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

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Abstract

Disinfection with chloramines is often used to reduce the production of regulated disinfection by-products (DBPs) such as trihalomethanes (THMs) and haloacetic acids (HAAs). However, chloramination can lead to the formation of N-nitrosamines, including N-nitrosodimethylamine (NDMA), a probable human carcinogen. Previous research used dimethylamine (DMA) as a model precursor of NDMA, but certain widely used tertiary dimethylamines (e.g. the pharmaceutical ranitidine) show much higher conversion rates to NDMA than DMA. This study investigates the NDMA formation potential of several tertiary amines including pharmaceuticals and herbicides. The reactivity of these molecules with monochloramine (NH_2Cl) is studied through the formation of NDMA, and other halogenated DBPs such as haloacetonitriles (HANs) and AOX (Adsorbable Organic Halides). 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 ($NHCl_2$) 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.

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39   **Keywords**

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

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1. Introduction

A large diversity of disinfection by-products (DBPs) are formed during water treatment processes using chlorination, including trihalomethanes (THMs) and haloacetic acids (HAAs). Disinfection with chloramines is known to significantly reduce the formation of regulated DBPs as compared to chlorination. However, chloramination favors the formation of *N*-nitrosamines, including *N*-nitrosodimethylamine (NDMA). The US Environmental Protection Agency classifies NDMA as a probable human carcinogen, evaluating a 10^{-6} risk level of cancer from NDMA concentration at 0.7 ng/L in drinking water (U.S. Environmental Protection Agency, 1987). Over the last decade, interest has been growing about NDMA formation during water treatment process. Several studies examined the mechanisms explaining the formation of NDMA during chlorination and chloramination. In most studies, dimethylamine (DMA) served as the model NDMA precursor (Choi and Valentine, 2002a; Choi and Valentine, 2002b; Choi and Valentine, 2003; Choi et al., 2002; Mitch and Sedlak, 2002; Schreiber and Mitch, 2005; Schreiber and Mitch, 2006). However, some studies indicated that the amount of dimethylamine present in surface waters (Gerecke and Sedlak, 2003) or secondary municipal wastewaters (Mitch and Sedlak, 2004) are not sufficient to explain the amount of NDMA formed. The role of tertiary amines presenting dimethylamine functional groups has been pointed out (Mitch and Sedlak, 2004; Schmidt et al., 2006). Recent studies looked at diuron as a precursor of NDMA. Results showed that the molar conversion rate is relatively low (< 1.5% of diuron forms NDMA) (Chen and Young, 2008; Chen and Young, 2009). Another tertiary amine ranitidine, a histamine antagonist widely used for peptic ulcer treatment was found to be an important NDMA precursor (62.9% NDMA yield obtained by Schmidt et al., 2006 and 89.9% by Shen and Andrews, 2011). Other tertiary amines led to less or equal NDMA formation than DMA, revealing the importance of structural characteristics of tertiary amine compounds for NDMA formation (Schmidt et al., 2006). Shen and Andrews (2011) 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-^{2}H] *N*-nitrosodimethylamine (NDMA-d6, 98%, 1 mg.mL^{-1} in

141 methylene chloride) and [14-^{2}H] *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 (NH_2Cl) stock solutions were prepared daily by slowly adding sodium hypochlorite

152 ($NaOCl$) into a rapidly stirred ammonium chloride (NH_4Cl) 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 NH_2Cl to dichloramine ($NHCl_2$), since $NHCl_2$ forms at $pH < 8$ (U.S.

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

157    $2NH_2Cl + H^+ = NHCl_2 + NH_4^+$ (1)
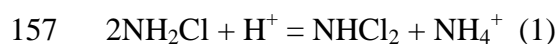
158 Free chlorine and total chlorine concentrations in the stock solutions of sodium hypochlorite were

159 determined iodometrically with sodium thiosulfate 0.1 M (Prolabo, >99.9%). Initial NH_2Cl and $NHCl_2$

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

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 N_2, 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 NH_2Cl at pH 8.5. NH_2Cl 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 (NH_2Cl) predominantly decays by self-disproportionation under our experimental

236   conditions (pH 8.5, 10 mM phosphate buffer). Hence, the consumption of NH_2Cl 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 µM amitriptyline and 1 µM

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 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 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. pH ~ 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 (pKa = 8.2) could explain the decrease of NDMA

330 formation when the protonated form of ranitidine decreases at pH > 8 (Figure 2). At 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 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.

345

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.

359    $NHCl_2 + H_2O \rightarrow NH_2Cl + HOCl$ (4)

360    $NHCl_2 + NH_3 + H^+ \rightarrow 2\ NH_2Cl + H^+$ (5)

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 O_2/L) compared to ambient O_2 concentration (~ 9 mg O_2/L) (molar yields of

379   4.01% and 54% respectively, Figure 5a).

380   Dissolved O_2 concentration did not affect AOX formation as much as NDMA formation (Figure 5b).

381   Moreover, DCAN formation was not influenced by dissolved O_2 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 O_2/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.

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427   **References**

428   Castiglioni, S., Bagnati, R., Fanelli, R., Pomati, F., Calamari, D., Zuccato, E., 2006. Removal of

429   Pharmaceuticals in Sewage Treatment Plants in Italy. Environ. Sci. Technol. 40 (1), 357-363.

430   Chen, W., Young, T.M., 2008. NDMA formation during chlorination and chloramination of aqueous

431   diuron solutions. Environ. Sci. Technol. 42 (4), 1072-1077.

432   Chen, W., Young, T.M., 2009. Influence of nitrogen source on NDMA formation during chlorination of

433   diuron. Water Res. 43 (12), 3047-3056.

434   Choi, J., Duirk, S.E., Valentine, R.L., 2002. Mechanistic studies of N-nitrosodimethylamine-(NDMA)

435   formation in chlorinated drinking water. J. Environ. Monit. 4 (2), 249-252.

436   Choi, J., Valentine, R.L., 2002. A kinetic model of N-nitrosodimethylamine (NDMA) formation during

437   water chlorination/chloramination. Water Sci. Technol. 46 (3), 65-71.

438   Choi, J., Valentine, R.L., 2002. Formation of N-nitrosodimethylamine (NDMA) from reaction of

439   monochloramine: A new disinfection by-product. Water Res. 36 (4), 817-824.

440   Choi, J., Valentine, R.L., 2003. N-Nitrosodimethylamine Formation by Free-Chlorine-Enhanced

441   Nitrosation of Dimethylamine. Environ. Sci. Technol. 37 (21), 4871-4876.

442   Croue, J.P., Reckhow, D.A., 1989. Destruction of chlorination byproducts with sulfite. ESandT

443   Contents 23 (11), 1412-1419.

444   Eaton, A.D., Clesceri, L.S., Greenberg, A.E., Eds. *Standard Methods for the Examination of Water and*

445   *Wastewater*, 19th ed.; American Public Health Association/American Water Works Association/Water

446   Environment Federation Publishers; Washington D.C., USA, 1995.

447   European Standard EN 1485 (1996) Water Quality Determination of Adsorbable Organically Bound

448   Halogens (AOX).

449   Gerecke, A.C., Sedlak, D.L., 2003. Precursors of N-nitrosodimethylamine in natural waters. Environ.

450   Sci. Technol. 37 (7), 1331-1336.

451   Hoigne, J., Bader, H., 1988. The formation of trichloronitromethane (chloropicrin) and chloroform in a

452   combined ozonation/chlorination treatment of drinking water. Water Res. 22 (3), 313-319.

453   Hureiki, L., Croué, J., Legube, B., 1994. Chlorination studies of free and combined amino acids. Water

454   Res. 28 (12), 2521-2531.

455   Jafvert, C.T., Valentine, R.L., 1992. Reaction scheme for the chlorination of ammoniacal water.

456   Environ. Sci. Technol. 26 (3), 577-786.

457   Jjemba, P.K., 2006. Excretion and ecotoxicity of pharmaceutical and personal care products in the

458   environment. Ecotoxicol. Environ. Saf. 63 (1), 113-130.

459   Joo, S.H., Mitch, W.A., 2007. Nitrile, Aldehyde, and Halonitroalkane Formation during

460   Chlorination/Chloramination of Primary Amines. Environmental Science & Technology 41 (4), 1288-

461   1296.

462   Kolpin, D.W., Furlong, E.T., Meyer, M.T., Thurman, E.M., Zaugg, S.D., Barber, L.B., Buxton, H.T.,

463   2002. Pharmaceuticals, Hormones, and Other Organic Wastewater Contaminants in U.S. Streams,

464   1999−2000: A National Reconnaissance. Environmental Science & Technology 36 (6), 1202-1211.

465   Le Roux, J., Gallard, H., Croue, J.P., 2010. Formation of NDMA by Chloramination of Nitrogenous

466   Pharmaceuticals. Water Practice & Technology 5 (4).

467   Mitch, W.A., Gerecke, A.C., Sedlak, D.L., 2003. A N-Nitrosodimethylamine (NDMA) precursor

468   analysis for chlorination of water and wastewater. Water Res. 37 (15), 3733-3741.

469   Mitch, W.A., Sedlak, D.L., 2002. Formation of N-nitrosodimethylamine (NDMA) from dimethylamine

470   during chlorination. Environ. Sci. Technol. 36 (4), 588-595.

471   Mitch, W.A., Sedlak, D.L., 2004. Characterization and Fate of N-Nitrosodimethylamine Precursors in

472   Municipal Wastewater Treatment Plants. Environ. Sci. Technol. 38 (5), 1445-1454.

473   Muellner, M.G., Wagner, E.D., Mccalla, K., Richardson, S.D., Woo, Y., Plewa, M.J., 2007.

474   Haloacetonitriles vs. regulated haloacetic acids: Are nitrogen-containing DBPs more toxic? Environ.

475   Sci. Technol. 41 (2), 645-651.

476   Munch, D.J., Hautman, D.P. (1995) EPA Method 551.1 Determination of chlorination disinfection

477   byproducts, chlorinated solvents, and halogenated pesticides/herbicides in drinking water by liquid-

478   liquid extraction and gas chromatography with electron-capture detection, revision 1.0. Available online

479   from http://www.epa.gov/sam/pdfs/EPA-551.1.pdf, accessed April 22, 2009.

480   National Cancer Institute (1978) Bioassay of chloropicrin for possible carcinogenicity (CAS No. 76-06-

481   2). *National Toxicology Program Carcinogenesis Technical Report Series, U.S. Department of Health*

482   *and Human*.

483 Padhye, L., Wang, P., Karanfil, T., Huang, C., 2010. Unexpected role of activated carbon in promoting

484 transformation of secondary amines to N -nitrosamines. Environ. Sci. Technol. 44 (11), 4161-4168.

485 Plewa, M.J., Wagner, E.D., Jazwierska, P., Richardson, S.D., Chen, P.H., McKague, A.B., 2004.

486 Halonitromethane drinking water disinfection byproducts: Chemical characterization and mammalian

487 cell cytotoxicity and genotoxicity. Environ. Sci. Technol. 38 (1), 62-68.

488 Radjenovic, J., Petrovic, M., Barceló, D., 2009. Fate and distribution of pharmaceuticals in wastewater

489 and sewage sludge of the conventional activated sludge (CAS) and advanced membrane bioreactor

490 (MBR) treatment. Water Res. 43 (3), 831-841.

491 Reckhow, D.A., MacNeill, A.L., Platt, T.L., MacNeill, A.L., McClellan, J.N., 2001. Formation and

492 degradation of dichloroacetonitrile in drinking waters. J. Water Supply Res. Technol. AQUA 50 (1), 1-

493 13.

494 Schmidt, C.K., Sacher, F., Brauch, H. (2006) Strategies for minimizing formation of NDMA and other

495 nitrosamines during disinfection of drinking water. Proceedings of the American Water Works

496 Association Water Quality Technology Conference, Denver, CO.

497 Schneider, M., Quistad, G.B., Casida, J.E., 1999. Glutathione activation of chloropicrin in the

498 Salmonella mutagenicity test. Mutation Research/Genetic Toxicology and Environmental Mutagenesis

499 439 (2), 233-238.

500 Schreiber, I.M., Mitch, W.A., 2005. Influence of the order of reagent addition on NDMA formation

501 during chloramination. Environ. Sci. Technol. 39 (10), 3811-3818.

502 Schreiber, I.M., Mitch, W.A., 2006. Nitrosamine formation pathway revisited: The importance of

503 chloramine speciation and dissolved oxygen. Environ. Sci. Technol. 40 (19), 6007-6014.

504   Shen, R., Andrews, S., 2011. Demonstration of 20 pharmaceuticals and personal care products (PPCPs)

505   as nitrosamine precursors during chloramine disinfection. Water Res. 45 (2), 944-952.

506   Thibaud, H., de Laat, J., Merlet, N., Doré, M., 1987. Chloropicrin formation in aqueous solution: Effect

507   of nitrites on precursors formation during the oxidation of organic compounds (Formation de

508   chloropicrine en milieu aqueux: Influence des nitrites sur la formation de precurseurs par oxydation de

509   composes organiques). Water Res. 21 (7), 813-821.

510   U.S. Environmental Protection Agency (1987) Integrated Risk Information System (IRIS), N-

511   nitrosodimethylamine. Office of Research and Development (ORD), National Center for Environmental

512   Assessment. Available online from www.epa.gov/iris/subst/0045.htm, accessed October 20, 2008.

513   U.S. Environmental Protection Agency (1999) Alternative disinfectants and oxidants. EPA guidance

514   manual. Available online from

515   http://www.epa.gov/OGWDW/mdbp/alternative_disinfectants_guidance.pdf, accessed April 10, 2009.

516   U.S. Environmental Protection Agency (2004) Method 521: determination of nitrosamines in drinking

517   water by solid phase extraction and capillary column gas chromatography with large volume injection

518   and chemical ionization tandem mass spectrometry (MS/MS). EPA/600/R-05/054. Available online

519   from http://www.epa.gov/nerlcwww/m_521.pdf, accessed October 20, 2008.

520   Valentine, R.L., Jafvert, C.T., 1988. General acid catalysis of monochloramine disproportionation.

521   Environmental Science & Technology 22 (6), 691-696.

522   Yang, X., Shang, C., Westerhoff, P., 2007. Factors affecting formation of haloacetonitriles, haloketones,

523   chloropicrin and cyanogen halides during chloramination. Water Res. 41 (6), 1193-1200.

524 Zuccato, E., Calamari, D., Natangelo, M., Fanelli, R., 2000. Presence of therapeutic drugs in the

525 environment. The Lancet 355 (9217), 1789-1790.

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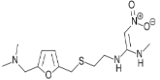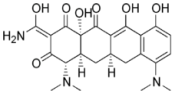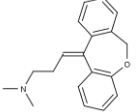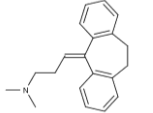
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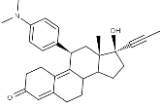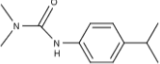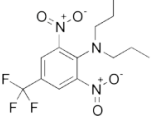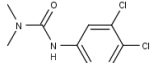
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Tables

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_2Cl 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.
Isoproturon		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 NH_2Cl 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

Table 2. Effect of pH and NO_2^- on NDMA formation from amitriptyline and mifepristone over 5 days with 10 mM buffer (phosphate for pH 8.5 and carbonate for pH 10).

Expt	Compound investigated	Compound concentration (µM)	NH$_2$Cl 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

[a]Molar yields were calculated based upon the initial compound concentration
[b]SD = Standard Deviation on 3 replicates

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560   Table 3. Effect of pH on NDMA and chlorinated DBPs formation from 3 μM ranitidine and 2.5 mM

561   NH$_2$Cl (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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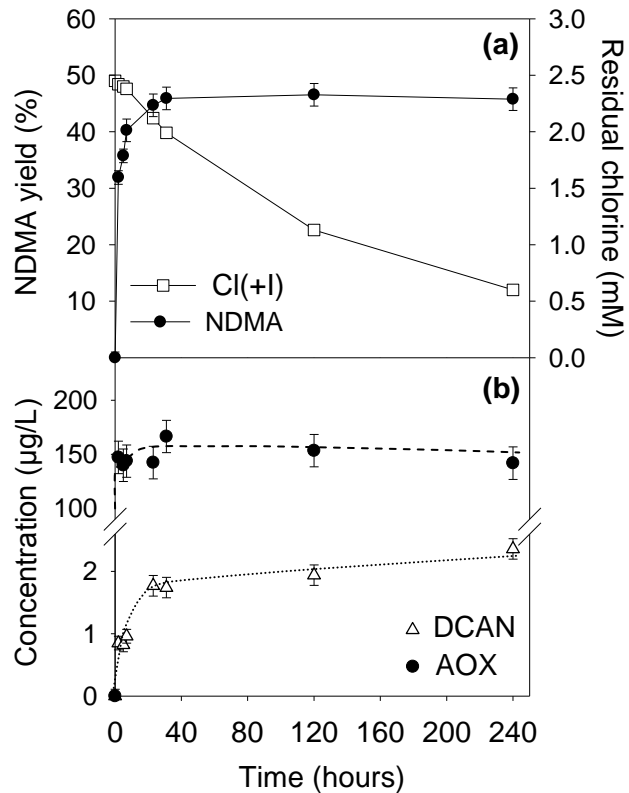
Figures

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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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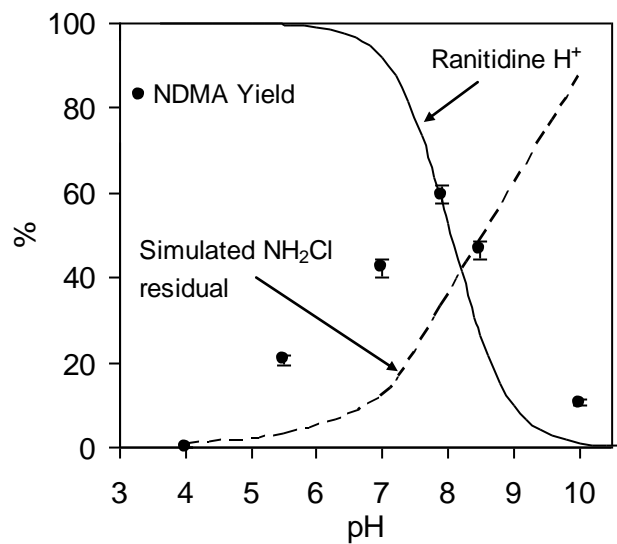
Figure 2. Effect of pH on NDMA formation from 3 μM ranitidine and 2.5 mM monochloramine over 5

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

NH_2Cl residuals calculated using Jafvert & Valentine model (1992). NDMA yields were calculated

based on the initial ranitidine concentration; percentages of NH_2Cl residuals were calculated based on

the initial NH_2Cl concentration.
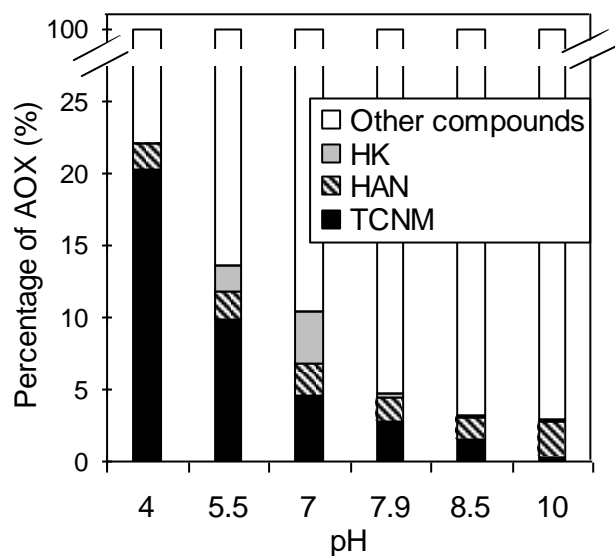
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595   Figure 3. AOX repartition between trichloronitromethane (TCNM), haloacetonitriles (HAN: sum of

596   DCAN and TCAN) and haloketones (HK: sum of 1,1-DCP and 1,1,1-TCP) at different pH from 3 µM

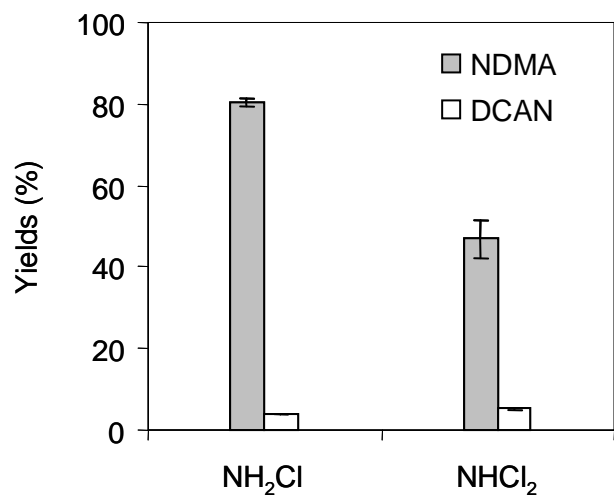597   ranitidine and 2.5 mM NH_2Cl. Note the scale break.

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

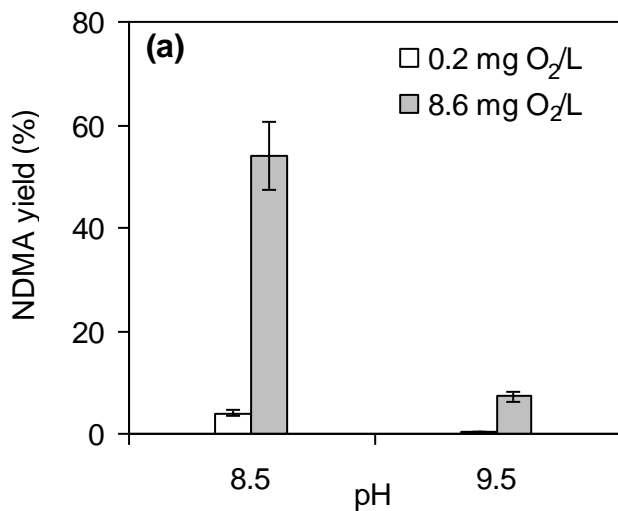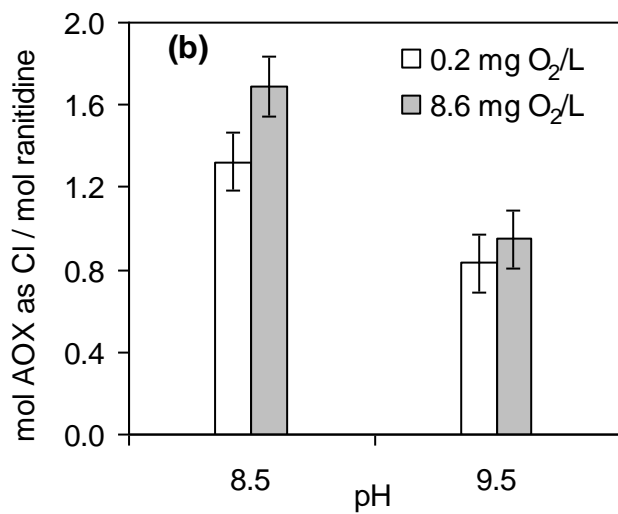or dichloramine to 100 nM ranitidine buffered at pH 8.
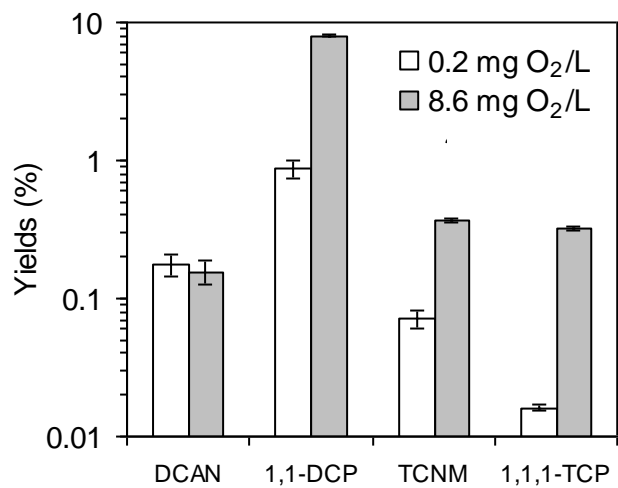
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615   Figure 5. Effect of dissolved oxygen and pH on (a) NDMA and (b) AOX formation from 3 μM

616   ranitidine and 2.7 mM NH_2Cl, over 2 h with 10 mM buffer. NDMA molar yields were calculated based

617   upon the initial ranitidine concentration.

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Figure 6. Effect of dissolved oxygen on DCAN, 1,1-DCP, TCNM and 1,1,1-TCP formation from 3 μM

ranitidine and 2.7 mM NH_2Cl over 2 h at pH 8.5 with 10 mM phosphate buffer.