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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 importance of structural characteristics of tertiary amines for NDMA formation. Among these compounds, the pharmaceutical ranitidine showed the highest molar conversion to NDMA. The pH and dissolved oxygen content of the solution were found to play a major role for the formation of NDMA from ranitidine. NDMA was formed in higher amounts at pH around pH 8 and a lower concentration of dissolved oxygen dramatically decreased NDMA yields. These findings seem to indicate that dichloramine ($NHCl_2$) is not the major oxidant involved in the formation of NDMA from ranitidine, results in contradiction with the reaction mechanisms proposed in the literature. Dissolved oxygen was also found to influence the formation of other oxygen-containing DBPs (i.e. trichloronitromethane and haloketones). The results of this study identify several anthropogenic precursors of NDMA, indicating that chloramination of waters impacted by these tertiary amines could lead to the formation of significant amounts of NDMA and other non-regulated DBPs of potential health concern (e.g. dichloroacetonitrile or trichloronitromethane). This could be of particular importance for the chloramination of wastewater effluents, especially during water reuse processes.

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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,b, 2003; Choi et al., 2002; Mitch and Sedlak, 2002; Schreiber and Mitch, 2005, 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, 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 nitrosamine precursors during chloramines disinfection. According to these authors, the presence of electron donating group such as furan can increase the electron density on the nitrogen atom and then favors the reaction with chlorine leading to high NDMA yields observed with some pharmaceuticals (especially ranitidine). Ranitidine is sold worldwide as a gastrointestinal drug and has been detected at concentrations ranging from 70 ng/L to 540 ng/L in primary effluents of wastewater treatment plants (WWTP) in Spain (Radjenovic et al., 2009) and at ~10 ng/L in several surface waters (Kolpin et al., 2002; Zuccato et al., 2000). Ranitidine and other pharmaceuticals are not well removed by biological treatments and can be found in river waters receiving the WWTP effluents (Castiglioni et al., 2006; Radjenovic et al., 2009). Chloramination of wastewaters (e.g. for wastewater reuse purposes) impacted by pharmaceuticals is of great concern because of the potential risk of NDMA formation.

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

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

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

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

2. Materials and methods

2.1. Materials

All experiments were conducted using deionized water (Milli-Q, Millipore) buffered with sodium acetate (pH = 4.0–5.5), a mixture of sodium phosphate monobasic and sodium phosphate dibasic (pH = 7.0–8.5), or sodium carbonate (pH = 10). pH values were adjusted as needed using sodium hydroxide or sulfuric acid (0.1 N, Fisher Scientific). Fluka Analytical methyl *tert*-butyl ether (>99%), Fisher Scientific methylene chloride (GLC grade) and Carlo Erba methanol (>99.9%) were used without further purification. Amitriptyline (>98%), diuron (>98%), doxepin (>98%), isoproturon (99.8%), mifepristone (>98%), minocycline (92%, 8% water), ranitidine and trifluralin (>99%) were used without further purification and were supplied through Sigma–Aldrich. Sodium hypochlorite (NaOCl, 13%, Acros Organics) and ammonium chloride (Fisher Scientific, 99.9%) were used to prepare chloramine reagents. Anhydrous sodium sulfite (Fisher Scientific) was used to quench residual chloramines. Isotopically labeled standards, [6-^{2}H] *N*-nitrosodimethylamine (NDMA-d6, 98%, 1 mg mL^{-1} in methylene chloride) and [14-^{2}H] *N*-nitrosodi-n-propylamine (DPNA-d14, 98%, 1 mg mL^{-1} in methylene chloride) were obtained from Cambridge Isotope Laboratories (Andover, MA, USA). A standard solution containing seven *N*-nitrosamines (2000 μg/mL each in methylene chloride) was purchased from Supelco (Sigma–Aldrich). The SPE materials used to extract nitrosamines from aqueous solutions consisted in Supelclean™ prepacked coconut charcoal EPA 521 tubes, 2 g/6 ml, supplied from Supelco. A mixed standard containing haloacetonitriles (HANs), trichloronitromethane (TCNM) and haloketones (HKs) (EPA 551B Halogenated Volatiles Mix) and internal standard 1,2-dibromopropane were supplied from Supelco. All reagents not specified were obtained from Fisher Scientific.

2.2. Preparation and analysis of chloramines

Monochloramine (NH_2Cl) stock solutions were prepared daily by slowly adding sodium hypochlorite (NaOCl) into a rapidly stirred ammonium chloride (NH_4Cl) solution adjusted to pH = 8.5 with sodium hydroxide, and using a Cl:N M ratio of at least 1:1.2 to avoid breakpoint chlorination resulting from local excess of hypochlorite (Mitch and Sedlak, 2002). Adjusting the pH at 8.5 minimizes the disproportionation of NH_2Cl to dichloramine ($NHCl_2$), since $NHCl_2$ forms at pH < 8 (U.S. Environmental Protection Agency, 1999) according to the equilibrium:

$$2NH_2Cl + H^+ = NHCl_2 + NH_4^+ \quad (1)$$

Free chlorine and total chlorine concentrations in the stock solutions of sodium hypochlorite were determined iodometrically with sodium thiosulfate 0.1 M (Prolabo, >99.9%). Initial NH_2Cl and $NHCl_2$ concentrations were determined by spectrophotometric measurement using their respective molar extinction coefficients at 245 nm and 295 nm and solving simultaneous equations (Schreiber and Mitch, 2005). Residual chloramines were analyzed iodometrically (Eaton et al., 1995).

2.3. Chloramination experiments

All glassware used during these experiments was washed with deionized water and baked at 500 °C for at least 5 h prior to use. Reactions were conducted in sealed 1 L amber glass bottles at 20 °C in a temperature-controlled room, under dark conditions to avoid photolysis of NDMA. Chloramination experiments were conducted following the approach of Mitch et al. (Mitch et al., 2003), using high concentrations of NH_2Cl (200–300 mg/L as Cl_2) and a reaction time of 5 days for most of our experiments. NH_2Cl remained in excess during all the reaction time. Solutions were prepared by dissolving a predetermined amount of compound in 1 L of 10 mM acetate, phosphate or carbonate buffer. 100 mL of preformed monochloramine was then added to the working solution. Chloramination experiments were conducted in triplicate. All series of experiments were completed with the chloramination of a corresponding blank solution.

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

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

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

AOX formation rates were calculated as follows:

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

2.4. Influence of dissolved O_2

Experiments were performed in saturated dissolved O_2 solution and in absence of oxygen. The removal of oxygen was operated prior to chloramination by bubbling nitrogen gas through a Teflon line until dissolved O_2 concentration was less than 0.3 mg O_2/L. The dissolved O_2 concentration was monitored using a WTW Oxi 330 oxygen meter. The samples were continuously bubbled until the end of the experiment (2 h contact time). Previous experiments were conducted with NDMA standard solutions in order to verify that nitrogen bubbling for 2 h did not lead to any significant NDMA or chlorinated DBPs stripping.

2.5. Analytical methods

2.5.1. Nitrosamines analysis

NDMA analysis was performed according to the US EPA method (U.S. Environmental Protection Agency, 2004), consisting in a solid-phase extraction (SPE) using coconut charcoal EPA 521 tubes followed by GC/MS analysis in EI mode. Analytical details are provided elsewhere (Le Roux et al., 2010) and summarized below. Chloramination reactions were quenched using 2.5 g sodium sulfite before SPE. Unlike previous studies (Chen and Young, 2009; Schreiber and Mitch, 2006), no ascorbic acid was used because it was found to degrade into furfural during SPE in coconut charcoal tubes, which led to poor NDMA recovery. Prior to the extraction, 200 ng of NDMA-d6 was added to each 1 L sample as an internal standard. Each sample was extracted at a continuous flow rate through the SPE tube. Analytes were eluted from the SPE bed with 15 mL of methylene chloride. Extracts were then filtered through 5 g anhydrous sodium sulfate column to remove residual water. Methylene chloride extracts were then concentrated down to 1 mL under a stream of N_2, after addition of DPNA-d14 (200 ng) used as recovery standard. Samples extracts were analyzed immediately after SPE using a HP 6890 series gas chromatograph system coupled with a HP 5973 mass selective detector (MSD) in electron impact (EI) mode. Samples were injected in pulsed splitless mode using helium as the carrier gas. A Varian VF-5ms capillary column (30 m by 0.25 mm i.d. by 0.25 μm film thickness) supplied through Interchim was used to separate the analytes. Quantitative analyses were performed in selected-ion monitoring (SIM) mode. Full scan mode (40–240 *m/z*) analyses were also conducted for complementary spectral information. This method reached extraction efficiencies of approximately 85%. The method detection limit (MDL) for NDMA at the 99% confidence level was determined to be 33 ng/L.

2.5.2. HANs, HKs, TCNM and AOX analysis

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

3. Results and discussion

Fig. 1 shows as example the kinetic results for AOX, DCAN and NDMA formation obtained with 3 μM ranitidine and 2.5 mM

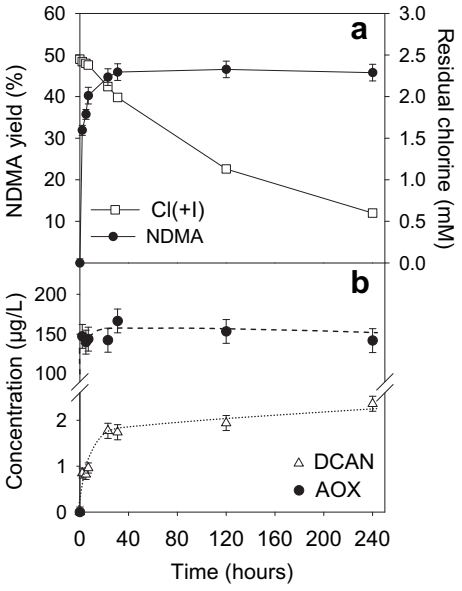
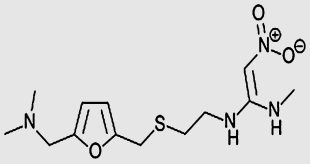
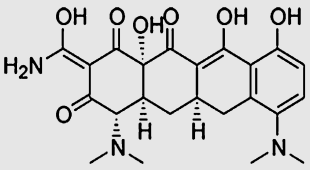
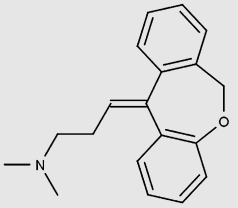
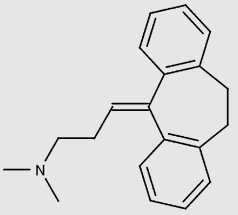
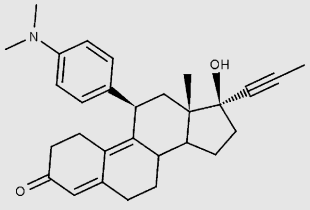
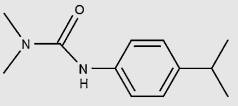
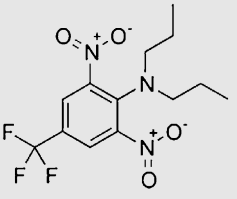


Fig. 1 – NDMA formation from 3 μM ranitidine at pH 8.5 with 10 mM phosphate buffer, 2.5 mM monochloramine. Error bars represent one standard deviation ($n = 3$). NDMA molar yields were calculated based upon the initial ranitidine concentration.

NH_2Cl at pH 8.5. NH_2Cl consumption over 120 h was always about 50% of the initial concentration. Same results were obtained for the other investigated compounds. Results from control samples exhibited similar chloramine decay. Kinetic modeling performed using Copasi software and Jafvert and Valentine's model (Jafvert and Valentine, 1992) confirmed that monochloramine (NH_2Cl) predominantly decays by self-disproportionation under our experimental conditions (pH 8.5, 10 mM phosphate buffer). Hence, the consumption of NH_2Cl by the model compounds investigated was insignificant and could not be quantified. AOX formation leveled off after only 2 h contact time, whereas NDMA and DCAN formation were slower and reached their maximum after 24 h. This observation is in accordance with results from the chlorination of proteins (one of the most important precursors of DCAN in drinking waters), that shows a two-step process (Reckhow et al., 2001). First, rapid reactions with reactive sites form THMs and Total Organic Halides (TOX) (Hureiki et al., 1994), then slow degradation of proteins leads to DCAN formation. A similar behavior for DBPs formation kinetics could occur during the chloramination of ranitidine.

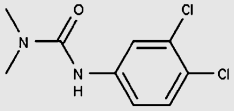
The formation of NDMA, HANs and AOX at pH 8.5 from selected compounds was monitored after 5 days of contact time (Table 1). Ranitidine exhibited the highest molar yield with 40.2% NDMA formed. Similar amounts of NDMA were produced after 5 days of contact time for initial monochloramine concentrations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

Table 1 – Nitrosamine and DCAN formation from compounds investigated at pH 8.5 (5 days contact 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	40.22 (1.43)	5.8 (0.2)	0.95 (0.18)
Minocycline		2820	2.5	8.21 (0.72)	1.5 (0.1)	8.98 (0.89)
Doxepine		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.

(continued on next page)

Table 1 (*continued*)

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	
Diuron		16560	4.0	0.15 (0.01)	N.D.	N.D.

N.D. = Not Detected.

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.

Compounds presenting heterocyclic ring in their structure (e.g. furan in ranitidine) produced more NDMA than compounds with DMA functions near carbonyl groups (i.e. diuron and isoproturon) (Schmidt et al., 2006) and compounds with aromatic rings (e.g. minocycline or mifepristone). According to Shen and Andrews (2011), the higher yield observed for ranitidine would be explained by the electron-donating effect of furan group that increases electron density on the nitrogen atom and thus enhance electrophilic substitution of chlorine atom. This mechanism would involve the formation of dimethylchloramine (DMCA), DMA and then NDMA (Mitch and Sedlak, 2004). However, the presence of DMA as a key intermediate could not explain the high yield obtained with ranitidine because the NDMA yields from DMA are always < 3% in literature. An alternative mechanism would involve the nucleophilic substitution of NH_2Cl on nitrogen atom instead of electrophilic substitution (i.e. chlorine transfer with formation of a DMCA group). Further research is needed to fully address the formation mechanism of NDMA from dimethylaminomethylfuran group.

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

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

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

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

3.1. *Influence of nitrites*

Previous research (Choi and Valentine, 2003) proposed an "enhanced nitrosation pathway" describing NDMA formation

from the reaction of DMA with nitrite and hypochlorite. Nitrites were also found to enhance the formation of NDMA during the chlorination of diuron (Chen and Young, 2009). Because low amount of free chlorine may be present in monochloramine solution, nitrites could contribute to the formation of NDMA by chloramination. Experiments conducted with 1 μM amitriptyline and 1 μM mifepristone showed that NDMA formation was not significantly different in presence and in absence of 1 μM nitrites (Table 2). These results indicate that the formation of NDMA from tertiary amines during chloramination is not enhanced by any nitrosation mechanism, which could have occurred in presence of free chlorine and nitrites.

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

3.2. *Effect of pH*

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

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

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

3.3. *Influence of dichloramine*

To evaluate the influence of $NHCl_2$ on NDMA formation from ranitidine, preformed $NHCl_2$ or NH_2Cl (1 mM) were applied to

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_2Cl 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.

ranitidine solutions. Previous research indicated that NDMA formation from DMA and $NHCl_2$ was much higher than in the presence of NH_2Cl (Schreiber and Mitch, 2006). Our results showed that NDMA formation from 100 nM ranitidine buffered at pH 8 and after 24 h was significantly lower with $NHCl_2$ than with NH_2Cl (46.8% and 80.2% molar yields respectively, Fig. 4).

Total chlorine decay during our experiments with $NHCl_2$ was about 85% after 24 h, while it was only 25% with NH_2Cl. Thus, $NHCl_2$ decomposition is more rapid than NH_2Cl at pH around pH 8, which could explain why less NDMA was formed in presence of $NHCl_2$. The autodecomposition of $NHCl_2$ in our experiments could be well simulated by the kinetic model of Jafvert and Valentine (1992). According to this model, the hydrolysis of dichloramine (Equation (4)) and inverse dismutation (Equation (5)) lead to the formation of significant amounts of monochloramine.

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

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

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

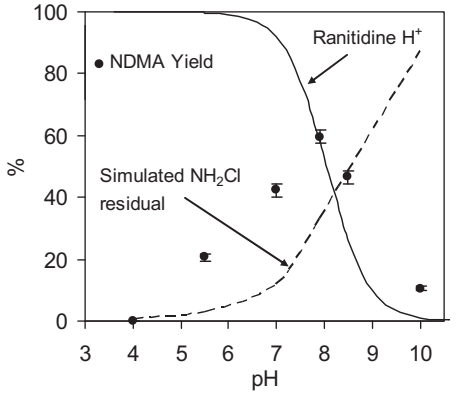


Fig. 2 – Effect of pH on NDMA formation from 3 μM ranitidine and 2.5 mM monochloramine over 5 days with 10 mM buffer (acetate for pH 4.0–5.5, phosphate for pH 7.0–8.5 and carbonate for pH 10); and NH_2Cl residuals calculated using Jafvert and Valentine model (1992). NDMA yields were calculated based on the initial ranitidine concentration; percentages of NH_2Cl residuals were calculated based on the initial NH_2Cl concentration.

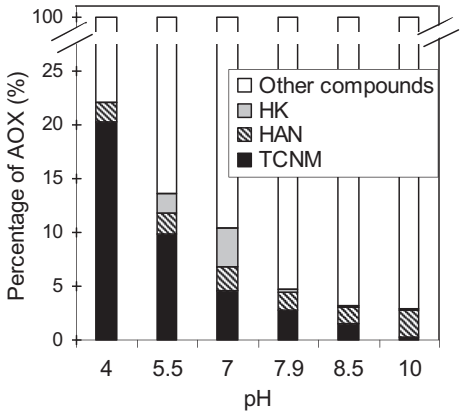


Fig. 3 – AOX repartition between trichloronitromethane (TCNM), haloacetonitriles (HAN: sum of DCAN and TCAN) and haloketones (HK: sum of 1,1-DCP and 1,1,1-TCP) at different pH from 3 μM ranitidine and 2.5 mM NH_2Cl. Note the scale break.

3.4. *Influence of dissolved oxygen*

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

In order to assess whether or not dissolved oxygen would influence the formation of NDMA from the chloramination of other model compounds, 2.7 mM NH_2Cl was applied to 3 μM ranitidine during 2 h in presence and in absence of dissolved O_2. NDMA formation was significantly inhibited for low oxygen concentration (~ 0.2 mg O_2/L) compared to ambient O_2 concentration (~ 9 mg O_2/L) (molar yields of 4.01% and 54% respectively, Fig. 5a).

Dissolved O_2 concentration did not affect AOX formation as much as NDMA formation (Fig. 5b). Moreover, DCAN

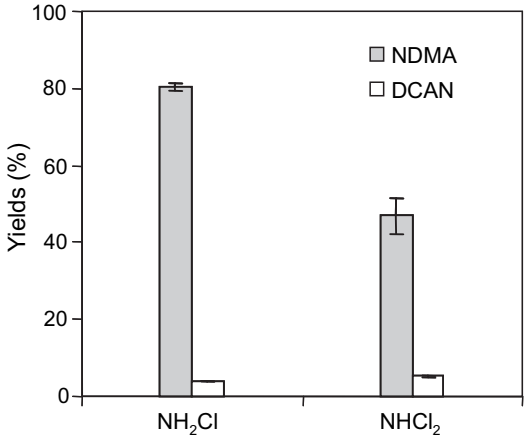


Fig. 4 – NDMA and DCAN formation after 24 h following the application of 1 mM monochloramine or dichloramine to 100 nM ranitidine buffered at pH 8.

formation was not influenced by dissolved O_2 concentration while the formation of other halogenated DBPs containing oxygen atoms (nitro or ketones functional groups, i.e. TCNM, 1,1-DCP and 1,1,1-TCP) was approximately an order of magnitude lower in the presence of 0.2 mg O_2/L (Fig. 6). This indicates that dissolved oxygen could be incorporated into those DBPs, i.e. an oxygen atom of dissolved oxygen could serve as a source for the oxygen atom in nitroso or ketone functions of DBPs. Further research with model compounds and using inhibitors of oxygen species need to be done to elucidate the mechanisms involved into the formation of NDMA and to understand the role of dissolved oxygen.

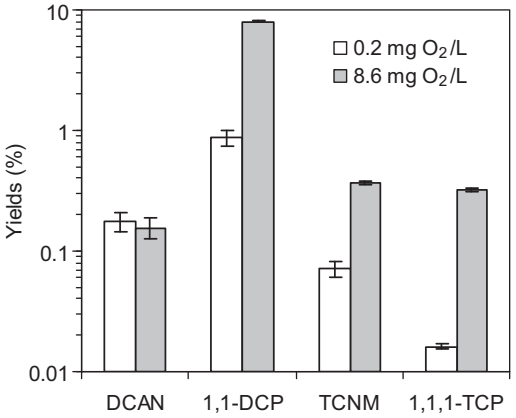


Fig. 6 – Effect of dissolved oxygen on DCAN, 1,1-DCP, TCNM and 1,1,1-TCP formation from 3 μM ranitidine and 2.7 mM NH_2Cl over 2 h at pH 8.5 with 10 mM phosphate buffer.

4. Conclusion

- Even if concentrations of compounds used for our study were relatively high and are not likely to be found in natural waters, we observed that several nitrogenous anthropic compounds can lead to important concentrations of N-DBPs including NDMA, DCAN, 1,1-DCP, or TCNM. From the seven compounds investigated in our study, four compounds contain dimethylamine functional groups and exhibited yields higher than 1.15% (ranitidine, minocycline, doxepin, amitriptyline). Especially, the pharmaceutical ranitidine is of great concern regarding its high molar yield into NDMA (~60% at pH 7.9), as shown in earlier studies.
- Such differences in NDMA formation can not be explained by the release of DMA and the reactions of DMA with chloramines. More simple compounds than those described in the present work need to be studied to improve our understanding of molecular structure influence on the formation of NDMA.
- Our results demonstrate that the reaction of $NHCl_2$ with ranitidine would not form more NDMA than NH_2Cl. However, we confirmed the implication of dissolved oxygen in NDMA formation mechanisms. Dissolved oxygen was found to play a role into the formation of other oxygen-containing DBPs (TCNM, 1,1-DCP and 1,1,1-TCP) but did not influence DCAN formation. These results need further investigation to better understand the incorporation of dissolved oxygen into DBPs.
- Considering the high conversion of ranitidine to NDMA, the use of chloramination as a disinfection for wastewaters containing ranitidine can lead to the formation of important amounts of NDMA. This could explain the high NDMA formation potentials observed at several WWTP, which are much higher than concentrations predicted based upon DMA concentrations in raw waters.

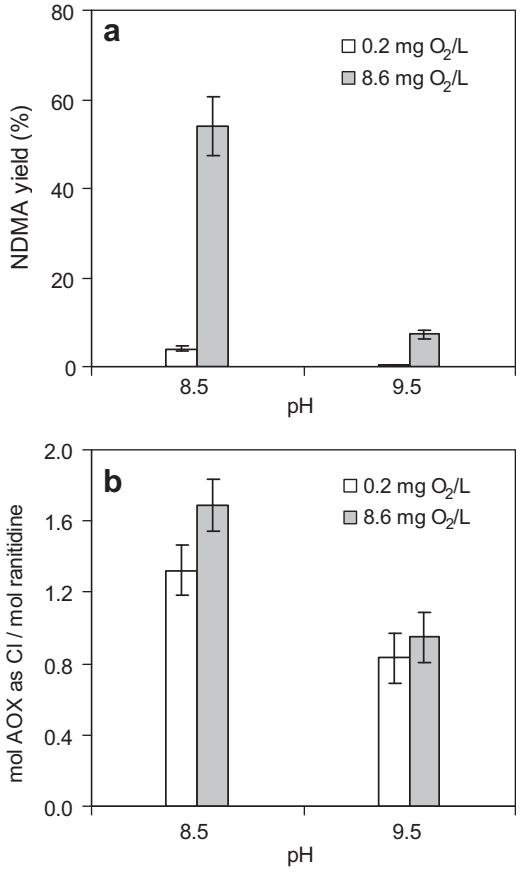


Fig. 5 – Effect of dissolved oxygen and pH on (a) NDMA and (b) AOX formation from 3 μM ranitidine and 2.7 mM NH_2Cl, over 2 h with 10 mM buffer. NDMA molar yields were calculated based upon the initial ranitidine concentration.

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