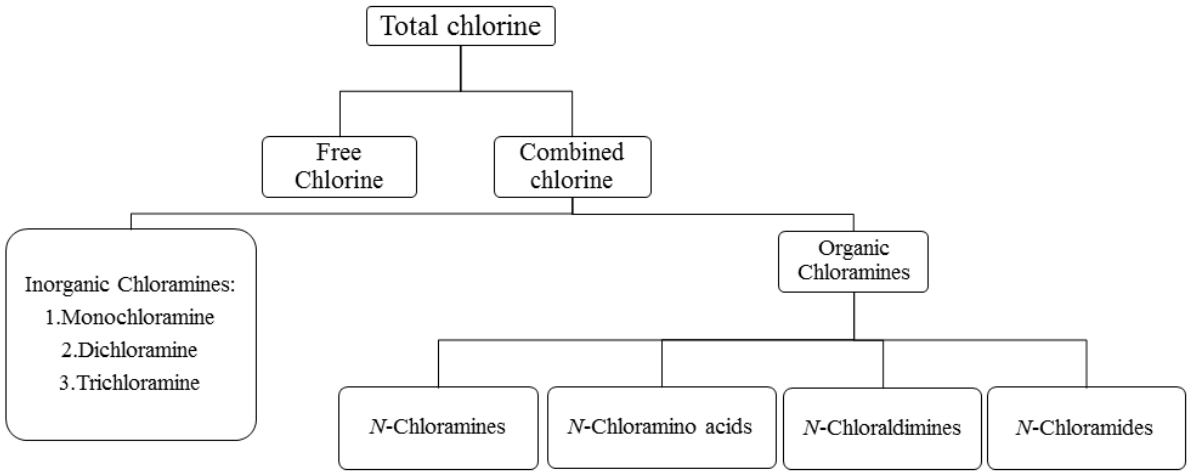
986 **Table 7** Cytotoxicity (LC_{50}) and genotoxicity (genotoxic potency) of organic chloramines,
987 regulated DBPs and haloacetamides. Values derived from the cell viability and micronuclei
988 data of Laingam et al. (2012) are estimated from linear regression, with the values in brackets
989 estimated from exponential regression.

Compounds	LC_{50} (mol/L)	Reference	Genotoxic potency (mol/L)	Reference
Organic Chloramines				
N-Chloroglycine[a]	$6(7)^{d} \times 10^{-5}$	Laingam et al. (2012)	$1(0.5)^{d} \times 10^{-4}$	Laingam et al. (2012)
N-Chloroethanolamine[a]	$3(3)^{d} \times 10^{-4}$	Laingam et al. (2012)	High cytotoxicity[c]	Laingam et al. (2012)
N-Chlorohistamine[a]	$3(3)^{d} \times 10^{-5}$	Laingam et al. (2012)	High cytotoxicity[c]	Laingam et al. (2012)
N-Chlorolysine[a]	$6(7)^{d} \times 10^{-5}$	Laingam et al. (2012)	$2(0.6)^{d} \times 10^{-4}$	Laingam et al. (2012)
N-Chloracetamide[b]	1.78×10^{-3}	Kimura et al. (2015)	Not genotoxic	Kimura et al. (2015)
N,2-Dichloracetamide[b]	2.56×10^{-4}	Kimura et al. (2013)	5.59×10^{-3}	Kimura et al. (2013)
Regulated DBPs				
Chloroform[b]	9.60×10^{-3}	Plewa and Wagner (2009)	Not genotoxic	Plewa and Wagner (2009)
Bromoform[b]	4.00×10^{-3}	Plewa and Wagner (2009)	Not genotoxic	Plewa and Wagner (2009)
Bromodichloromethane[b]	1.20×10^{-2}	Plewa and Wagner (2009)	Not genotoxic	Plewa and Wagner (2009)
Dibromochloromethane[b]	9.60×10^{-3}	Plewa and Wagner (2009)	Not genotoxic	Plewa and Wagner (2009)
Chloroacetic acid[b]	8.10×10^{-4}	Plewa et al. (2010)	6.80×10^{-3}	Muller et al. (2010)
Dichloroacetic acid[b]	7.30×10^{-3}	Plewa et al. (2010)	Not genotoxic	Plewa et al. (2002)
Trichloroacetic acid[b]	2.40×10^{-3}	Plewa et al. (2010)	Not genotoxic	Plewa et al. (2002)
Bromoacetic acid[b]	1.0×10^{-5}	Plewa et al. (2010)	1.7×10^{-5}	Plewa et al. (2002)
Dibromoacetic acid[b]	5.90×10^{-4}	Plewa et al. (2010)	1.8×10^{-3}	Plewa et al. (2002)
Haloacetamides				
Chloracetamide[b]	1.48×10^{-4}	Plewa et al. (2008a)	1.38×10^{-3}	Plewa et al. (2008a)
Dichloracetamide[b]	1.92×10^{-3}	Plewa et al. (2008a)	7.95×10^{-4}	Plewa et al. (2008a)
Trichloracetamide[b]	2.05×10^{-3}	Plewa et al. (2008a)	6.54×10^{-3}	Plewa et al. (2008a)

990 [a]WIL2-NS cells used for both cytotoxicity and genotoxicity assay, exposure time was 3 hr for both assay.
991 Cytotoxicity was measured using MTS assay, while genotoxicity was measured using flow cytometry-based
992 micronucleus assay.
993 [b]Chinese hamster ovary cells used for both cytotoxicity and genotoxicity assay, exposure time was 72 hr for
994 cytotoxicity assay and 4 hr for genotoxicity assay. Cytotoxicity was measured using cell chronic cytotoxicity
995 assay, while genotoxicity was measured using single cell gel electrophoresis assay.
996 [c]Genotoxicity not determined due to high cytotoxicity of the compounds.
997 [d]Value in brackets is from exponential regression analysis.

998 Figures



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1000 **Fig 1.** Chlorine species measured in water after chlorination or chloramination.

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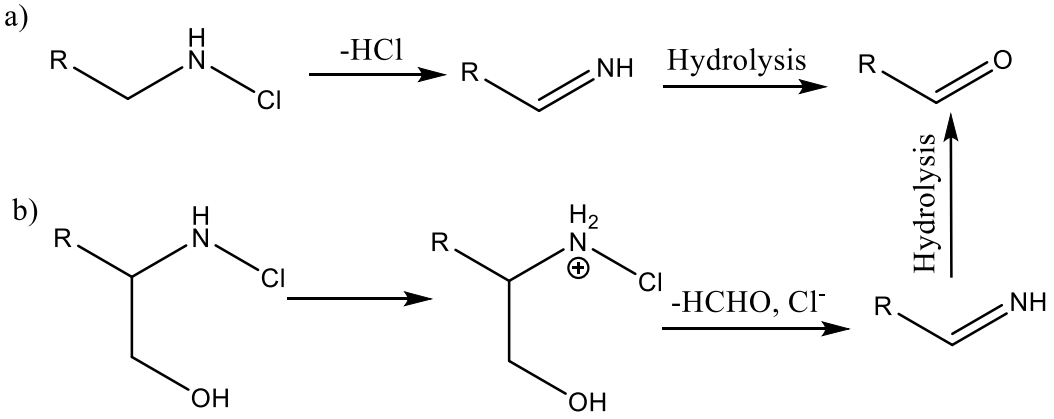

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1004 **Fig 2**. a) Degradation mechanism of *N*-chloramines, b) Degradation mechanism of *N*-
1005 chloralkanolamines, adapted from Antelo et al. (1996).

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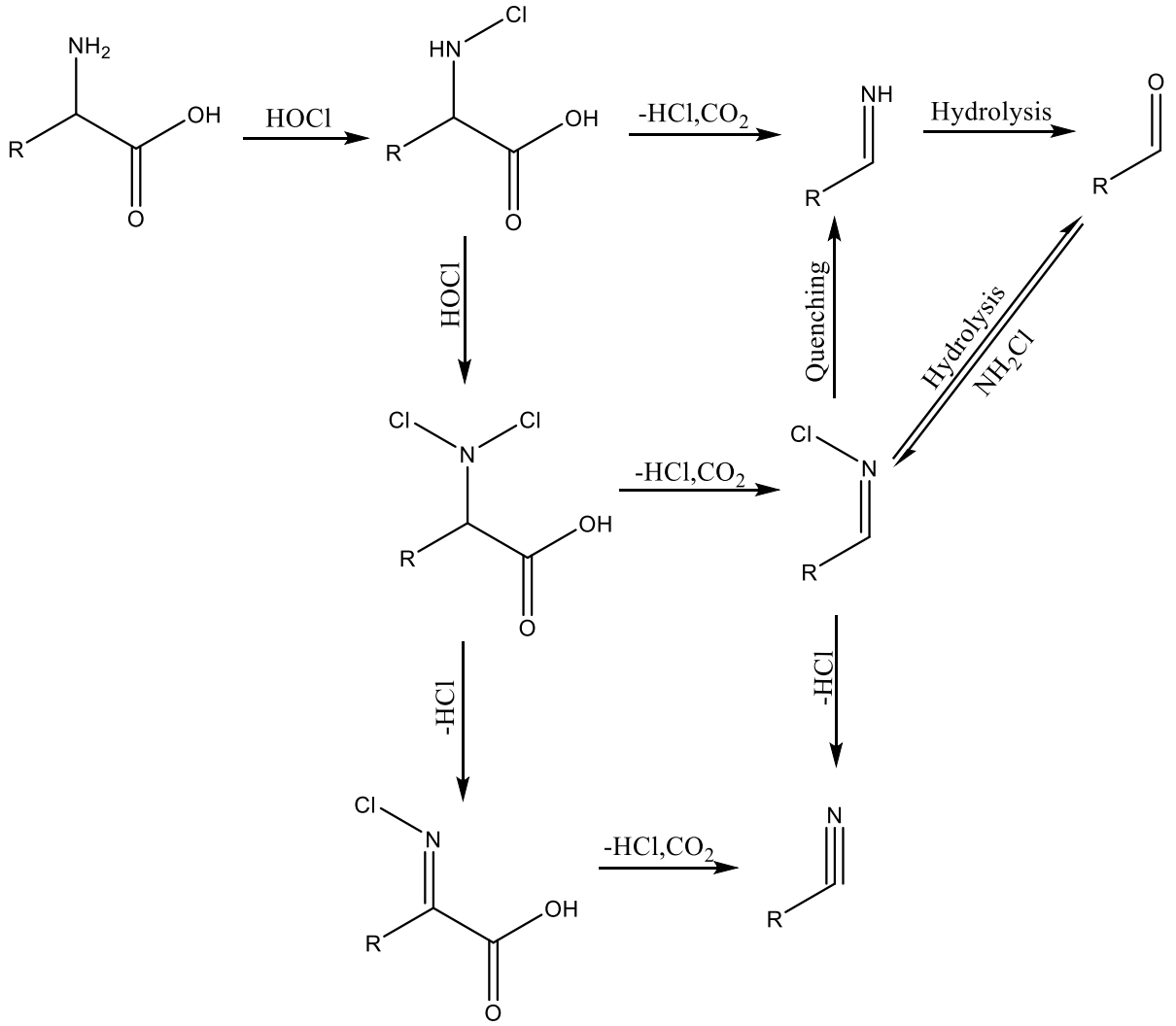

Fig 3. Reaction pathways for the reaction of amino acids and chlorine, adapted from Conyers and Scully (1993). *N*-Chloraldimines were suggested as intermediates for the formation of nitriles and aldehydes.

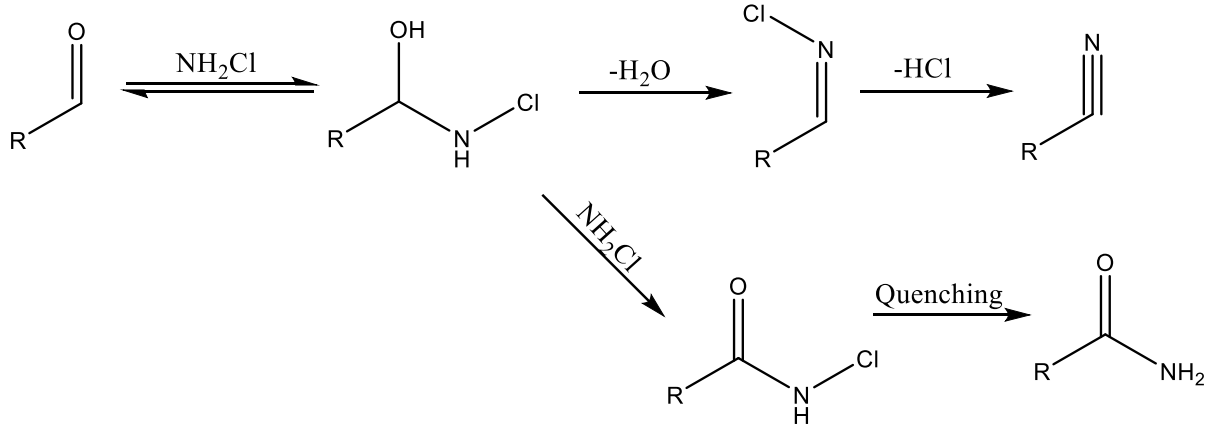

Fig 4. Reaction pathways for the reaction of aldehydes and inorganic monochloramine, adapted from Kimura et al. (2015). *N*-Chloraldimine was suggested as an intermediate for the formation of the nitrile.