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1 Chloramination of nitrogenous contaminants (pharmaceuticals and
2 pesticides): NDMA and halogenated DBPs formation

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13
14 **Abstract**

15 Disinfection with chloramines is often used to reduce the production of regulated disinfection
16 by-products (DBPs) such as trihalomethanes (THMs) and haloacetic acids (HAAs). However,
17 chloramination can lead to the formation of N-nitrosamines, including N-nitrosodimethylamine
18 (NDMA), a probable human carcinogen. Previous research used dimethylamine (DMA) as a model
19 precursor of NDMA, but certain widely used tertiary dimethylamines (e.g. the pharmaceutical
20 ranitidine) show much higher conversion rates to NDMA than DMA. This study investigates the
21 NDMA formation potential of several tertiary amines including pharmaceuticals and herbicides. The
22 reactivity of these molecules with monochloramine (NH₂Cl) is studied through the formation of NDMA,
23 and other halogenated DBPs such as haloacetonitriles (HANs) and AOX (Adsorbable Organic Halides).
24 Several compounds investigated formed NDMA in greater amounts than DMA, revealing the

25 importance of structural characteristics of tertiary amines for NDMA formation. Among these
26 compounds, the pharmaceutical ranitidine showed the highest molar conversion to NDMA. The pH and
27 dissolved oxygen content of the solution were found to play a major role for the formation of NDMA
28 from ranitidine. NDMA was formed in higher amounts at pH around pH 8 and a lower concentration of
29 dissolved oxygen dramatically decreased NDMA yields. These findings seem to indicate that
30 dichloramine (NHCl₂) is not the major oxidant involved in the formation of NDMA from ranitidine,
31 results in contradiction with the reaction mechanisms proposed in the literature. Dissolved oxygen was
32 also found to influence the formation of other oxygen-containing DBPs (i.e. trichloronitromethane and
33 haloketones). The results of this study identify several anthropogenic precursors of NDMA, indicating
34 that chloramination of waters impacted by these tertiary amines could lead to the formation of
35 significant amounts of NDMA and other non-regulated DBPs of potential health concern (e.g.
36 dichloroacetonitrile or trichloronitromethane). This could be of particular importance for the
37 chloramination of wastewater effluents, especially during water reuse processes.

38

39 **Keywords**

40 NDMA, Nitrosamine, Chloramination, Disinfection By-products, Ranitidine

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49 **1. Introduction**

50 A large diversity of disinfection by-products (DBPs) are formed during water treatment processes using
51 chlorination, including trihalomethanes (THMs) and haloacetic acids (HAAs). Disinfection with
52 chloramines is known to significantly reduce the formation of regulated DBPs as compared to
53 chlorination. However, chloramination favors the formation of *N*-nitrosamines, including
54 *N*-nitrosodimethylamine (NDMA). The US Environmental Protection Agency classifies NDMA as a
55 probable human carcinogen, evaluating a 10^{-6} risk level of cancer from NDMA concentration at
56 0.7 ng/L in drinking water (U.S. Environmental Protection Agency, 1987). Over the last decade, interest
57 has been growing about NDMA formation during water treatment process. Several studies examined the
58 mechanisms explaining the formation of NDMA during chlorination and chloramination. In most
59 studies, dimethylamine (DMA) served as the model NDMA precursor (Choi and Valentine, 2002a; Choi
60 and Valentine, 2002b; Choi and Valentine, 2003; Choi et al., 2002; Mitch and Sedlak, 2002; Schreiber
61 and Mitch, 2005; Schreiber and Mitch, 2006). However, some studies indicated that the amount of
62 dimethylamine present in surface waters (Gerecke and Sedlak, 2003) or secondary municipal
63 wastewaters (Mitch and Sedlak, 2004) are not sufficient to explain the amount of NDMA formed. The
64 role of tertiary amines presenting dimethylamine functional groups has been pointed out (Mitch and
65 Sedlak, 2004; Schmidt et al., 2006). Recent studies looked at diuron as a precursor of NDMA. Results
66 showed that the molar conversion rate is relatively low ($< 1.5\%$ of diuron forms NDMA) (Chen and
67 Young, 2008; Chen and Young, 2009). Another tertiary amine ranitidine, a histamine antagonist widely
68 used for peptic ulcer treatment was found to be an important NDMA precursor (62.9% NDMA yield
69 obtained by Schmidt et al., 2006 and 89.9% by Shen and Andrews, 2011). Other tertiary amines led to
70 less or equal NDMA formation than DMA, revealing the importance of structural characteristics of
71 tertiary amine compounds for NDMA formation (Schmidt et al., 2006). Shen and Andrews (2011)
72 demonstrated that several tertiary amines including pharmaceuticals and personal care products are

73 nitrosamine precursors during chloramines disinfection. According to these authors, the presence of
74 electron donating group such as furan can increase the electron density on the nitrogen atom and then
75 favors the reaction with chlorine leading to high NDMA yields observed with some pharmaceuticals
76 (especially ranitidine). Ranitidine is sold worldwide as a gastrointestinal drug and has been detected at
77 concentrations ranging from 70 ng/L to 540 ng/L in primary effluents of wastewater treatment plants
78 (WWTP) in Spain (Radjenovic et al., 2009) and at ~10 ng/L in several surface waters (Kolpin et al.,
79 2002; Zuccato et al., 2000). Ranitidine and other pharmaceuticals are not well removed by biological
80 treatments and can be found in river waters receiving the WWTP effluents (Castiglioni et al., 2006;
81 Radjenovic et al., 2009). Chloramination of wastewaters (e.g. for wastewater reuse purposes) impacted
82 by pharmaceuticals is of great concern because of the potential risk of NDMA formation.

83 NDMA formation occurring during chloramination has previously been explained as a nucleophilic
84 substitution reaction between monochloramine (NH_2Cl) and dimethylamine (DMA) to form an
85 unsymmetrical dimethylhydrazine intermediate (UDMH) (Choi and Valentine, 2002b; Choi et al., 2002;
86 Mitch and Sedlak, 2002). UDMH is then rapidly oxidized by NH_2Cl to NDMA at <3% yields. Over the
87 past few years, studies have addressed the importance of chloramines speciation and dissolved oxygen
88 (Schreiber and Mitch, 2006). Dichloramine (NHCl_2) was found to contribute to the production of
89 NDMA during chloramine disinfection, occurring through the formation of a chlorinated UDMH
90 (UDMH-Cl) as an intermediate rather than UDMH. Enhancing the formation of NHCl_2 by increasing
91 the Cl:N ratio also lead to higher yields of NDMA during chloramination of tertiary amines (Shen and
92 Andrews, 2011). Dissolved oxygen was also described as a critical parameter (Schreiber and Mitch,
93 2006). The authors proposed that the last step of the formation of NDMA consists in the incorporation
94 of dissolved O_2 into UDMH-Cl, which would then lead to NDMA.

95 Degradation of tertiary amines may form other nitrogenous disinfection byproducts (N-DBPs) of
96 potentially health concern, such as haloacetonitriles (HANs), halonitromethanes (HNMs), haloketones

97 (HKs) or cyanogen chloride (CNCl). HANs have been proved to be more toxic than HAAs and other
98 regulated DBPs (Muellner et al., 2007; Muellner et al., 2007). Trichloronitromethane (TCNM), also
99 known as chloropicrin, was the first of the HNMs to be identified as a DBP in drinking water (Hoigne
100 and Bader, 1988; Thibaud et al., 1987). Potential health effects of HNMs have already been studied
101 (National Cancer Institute, 1978; Schneider et al., 1999). They were found to be more mutagenic than
102 the corresponding halomethanes, and TCNM has been demonstrated to be particularly genotoxic (Plewa
103 et al., 2004). TCNM formation mechanisms have been proposed by chlorination and chloramination of
104 monomethylamine and n-propylamine (Joo and Mitch, 2007). TCNM formation is expected to increase
105 with pH during chlorination, and to be more important during chlorination than during chloramination.
106 TCNM formation from chlorination of lake waters was 40 times lower than that of chloroform (Hoigne
107 and Bader, 1988). Major haloketones (HKs) identified in chlorinated or chloraminated waters are
108 1,1-dichloro-2-propanone (1,1-DCP) and 1,1,1-trichloro-2-propanone (1,1,1-TCP). DCAN, 1,1-DCP
109 and CNCl formation were found to decrease when increasing pH, with maximum yields around pH 5-6
110 (Yang et al., 2007). DCAN formation during chloramination was much lower than during chlorination,
111 whereas CNCl and 1,1-DCP yields were higher in chloraminated water (Yang et al., 2007).

112 The goal of this study was to investigate the reactivity of several nitrogen-containing organic
113 compounds with monochloramine, through the formation of NDMA, HANs and AOX (Adsorbable
114 Organic Halides). Model compounds investigated included three herbicides (diuron, isoproturon,
115 trifluralin) and five pharmaceuticals: ranitidine (peptic ulcer treatment); doxepin and amitriptyline
116 (tricyclic antidepressants); mifepristone (an abortifacient) and minocycline (an antibiotic used for acne
117 treatment). All of them are tertiary amines presenting DMA functional groups. These anthropogenic
118 compounds are likely to enter natural waters via wastewater discharges (i.e. pharmaceuticals) or
119 agricultural runoff (i.e. herbicides). Because our objective was to study byproducts formation
120 mechanisms, solutions of model compounds were prepared at concentrations that are significantly

121 higher than what can be found in natural waters or wastewater effluents. As a result, DBPs were formed
122 at relatively high concentrations that are not likely to be found in treated waters. The influence of
123 several parameters (i.e. nitrites concentration, pH, chloramines speciation and dissolved oxygen
124 concentration) was investigated in order to better understand the reaction mechanisms that lead to the
125 formation of NDMA and some other DBPs (HANs, HKs, TCNM, AOX) during chloramination of
126 tertiary amines.

127

128 **2. Materials and methods**

129 **2.1. Materials**

130 All experiments were conducted using deionized water (Milli-Q, Millipore) buffered with sodium
131 acetate (pH = 4.0-5.5), a mixture of sodium phosphate monobasic and sodium phosphate dibasic
132 (pH = 7.0-8.5), or sodium carbonate (pH = 10). pH values were adjusted as needed using sodium
133 hydroxide or sulfuric acid (0.1 N, Fisher Scientific). Fluka Analytical methyl *tert*-butyl ether (>99%),
134 Fisher Scientific methylene chloride (GLC grade) and Carlo Erba methanol (>99.9%) were used without
135 further purification. Amitriptyline (>98%), diuron (>98%), doxepin (>98%), isoproturon (99.8%),
136 mifepristone (>98%), minocycline (92%, 8% water), ranitidine and trifluralin (>99%) were used without
137 further purification and were supplied through Sigma-Aldrich. Sodium hypochlorite (NaOCl, 13%,
138 Acros Organics) and ammonium chloride (Fisher Scientific, 99.9%) were used to prepare chloramine
139 reagents. Anhydrous sodium sulfite (Fisher Scientific) was used to quench residual chloramines.
140 Isotopically labeled standards, [6-²H] *N*-nitrosodimethylamine (NDMA-d6, 98%, 1 mg.mL⁻¹ in
141 methylene chloride) and [14-²H] *N*-nitrosodi-*n*-propylamine (DPNA-d14, 98%, 1 mg.mL⁻¹ in methylene
142 chloride) were obtained from Cambridge Isotope Laboratories (Andover, MA, USA). A standard
143 solution containing seven *N*-nitrosamines (2000 µg/mL each in methylene chloride) was purchased from
144 Supelco (Sigma-Aldrich). The SPE materials used to extract nitrosamines from aqueous solutions

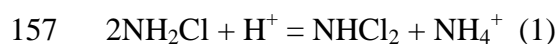
145 consisted in Supelclean™ prepacked coconut charcoal EPA 521 tubes, 2g/6ml, supplied from Supelco.
146 A mixed standard containing haloacetonitriles (HANs), trichloronitromethane (TCNM) and haloketones
147 (HKs) (EPA 551B Halogenated Volatiles Mix) and internal standard 1,2-dibromopropane were supplied
148 from Supelco. All reagents not specified were obtained from Fisher Scientific.

149

150 **2.2. Preparation and analysis of chloramines**

151 Monochloramine (NH₂Cl) stock solutions were prepared daily by slowly adding sodium hypochlorite
152 (NaOCl) into a rapidly stirred ammonium chloride (NH₄Cl) solution adjusted to pH = 8.5 with sodium
153 hydroxide, and using a Cl:N molar ratio of at least 1:1.2 to avoid breakpoint chlorination resulting from
154 local excess of hypochlorite (Mitch and Sedlak, 2002). Adjusting the pH at 8.5 minimizes the
155 disproportionation of NH₂Cl to dichloramine (NHCl₂), since NHCl₂ forms at pH < 8 (U.S.

156 Environmental Protection Agency, 1999) according to the equilibrium:



158 Free chlorine and total chlorine concentrations in the stock solutions of sodium hypochlorite were
159 determined iodometrically with sodium thiosulfate 0.1 M (Prolabo, >99.9%). Initial NH₂Cl and NHCl₂
160 concentrations were determined by spectrophotometric measurement using their respective molar
161 extinction coefficients at 245 nm and 295 nm and solving simultaneous equations (Schreiber and Mitch,
162 2005). Residual chloramines were analyzed iodometrically (Eaton et al., 1995).

163

164 **2.3. Chloramination experiments**

165 All glassware used during these experiments was washed with deionized water and baked at 500 °C for
166 at least 5 hours prior to use. Reactions were conducted in sealed 1 L amber glass bottles at 20 °C in a
167 temperature-controlled room, under dark conditions to avoid photolysis of NDMA. Chloramination
168 experiments were conducted following the approach of Mitch et al. (Mitch et al., 2003), using high

169 concentrations of NH_2Cl (200 to 300 mg/L as Cl_2) and a reaction time of 5 days for most of our
170 experiments. NH_2Cl remained in excess during all the reaction time. Solutions were prepared by
171 dissolving a pre-determined amount of compound in 1 L of 10 mM acetate, phosphate or carbonate
172 buffer. 100 mL of preformed monochloramine was then added to the working solution. Chloramination
173 experiments were conducted in triplicate. All series of experiments were completed with the
174 chloramination of a corresponding blank solution.

175 At given contact times, 350 mL of samples were transferred for residual chlorine, HANs and AOX
176 analyses, and 750 mL were processed for nitrosamines analyses.

177 Percent molar yields were calculated using the initial molar concentration of the studied compounds,
178 following Equation 2.

$$179 \text{ DBP yield (\%)} = \frac{[\text{DBP}] (\text{nM})}{[\text{Organic compound}]_0 (\text{nM})} \times 100 \quad (2)$$

180

181 AOX formation rates were calculated as follows:

$$182 \text{ AOX formation rate (mol/mol)} = \frac{[\text{AOX}] (\mu\text{g/L as Cl}) / 35.5}{[\text{Organic compound}]_0 (\mu\text{M})} \quad (3)$$

183

184 **2.4. Influence of dissolved O_2**

185 Experiments were performed in saturated dissolved O_2 solution and in absence of oxygen. The removal
186 of oxygen was operated prior to chloramination by bubbling nitrogen gas through a Teflon line until
187 dissolved O_2 concentration was less than 0.3 mg O_2 /L. The dissolved O_2 concentration was monitored
188 using a WTW Oxi 330 oxygen meter. The samples were continuously bubbled until the end of the
189 experiment (2 h contact time). Previous experiments were conducted with NDMA standard solutions in

190 order to verify that nitrogen bubbling for 2 hours did not lead to any significant NDMA or chlorinated
191 DBPs stripping.

192

193 **2.5. Analytical methods**

194 **2.5.1. Nitrosamines analysis**

195 NDMA analysis was performed according to the US EPA method (U.S. Environmental Protection
196 Agency, 2004), consisting in a solid-phase extraction (SPE) using coconut charcoal EPA 521 tubes
197 followed by GC/MS analysis in EI mode. Analytical details are provided elsewhere (Le Roux et al.,
198 2010) and summarized below. Chloramination reactions were quenched using 2.5 g sodium sulfite
199 before SPE. Unlike previous studies (Chen and Young, 2009; Schreiber and Mitch, 2006), no ascorbic
200 acid was used because it was found to degrade into furfural during SPE in coconut charcoal tubes,
201 which led to poor NDMA recovery. Prior to the extraction, 200 ng of NDMA-d6 was added to each 1 L
202 sample as an internal standard. Each sample was extracted at a continuous flow rate through the SPE
203 tube. Analytes were eluted from the SPE bed with 15 mL of methylene chloride. Extracts were then
204 filtered through 5 g anhydrous sodium sulfate column to remove residual water. Methylene chloride
205 extracts were then concentrated down to 1 mL under a stream of N₂, after addition of DPNA-d14
206 (200 ng) used as recovery standard. Samples extracts were analyzed immediately after SPE using a HP
207 6890 series gas chromatograph system coupled with a HP 5973 mass selective detector (MSD) in
208 electron impact (EI) mode. Samples were injected in pulsed splitless mode using helium as the carrier
209 gas. A Varian VF-5ms capillary column (30 m by 0.25 mm i.d. by 0.25 µm film thickness) supplied
210 through Interchim was used to separate the analytes. Quantitative analyses were performed in selected-
211 ion monitoring (SIM) mode. Full scan mode (40 - 240 m/z) analyses were also conducted for
212 complementary spectral information. This method reached extraction efficiencies of approximately

213 85%. The method detection limit (MDL) for NDMA at the 99% confidence level was determined to be
214 33 ng/L.

215 **2.5.2. HANs, HKs, TCNM and AOX analysis**

216 Chloramination reactions were stopped using 250 mg ascorbic acid prior to HAN and AOX analysis to
217 avoid HANs degradation occurring in the presence of excess sodium sulfite (Croue and Reckhow,
218 1989). HANs, HKs and TCNM analysis was based on the US EPA 551.1 method (Munch and Hautman,
219 1995). 50 mL of samples were transferred to amber glass bottles and 1,2-dibromopropane (100 µg/L)
220 was added as an internal standard. Samples were extracted by shaking for 4 min into 3 mL MTBE.
221 Extracts were analyzed using GC/MS (same equipment as used for nitrosamines analysis), along with
222 HANs, HKs and TCNM calibration standards. 1 µL was injected in pulsed splitless mode with an inlet
223 temperature of 150 °C. The column temperature program was 40 °C held for 3 min, ramping to 55 °C at
224 2 °C/min and holding for 1 min, then a ramp of 5 °C/min to 85 °C, and a final ramp of 40 °C/min to
225 200 °C held for 1 min. The MDL for this method is about 0.1 µg/L. AOX were determined using a
226 Dohrmann DX 20 analyzer after adsorption onto activated carbon (European Standard EN 1485, 1996).
227 The detection limit for this method is about 20 µg as Cl/L.

228

229 **3. Results and discussion**

230 Figure 1 shows as example the kinetic results for AOX, DCAN and NDMA formation obtained with
231 3 µM ranitidine and 2.5 mM NH₂Cl at pH 8.5. NH₂Cl consumption over 120 hours was always about
232 50% of the initial concentration. Same results were obtained for the other investigated compounds.
233 Results from control samples exhibited similar chloramine decay. Kinetic modeling performed using
234 Copasi software and Jafvert and Valentine's model (Jafvert and Valentine, 1992) confirmed that
235 monochloramine (NH₂Cl) predominantly decays by self-disproportionation under our experimental
236 conditions (pH 8.5, 10 mM phosphate buffer). Hence, the consumption of NH₂Cl by the model

237 compounds investigated was insignificant and could not be quantified. AOX formation leveled off after
238 only 2 h contact time, whereas NDMA and DCAN formation were slower and reached their maximum
239 after 24 h. This observation is in accordance with results from the chlorination of proteins (one of the
240 most important precursors of DCAN in drinking waters), that shows a two-step process (Reckhow,
241 2001). First, rapid reactions with reactive sites form THMs and Total Organic Halides (TOX) (Hureiki
242 et al., 1994), then slow degradation of proteins leads to DCAN formation. A similar behavior for DBPs
243 formation kinetics could occur during the chloramination of ranitidine.

244

245 The formation of NDMA, HANs and AOX at pH 8.5 from selected compounds was monitored after 5
246 days of contact time (Table 1). Ranitidine exhibited the highest molar yield with 40.2% NDMA formed.
247 Similar amounts of NDMA were produced after 5 days of contact time for initial monochloramine
248 concentrations of 0.5 mM to 2.5 mM and 100 nM ranitidine solutions i.e. for large excess of
249 monochloramine. Yields for the other pharmaceuticals ranged from 0.4 to 8.2% and less than 0.4% for
250 diuron and isoproturon. NDMA formation from DMA is known to be < 3% molar conversion (Schmidt
251 et al., 2006; Schreiber and Mitch, 2006) Minocycline and especially ranitidine exhibited higher molar
252 yields than other tertiary amines or DMA.

253 Compounds presenting heterocyclic ring in their structure (e.g. furan in ranitidine) produced more
254 NDMA than compounds with DMA functions near carbonyl groups (i.e. diuron and isoproturon)
255 (Schmidt et al., 2006) and compounds with aromatic rings (e.g. minocycline or mifepristone).

256 According to Shen and Andrews (2011), the higher yield observed for ranitidine would be explained by
257 the electron-donating effect of furan group that increases electron density on the nitrogen atom and thus
258 enhance electrophilic substitution of chlorine atom. This mechanism would involve the formation of
259 dimethylchloramine (DMCA), DMA and then NDMA (Mitch and Sedlak, 2004). However, the presence
260 of DMA as a key intermediate could not explain the high yield obtained with ranitidine because the

261 NDMA yields from DMA are always < 3% in literature. An alternative mechanism would involve the
262 nucleophilic substitution of NH_2Cl on nitrogen atom instead of electrophilic substitution (i.e. chlorine
263 transfer with formation of a DMCA group). Further research is needed to fully address the formation
264 mechanism of NDMA from dimethylaminomethylfuran group.

265 As suggested by (Shen et Andrews, 2011), ranitidine can be considered as a significant NDMA
266 precursor because 6 to 39% of ranitidine is excreted as the parent form by human body (Jjemba, 2006)
267 and its metabolites maintain the furan and DMA groups in their structures. Moreover, the removal of
268 ranitidine through WWTP can be relatively low (Castiglioni et al., 2006). The presence of ranitidine and
269 its metabolites in wastewaters could contribute significantly to the high NDMA formation potentials
270 observed at several WWTP, which are much higher than concentrations predicted based upon DMA
271 concentrations in raw waters and calculated following previously proposed formation mechanisms
272 (Mitch and Sedlak, 2004; Mitch et al., 2003).

273 Minocycline, the second highest NDMA precursor of the pool of compounds studied (8.2% NDMA
274 molar conversion) contains two dimethylamine functional groups that probably partly explain the
275 significant formation of NDMA. Amitriptyline and doxepin have similar molecular structures and
276 formed 1.15 and 2.32% of NDMA, respectively. The three carbon atoms between the DMA group and
277 the three rings could explain their lower reactivity compared to ranitidine (Shen and Andrews, 2011).
278 The presence of the oxygen atom in doxepin would explain the higher yield of NDMA for this molecule
279 compared to amitriptyline. Chloramination of trifluralin led to the formation of 0.18% DPNA, half the
280 formation of NDMA obtained from mifepristone that also incorporates an aromatic ring substituted with
281 a dialkylamine group. The lower yield for trifluralin can be attributed to the electron withdrawing effect
282 of the two nitro groups. The electron withdrawing effect of the carbonyl group would also explain the
283 low formation yield of NDMA from isoproturon and diuron (Schmidt et al., 2006).

284 In full scan mode, the GC/MS chromatogram of the extracts revealed the presence of
285 dimethylformamide (DMF) and dimethylcyanamide (DMC) as by-products of the reaction of
286 monochloramine with diuron or ranitidine. These compounds are known to be UDMH oxidation
287 products, as well as NDMA (Mitch and Sedlak, 2002). However, formation mechanisms of DMC and
288 DMF remain unclear. No other nitrosamine was detected during the experiments with compounds
289 containing dimethylamine functional groups.

290

291 Ranitidine formed about 10 times less DCAN than NDMA (Table 1). Minocycline was the second
292 highest DCAN precursor (1.5% DCAN yield). For the other compounds studied, the amounts of DCAN
293 formed were quite similar to those of NDMA (< 1% yield). No TCAN formation was detected during
294 these experiments. No correlation could be made between NDMA formation and DCAN formation but
295 more DCAN was generally formed when NDMA was produced in higher amounts. Minocycline
296 exhibited the highest AOX formation rate (8.98 mol/mol), which could be related to its highly aromatic
297 and oxygen-containing structure. Ranitidine was the second AOX precursor with 0.95 mol/mol
298 formation rate. The other compounds investigated did not lead to any significant AOX formation in our
299 experimental conditions. These results indicate that compounds producing high amount of NDMA tend
300 also to form more of other DBPs (AOX, and especially DCAN).

301

302 **3.1. Influence of Nitrites**

303 Previous research (Choi and Valentine, 2003) proposed an “enhanced nitrosation pathway” describing
304 NDMA formation from the reaction of DMA with nitrite and hypochlorite. Nitrites were also found to
305 enhance the formation of NDMA during the chlorination of diuron (Chen and Young, 2009). Because
306 low amount of free chlorine may be present in monochloramine solution, nitrites could contribute to the
307 formation of NDMA by chloramination. Experiments conducted with 1 μ M amitriptyline and 1 μ M

308 mifepristone showed that NDMA formation was not significantly different in presence and in absence of
309 1 μM nitrites (Table 2). These results indicate that the formation of NDMA from tertiary amines during
310 chloramination is not enhanced by any nitrosation mechanism, which could have occurred in presence
311 of free chlorine and nitrites.

312

313 **3.2. Effect of pH**

314 To assess the influence of pH on the formation of DBPs, NH_2Cl (2.5 mM) was applied to ranitidine
315 solutions (3 μM) in deionized water buffered at pH ranging from 4 to 10 (Table 3). NDMA, HANs,
316 HKs, and TCNM were analyzed after a contact time of 5 days. NDMA formation from chloramination
317 of ranitidine exhibited a maximum (59.6% yield) at pH 7.9, which is similar to 62.9% reported in
318 Schmidt et al. (2006) for the same conditions. Amitriptyline and mifepristone followed similar trends,
319 forming much less NDMA at pH 10 than at pH 8 (Table 2). Other studies showed that NDMA
320 formation from chloramination of DMA or diuron varied with pH with a maximum formation rate
321 between pH 7 and 9 (Chen and Young, 2008; Mitch and Sedlak, 2002; Schreiber and Mitch, 2006).
322 Self-decomposition and hydrolysis of NH_2Cl at $\text{pH} < 8$ are known to lead to the formation of NHCl_2
323 (Valentine and Jafvert, 1988). Because NHCl_2 is known to enhance NDMA formation (Schreiber and
324 Mitch, 2006), then acid-catalyzed disproportionation of NH_2Cl into NHCl_2 could explain the higher
325 formation of NDMA at pH 7.9 compared to $\text{pH} > 8$. However, kinetic modeling of NH_2Cl
326 decomposition indicates that NHCl_2 is not present in important amounts at pH 7.9. Furthermore, NDMA
327 formation from ranitidine at pH where NHCl_2 is the major specie (i.e. $\text{pH} \sim 4$) was much lower than at
328 pH 8, indicating that other factors than chloramines speciation may play a role in NDMA formation
329 mechanisms. Thus, ranitidine acid-base equilibrium ($\text{pK}_a = 8.2$) could explain the decrease of NDMA
330 formation when the protonated form of ranitidine decreases at $\text{pH} > 8$ (Figure 2). At $\text{pH} < 8$, NDMA

331 formation seems to be strongly dependent on the NH_2Cl concentration in the solution, and was not
332 enhanced by the presence of NHCl_2 .

333 As shown in Table 3, important amounts of trichloronitromethane (TCNM) were formed from ranitidine
334 at acidic pH (12.57% at pH 4). The amounts of TCNM formed decreased as the pH was raised from
335 pH 4 to pH 10, but were still higher than other chlorinated DBPs at neutral and basic pH. Whereas
336 NDMA formation was maximum around pH 8, DCAN, 1,1-DCP and 1,1,1-TCP exhibited a maximum
337 formation yield at pH 7. Moreover, TCAN formation from ranitidine was low and relatively constant
338 when varying pH from 4 to 10. The lower concentrations of DCAN and 1,1-DCP at $\text{pH} > 7$ can be
339 explained by base-catalyzed decomposition (Croue and Reckhow, 1989; Reckhow, 2001; Yang et al.,
340 2007).

341 AOX formation was constant from pH 4 to 7 and then decreased at alkaline pH (Table 3). As shown in
342 Figure 3, analyzed DBPs represent only a few percent of the AOX formed. TCNM accounts for 20% of
343 the produced AOX at pH 4. However, the proportion of identified DBPs is decreasing when increasing
344 pH.

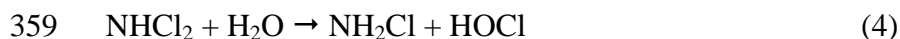
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346 **3.3. Influence of dichloramine**

347 To evaluate the influence of NHCl_2 on NDMA formation from ranitidine, preformed NHCl_2 or NH_2Cl
348 (1 mM) were applied to ranitidine solutions. Previous research indicated that NDMA formation from
349 DMA and NHCl_2 was much higher than in the presence of NH_2Cl (Schreiber and Mitch, 2006). Our
350 results showed that NDMA formation from 100 nM ranitidine buffered at pH 8 and after 24 h was
351 significantly lower with NHCl_2 than with NH_2Cl (46.8% and 80.2% molar yields respectively,
352 Figure 4).

353 Total chlorine decay during our experiments with NHCl_2 was about 85% after 24 hours, while it was
354 only 25% with NH_2Cl . Thus, NHCl_2 decomposition is more rapid than NH_2Cl at pH around pH 8, which

355 could explain why less NDMA was formed in presence of NHCl_2 . The autodecomposition of NHCl_2 in
356 our experiments could be well simulated by the kinetic model of Jafvert and Valentine (1992).
357 According to this model, the hydrolysis of dichloramine (Equation 4) and inverse dismutation
358 (Equation 5) lead to the formation of significant amounts of monochloramine.



361 The use of the model showed that the residual chlorine concentrations of 0.3 mM analyzed after 24h of
362 contact time could be explained by the formation of NH_2Cl from NHCl_2 decomposition, which is almost
363 complete after 24h. In this condition, the simulated NH_2Cl exposure (i.e. the C.t value) represents about
364 38% of the NH_2Cl exposure from direct NH_2Cl addition. Thus, NH_2Cl formed from the decomposition
365 of NHCl_2 could explain the amounts of NDMA formed during the chloramination of ranitidine using
366 dichloramine. These results seem to indicate that dichloramine would not be involved into the formation
367 of NDMA from ranitidine. No significant differences were observed for DCAN formation after the
368 application of either NH_2Cl or NHCl_2 to 100 nM ranitidine at pH 8 (Figure 4).

369

370 **3.4. Influence of dissolved oxygen**

371 It has been demonstrated that dissolved oxygen concentration plays a major role in the formation of
372 NDMA by chloramination of DMA (Schreiber and Mitch, 2006). Moreover, a recent study showed that
373 the formation of NDMA from DMA could be catalyzed by activated carbon, and that the presence of
374 oxygen was a critical factor in this mechanism (Padhye et al., 2010).

375 In order to assess whether or not dissolved oxygen would influence the formation of NDMA from the
376 chloramination of other model compounds, 2.7 mM NH_2Cl was applied to 3 μM ranitidine during 2h in
377 presence and in absence of dissolved O_2 . NDMA formation was significantly inhibited for low oxygen

378 concentration (~ 0.2 mg O₂/L) compared to ambient O₂ concentration (~ 9 mg O₂/L) (molar yields of
379 4.01% and 54% respectively, Figure 5a).
380 Dissolved O₂ concentration did not affect AOX formation as much as NDMA formation (Figure 5b).
381 Moreover, DCAN formation was not influenced by dissolved O₂ concentration while the formation of
382 other halogenated DBPs containing oxygen atoms (nitro or ketones functional groups, i.e. TCNM,
383 1,1-DCP and 1,1,1-TCP) was approximately an order of magnitude lower in the presence of
384 0.2 mg O₂/L (Figure 6). This indicates that dissolved oxygen could be incorporated into those DBPs, i.e.
385 an oxygen atom of dissolved oxygen could serve as a source for the oxygen atom in nitroso or ketone
386 functions of DBPs. Further research with model compounds and using inhibitors of oxygen species need
387 to be done to elucidate the mechanisms involved into the formation of NDMA and to understand the
388 role of dissolved oxygen.

389

390 **4. Conclusion**

- 391 • Even if concentrations of compounds used for our study were relatively high and are not likely
392 to be found in natural waters, we observed that several nitrogenous anthropic compounds can
393 lead to important concentrations of N-DBPs including NDMA, DCAN, 1,1-DCP, or TCNM.
394 From the seven compounds investigated in our study, four compounds contain dimethylamine
395 functional groups and exhibited yields higher than 1.15% (ranitidine, minocycline, doxepin,
396 amitriptyline). Especially, the pharmaceutical ranitidine is of great concern regarding its high
397 molar yield into NDMA (~60% at pH 7.9), as shown in earlier studies.
- 398 • Such differences in NDMA formation can not be explained by the release of DMA and the
399 reactions of DMA with chloramines. More simple compounds than those described in the
400 present work need to be studied to improve our understanding of molecular structure influence
401 on the formation of NDMA.

- 402 • Our results demonstrate that the reaction of NHCl_2 with ranitidine would not form more NDMA
403 than NH_2Cl . However, we confirmed the implication of dissolved oxygen in NDMA formation
404 mechanisms. Dissolved oxygen was found to play a role into the formation of other
405 oxygen-containing DBPs (TCNM, 1,1-DCP and 1,1,1-TCP) but did not influence DCAN
406 formation. These results need further investigation to better understand the incorporation of
407 dissolved oxygen into DBPs.
- 408 • Considering the high conversion of ranitidine to NDMA, the use of chloramination as a
409 disinfection for wastewaters containing ranitidine can lead to the formation of important
410 amounts of NDMA. This could explain the high NDMA formation potentials observed at several
411 WWTP, which are much higher than concentrations predicted based upon DMA concentrations
412 in raw waters.

413

414

415 **Acknowledgement**

416 We would like to thank the French Ministry of Higher Education and Research (Ministère de
417 l'Enseignement Supérieur et de la Recherche) for its financial support.

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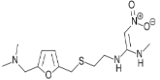
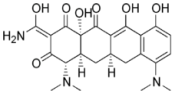
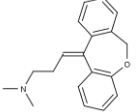
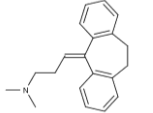
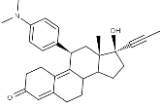
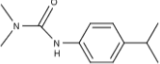
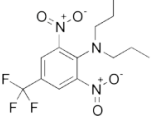
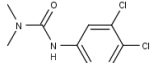
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547 **Tables**

548 Table 1. Nitrosamine and DCAN formation from compounds investigated at pH 8.5 (5 days contact
 549 time)

Compound investigated	Molecular structure	Compound concentration (nM)	NH ₂ Cl concentration ^a (mM)	Molar yield ^b (%) (SD ^c)		AOX formation rate ^e (mol/mol) (SD ^c)
				Nitrosamine ^d	DCAN	
Ranitidine		14760	4.0	40.2 (1.4)	5.8 (0.2)	0.95 (0.18)
Minocycline		2820	2.5	8.2 (0.7)	1.5 (0.1)	8.98 (0.89)
Doxepin		1730	2.5	2.32 (0.01)	0.5 (0.1)	N.D.
Amitriptyline		3480	2.5	1.15 (0.04)	0.8 (0.4)	N.D.
Mifepristone		3170	2.5	0.39 (0.02)	0.2 (0.1)	N.D.
Isoproteron		5290	2.5	0.34 (0.02)	N.D.	N.D.
Trifluralin		810	2.5	0.18 (0.01)	N.D.	N.D.
Diuron		16560	4.0	0.15 (0.01)	N.D.	N.D.

^a Initial NH₂Cl concentration applied to a solution containing a compound investigated in deionized water with 10 mM phosphate buffer (pH 8.5)

^b Molar yields were calculated based upon the initial compound concentration

^c SD = Standard Deviation on 3 replicates

^d Nitrosamine formed is NDMA except for trifluralin (DPNA)

^e AOX formation rates expressed as mol AOX as Cl⁻ / mol of initial compound

N.D. = Not Detected

550 Table 2. Effect of pH and NO₂⁻ on NDMA formation from amitriptyline and mifepristone over 5 days
 551 with 10 mM buffer (phosphate for pH 8.5 and carbonate for pH 10).

Expt	Compound investigated	Compound concentration (μM)	NH₂Cl concentration (mM)	NDMA yield^a (%) (SD^b)	pH
1	Amitriptyline	0.38	3.8	2.37 (0.34)	8.5
		0.38	3.8	0.08 (0.01)	10
	Mifepristone	0.35	3.8	1.00 (0.30)	8.5
		0.35	3.8	0.04 (0.01)	10
2	Amitriptyline	1	3.4	1.93 (0.15)	8.5
	Amitriptyline + 1 μM NO ₂ ⁻	1	3.4	1.72 (0.15)	8.5
	Mifepristone	1	3.4	0.89 (0.09)	8.5
	Mifepristone + 1 μM NO ₂ ⁻	1	3.4	0.97 (0.09)	8.5

^aMolar yields were calculated based upon the initial compound concentration

^bSD = Standard Deviation on 3 replicates

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560 Table 3. Effect of pH on NDMA and chlorinated DBPs formation from 3 μ M ranitidine and 2.5 mM
 561 NH_2Cl (5 days contact time).

pH	Molar yield (%)						AOX formation rate (mol/mol)
	NDMA	DCAN	TCAN	TCNM	1,1-DCP	1,1,1-TCP	
4	0.2	1.33	0.31	12.57	N.D.	N.D.	1.63
5.5	20.6	1.08	0.49	6.14	1.06	0.38	1.63
7	42.2	1.65	0.31	3.05	1.51	1.37	1.74
7.9	59.6	0.81	0.28	1.43	0.24	0.03	1.31
8.5	46.6	0.55	0.33	0.70	0.12	N.D.	1.07
10	10.4	0.06	0.61	0.09	N.D.	0.02	0.56

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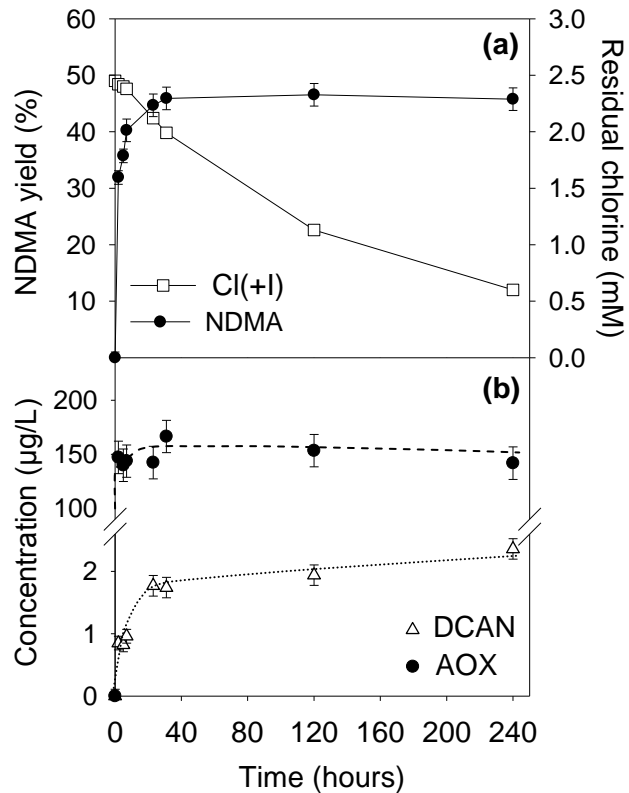
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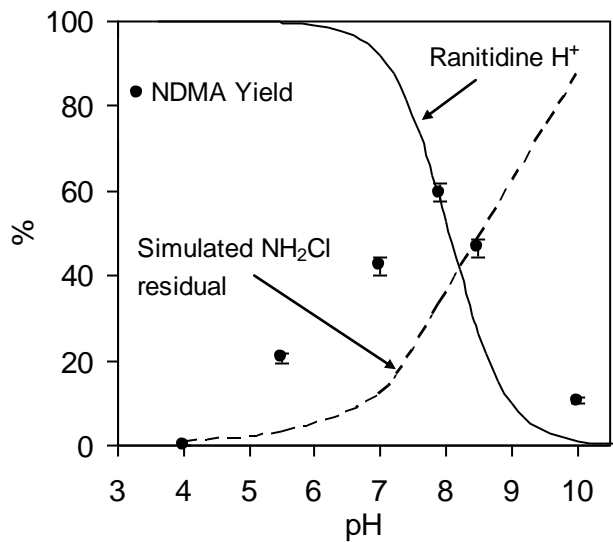
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580 Figure 1. NDMA formation from 3 μM ranitidine at pH 8.5 with 10 mM phosphate buffer, 2.5 mM
 581 monochloramine. Error bars represent one standard deviation ($n = 3$). NDMA molar yields were
 582 calculated based upon the initial ranitidine concentration.

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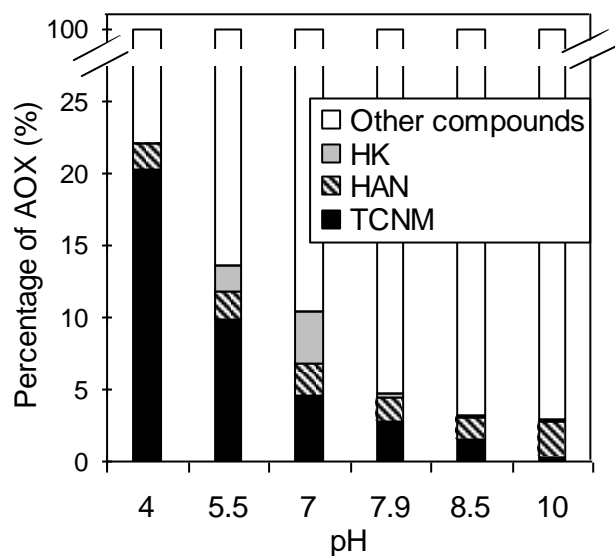
585 Figure 2. Effect of pH on NDMA formation from 3 μ M ranitidine and 2.5 mM monochloramine over 5
 586 days with 10 mM buffer (acetate for pH 4.0-5.5, phosphate for pH 7.0-8.5 and carbonate for pH 10); and
 587 NH₂Cl residuals calculated using Jafvert & Valentine model (1992). NDMA yields were calculated
 588 based on the initial ranitidine concentration; percentages of NH₂Cl residuals were calculated based on
 589 the initial NH₂Cl concentration.

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595 Figure 3. AOX repartition between trichloronitromethane (TCNM), haloacetonitriles (HAN: sum of
 596 DCAN and TCAN) and haloketones (HK: sum of 1,1-DCP and 1,1,1-TCP) at different pH from 3 μ M
 597 ranitidine and 2.5 mM NH_2Cl . Note the scale break.

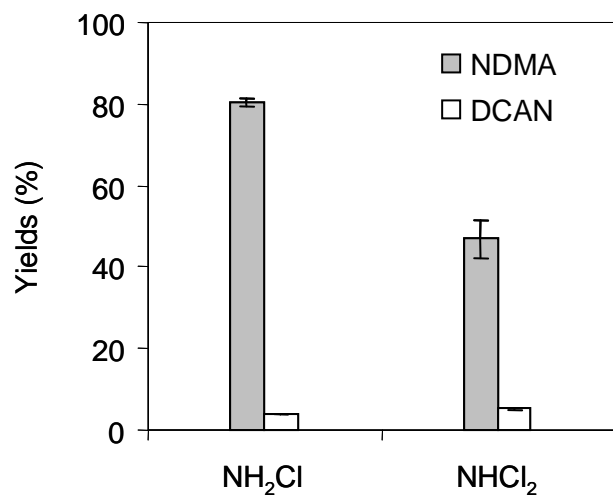
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604 Figure 4. NDMA and DCAN formation after 24 h following the application of 1 mM monochloramine

605 or dichloramine to 100 nM ranitidine buffered at pH 8.

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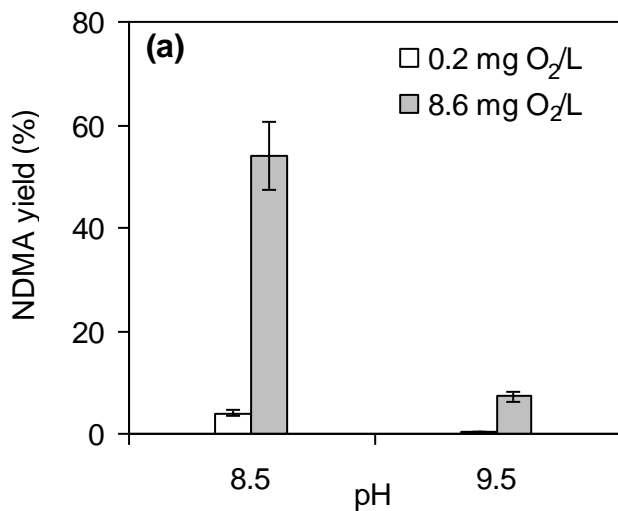
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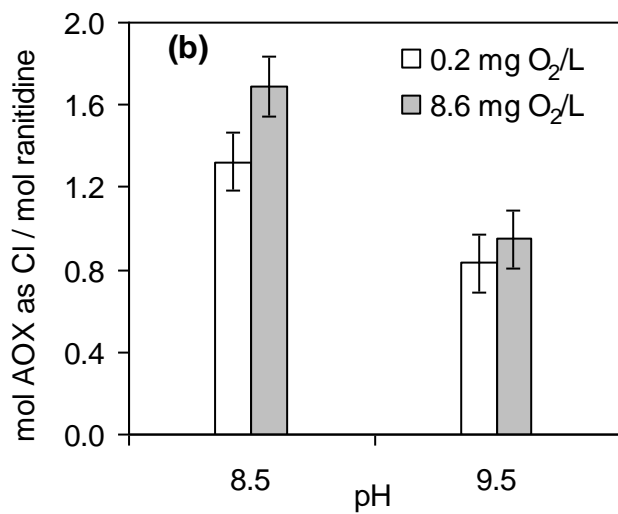
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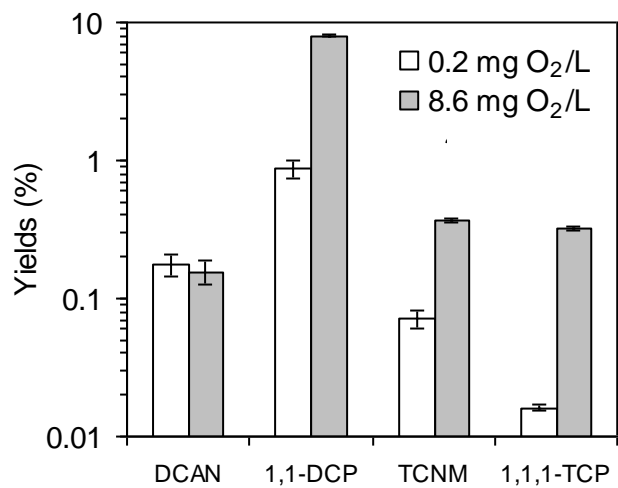


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615 Figure 5. Effect of dissolved oxygen and pH on (a) NDMA and (b) AOX formation from 3 μM
 616 ranitidine and 2.7 mM NH₂Cl, over 2 h with 10 mM buffer. NDMA molar yields were calculated based
 617 upon the initial ranitidine concentration.



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619 Figure 6. Effect of dissolved oxygen on DCAN, 1,1-DCP, TCNM and 1,1,1-TCP formation from 3 μ M
620 ranitidine and 2.7 mM NH₂Cl over 2 h at pH 8.5 with 10 mM phosphate buffer.