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# Demonstration of 20 pharmaceuticals and personal care products (PPCPs) as nitrosamine precursors during chloramine disinfection

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ABSTRACT

The worldwide detection of pharmaceuticals and personal care products (PPCPs) in the aquatic environment and drinking water has been a cause for concern in recent years. The possibility for concurrent formation of nitrosamine DBPs (disinfection by-products) during chloramine disinfection has become another significant concern for delivered drinking water quality because of their potent carcinogenicity. This study demonstrates that a group of PPCPs containing amine groups can serve as nitrosamine precursors during chloramine disinfection. Molar yields higher than 1% are observed for eight pharmaceuticals, with ranitidine showing the strongest potential to form N-nitrosodimethylamine (NDMA). The molar conversion increases with the $Cl_2$:N mass ratio, suggesting that dichloramine is relevant to the formation of NDMA from these precursors. Although the trace level of PPCPs in the environment suggests that they may not account for the majority of nitrosamine precursors during the disinfection process, this study demonstrates a connection between the transformation of PPCPs and the formation of nitrosamines during chloramine disinfection. This both expands the pool of potential nitrosamine precursors, and provides a possible link between the presence of trace levels of certain PPCPs in drinking water sources and potential adverse health effects.



## 1. Introduction

Pharmaceuticals and personal care products (PPCPs) are a group of compounds including pharmaceutical drugs, cosmetic ingredients, food supplements, and ingredients in other consumer products such as shampoos and lotions. They have gained much attention in recent years with the worldwide increasing consumption of these substances and their frequent detection in the aquatic and terrestrial environment, ranging from ng/L to lower μg/L (Calamari et al., 2003; Conley et al., 2008; Godfrey et al., 2007; Jasim et al., 2006; Kasprzyk-Hordern et al., 2008; Kolpin et al., 2002, 2004; Metcalfe et al., 2003; Servos et al., 2007; Zuccato et al., 2005). However, many of the compounds that have been detected and studied only comprise a small subset of the whole PPCP family. Most research projects have been focused on the removal of PPCPs using different treatment processes, but data in terms of their degradation or transformation products during these processes are largely lacking. In particular, there is quite limited information on the transformation of PPCPs upon drinking water disinfection.

Concurrently, formation of nitrosamines during chloramine disinfection has become a significant issue for delivered drinking water quality because of their potential

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carcinogenicity, especially with the switch of secondary disinfectant from free chlorine to chloramine gaining much popularity in recent years. Compared with free chlorine, chloramine can maintain a more stable residual in the distribution system and can form less regulated disinfection by-products (DBPs) such as trihalomethans (THMs) and haloacetic acids (HAAs). However, chloramine has been more commonly associated with the formation of emerging nitrosamine DBPs than free chlorine. Up to now, there are no federal regulations about nitrosamines in North America, but the USEPA has placed six nitrosamines on the Unregulated Contaminant Monitoring Rule List 2 (USEPA, 2006). The Ontario Ministry of the Environment (MOE) has established an interim maximum acceptable concentration of 9 ng/L for N-Nitrosodimethylamine (NDMA) in drinking water (MOE, 2003). The California Department of Health Services (CDHS) has implemented a notification limit of 10 ng/L of NDMA, and the California Office of Environmental Health Hazard Assessment (OEHHA) has set up a public health goal for NDMA at 3 ng/L (OEHHA, 2006).

A considerable amount of research has been conducted to investigate the potential precursors of nitrosamines, especially NDMA. The most well-known NDMA precursors related to water and wastewater treatment include dimethylamine (DMA; Mitch et al., 2003), tertiary and quaternary amines containing DMA groups (Kemper et al., 2010; Lee et al., 2007), natural organic matter (NOM) (Chen and Valentine, 2007; Dotson et al., 2007; Gerecke and Sedlak, 2003; Krasner et al., 2008; Mitch and Sedlak, 2004), polyelectrolytes and resins used in water and wastewater treatment plants (Kohut and Andrews, 2003; Mitch and Sedlak, 2004; Najm and Trussell, 2001; Wilczak et al., 2003), and some agriculturally related fungicides and herbicides (Chen and Young, 2008; Graham et al., 1995; Schmidt and Brauch, 2008). However, current research regarding the potential precursors cannot account for all the nitrosamines detected, based on their yields during drinking water disinfection, indicating the possibility of other as yet unknown precursors. Ranitidine, one of the most prescribed drugs in the world, has been demonstrated to render a high conversion rate to NDMA upon chloramination (Sacher et al., 2008; Schmidt et al., 2006). Some early studies have also reported the formation of nitrosamines via amine drugs in the stomach (Lijinsky and Taylor, 1977; Andrews et al., 1980). Therefore, it is possible that drugs with tertiary or quaternary amine groups might contribute to the formation of nitrosamines during drinking water disinfection. So far, very limited information is available regarding the formation of nitrosamines via PPCPs. Krasner (2009) has suggested the possibility of amine-based pharmaceuticals and their breakdown products to be part of the NDMA precursor pool in wastewater effluent organic matter (EfOM), but no further results have been reported so far.

The current study demonstrates the transformation of 20 selected PPCPs to form nitrosamines. PPCPs containing DMA or diethylamine (DEA) in their structures were selected as potential precursors for NDMA and N-Nitrosodiethylamine (NDEA), respectively. Selection of target compounds was also based on their prevalence in the North American pharmaceutical markets and/or their frequent detection in the environment.

## 2. Materials and methods

Experiments were conducted using both Milli-Q® water produced from an Ultra Pure Water System (MilliPore, Bioprocess Division, Etobicoke, Ontario) and tap water from Toronto, Ontario. Nineteen pharmaceutical compounds and one personal care product (i.e., N, N-diethyltoluamide (DEET)) were tested in terms of their potential to form nitrosamines during chloramination.

### 2.1. Materials

Chemical structures of the selected PPCPs are summarized in Fig. 1. Stock solutions of PPCPs were prepared in methanol and stored at 4 °C until use. NDMA and NDEA (reagent grade) were used as standards, and deuterated NDMA ($d_6$-NDMA, 98 atom % D) was used as the internal standard for both compounds. All of these chemicals were purchased from Sigma–Aldrich Canada (Oakville, Ontario).

Phosphate buffer (pH = 7.0) was made by dissolving 62 g $KH_2PO_4$ and 78 g $Na_2HPO_4$ into 1 L of Milli-Q® water. Chlorine stock solution (4000–6000 mg/L as $Cl_2$) was prepared by diluting 10 times of the 4–6% bleach and stored at 4 °C. Monochloramine dosing solution was prepared fresh daily by mixing an ammonium chloride solution and a chlorine stock solution at a desired $Cl_2$:N mass ratio, and equilibrating for at least 1 h before use. The actual concentrations of chlorine stock solution, monochloramine dosing solution, and the final test solutions were determined using DPD colorimetry (DR2010 HACH-Kit). L-ascorbic acid was used to quench chloramine and stop the reaction following each test period.

### 2.2. Nitrosamine formation tests

Nitrosamine formation potential (FP) tests were conducted in 1 L amber bottles with LDPE (low-density polyethylene) caps, adopted from standard operating procedures for DBP yields under uniform formation conditions (Summers et al., 1996). FP tests usually apply high doses of disinfectants to predict the ultimate formation potential; while the Simulated Distribution System (SDS) tests (Koch et al., 1991) simulate the conditions common to water treatment plants and distribution systems. The two sets of general experimental conditions applied in the current study are summarized in Table 1, only differing in the concentrations of chloramine applied: 28.4 mg/L for the modified FP (MFP) tests was adopted from Schmidt et al. (2006), while 2.5 mg/L for the SDS tests met the requirement for chloraminated distribution system allowed by the Ontario Drinking Water Quality Standards (MOE, 2006). Sample pH was controlled by the addition of 2 mL/L of phosphate buffer solution. Reactions were halted after 24 h by the addition of excess ascorbic acid powder (approximately 300 mg per 1 L water sample).

### 2.3. Nitrosamine analysis

The procedure for extraction and concentration of nitrosamines (NDMA and NDEA) in water samples was adopted from that reported by Taguchi et al. (1994). An aliquot of 500 mL

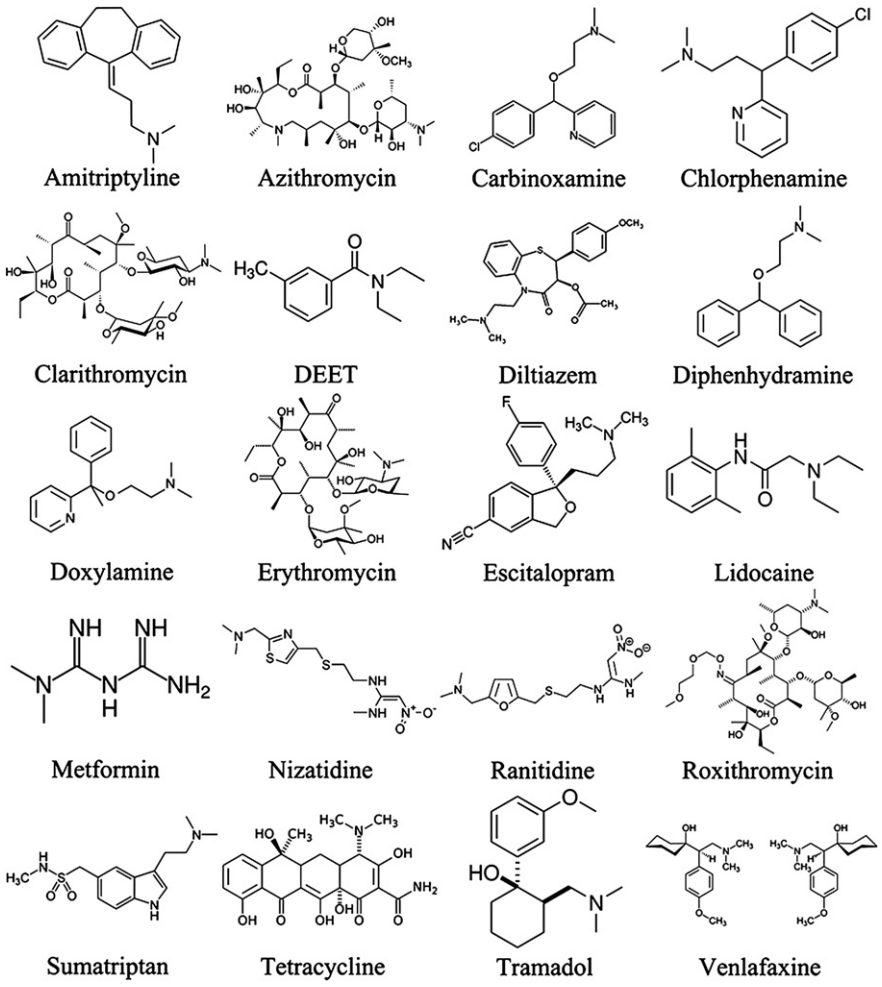


**Fig. 1 – Structures of selected PPCPs.**

sample was transferred to a clean 1 L amber bottle with an LDPE cap. After the addition of internal standard $d_6$-NDMA (50 ng/L in 500 mL sample) and 200 mg of Lewatit® AF 5 beads (conditioned at 320 °C for 3 h before use), the bottle was swirled at 250 rpm for 1 h on an orbit shaker (Thermolyne Bigger Bill M49235, Barnstead International, Asheville, N.C., USA). The beads were then collected by filtration, air dried for 20 min, transferred to a 2.0 mL autosampler vial, and further air dried for at least 1 h. Finally, 500 μL of dichloromethane (DCM, 99.9%) was added to extract nitrosamines from the beads. The cap for the GC vial was Teflon-lined and contained no rubber. Extracted nitrosamines in DCM could be stored in amber vials at −15 °C or less for up to 28 days after sample extraction (Munch and Bassett, 2004).

The extracted samples were analyzed via a Varian 3800 GC coupled with a Varian 4000 ion trap mass spectrometer and CombiPAL autosampler. The injector was fitted with a Carbofrit liner (Chromatographic Specialties; 3.4 mm ID and 5.0 mm OD; 54 mm length) and a programmed temperature vaporizer (PTV), and a DB 1701 column (30 m × 0.25 mm × 0.25 μm) was employed. Chemical ionization (CI) was applied with methanol as the reagent liquid. 8 μL of sample was injected into the GC through the PTV inlet, with the initial temperature of 25 °C held for 0.8 min, increased by 200 °C/min to 240 °C, and held for 24 min. Coolant was enabled at 200 °C after the run to bring the injector back to the initial temperature. Column flow was 1.2 mL/min, with a pressure pulse of 19 psi held for 4 min. Oven temperature was initially held at 35 °C for 5.5 min, increased by 15 °C/min to 155 °C, and further increased by 40 °C/min to 240 °C which was held for 10 min. Filament delay was 8.2 min. CI parameters were as follow: 3 μScan; emission current of 50 μAmps; electron multiplier offset of +300 V. NDMA and $d_6$-NDMA were both eluted at a retention time of 8.6 min, with indicating ions monitored at 75 and 81 amu, respectively. NDEA was eluted at a retention time of 10.5 min with the major indicating ion monitored at 103 amu.

### 2.4. QA/QC

Quantification of nitrosamines was attained through internal calibration using deuterated internal standard ($d_6$-NDMA). The calibration standards were subjected to the same extraction process as water samples in order to account for recovery. A calibration curve was prepared together with each set of water samples. Interference from the background of water samples was accounted for using blank control sample.

**Table 1 – Nitrosamine-FP experimental conditions.**

| Experimental conditions | MFP | SDS |
|---|---|---|
| pH | 7.0 ± 0.1 | 7.0 ± 0.1 |
| Temperature | 21 °C | 21 °C |
| Incubation time | 24 h | 24 h |
| $Cl_2$:N mass ratio | 4.2:1 | 4.2:1 |
| Chloramine dosage | 28.4 ± 0.2 mg/L | 2.5 ± 0.2 mg/L |

All samples and blanks were prepared in triplicate. Error bars in all the graphs demonstrate the variability due to multiple formation potential tests ($n$ = 3) under the same reaction conditions.

## 3. Results and discussion

### 3.1. Nitrosamine-FP under MFP conditions

Nitrosamine-FP upon chloramination was determined for all twenty selected PPCPs under the MFP conditions, in both Milli-Q® and tap water. Results are summarized in Fig. 2. Among the tested PPCPs, eight pharmaceuticals showed molar conversions higher than 1% (i.e., 18.5 ng/L of NDMA or 25.5 ng/L of NDEA formed). Ranitidine rendered the highest conversion (89.9–94.2%), followed by doxylamine (8.0–9.7%), sumatriptan (6.1%), chlorphenamine (5.2–5.5%), nizatidine (4.5–4.8%), diltiazem (2.1–2.6%), carbinoxamine (1.0–1.4%) and then tetracycline (0.8–1.2%). In both types of water, the nitrosamine-FP varied generally within ±25% for most compounds, with somewhat higher variability observed for limited tests in Milli-Q® water with the four macrolide antibiotics (azithromycin, clarithromycin, erythromycin, and roxithromycin; ±30–60%). Additional MFP tests that were performed with ranitidine indicated that the overall NDMA-FP from ranitidine varied within ±5% ($n$ = 9).

The selected PPCPs can be treated as tertiary amines containing DMA/DEA functional groups. Mitch and Schreiber (2008) have discussed the degradation pathways for model tertiary amines to form nitrosamines during chloramination, involving a chlorine transfer from the chloramine to the nitrogen atom in the tertiary amines as the rate-limiting step. Because it is an electrophilic chlorine substitution, the nature of moieties close to the DMA/DEA group can influence the reaction rate and thus affect the molar conversions. Generally, an electron-donating group (EDG) close to the DMA/DEA group can increase the electron density on the nitrogen atom and thus help attract chlorine; while an electron-withdrawing group (EWG) can decrease the electron density and slow down the reaction. Moreover, the reactivity may also be affected by the steric hindrance between the EDG/EWG and the electrophile (i.e., chlorine).

In this study, the eight pharmaceuticals showing high NDMA-FPs all have the DMA group bound to an electron-rich moiety. Ranitidine and nizatidine, two $H_2$-antihistamines, both have the DMA group bound to the C2 site of a five-element heterocyclic ring; but ranitidine has a much higher molar conversion than nizatidine. This is because C2 on the furan ring of ranitidine is a strong electrophilic site due to the electron-donating effect of the oxygen heteroatom, while C2 on the thiazole ring of nizatidine is a slight nucleophilic site because of the combined effects from the nitrogen and the sulfur atoms. Sumatriptan and diltiazem have the DMA bound to an electron-donating indole and benzothiazepine structure, respectively; however, there are two carbons between the EDG and the DMA group, weakening the electron-donating effects. In terms of the three structurally similar $H_1$-antihistamines

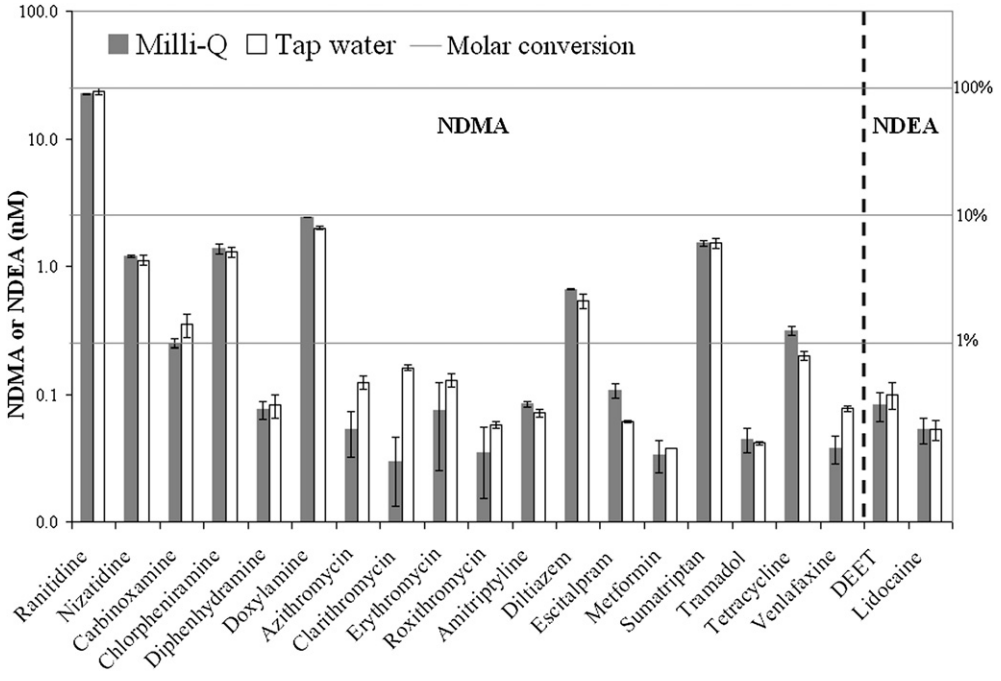


**Fig. 2 – Nitrosamine-FPs for selected PPCPs under the MFP conditions (Initial concentration of PPCPs = 25 nM).**

**Table 2 – Comparisons with literature (MFP conditions: pH = 7, chloramine = 28.4 mg/L, PPCPs = 25 nM, room temperature).**

| Compound | Schmidt et al., 2006 (Drinking water, 7d) | | Present data (Milli-Q® water, 24 h) | | Present data (Tap water, 24 h) | |
|---|---|---|---|---|---|---|
| | NDMA (ng/L) | Molar conversion (%) | NDMA (ng/L) | Molar conversion (%) | NDMA (ng/L) | Molar conversion (%) |
| Ranitidine | 1200 | 62.9 | 1665 ± 6 | 89.9 ± 0.3 | 1744 ± 82 | 94.2 ± 4.4 |
| Nizatidine | 91 | 4.9 | 88.0 ± 1.3 | 4.8 ± 0.1 | 82.7 ± 6.9 | 4.5 ± 0.4 |
| Tetracycline | 23 | 1.2 | 23.0 ± 1.6 | 1.2 ± 0.1 | 14.9 ± 1.0 | 0.8 ± 0.1 |

(carbinoxamine, chlorphenamine, and doxylamine), they all have the electron-rich bulky aromatic system in their structures, but the distance between the aromatic structure and the DMA group is farther than that of ranitidine, resulting in the overall lower molar conversions.

For the rest of the PPCPs showing low molar conversions, lidocaine and DEET have the DEA bound to an electron-withdrawing carbonyl group, and thus both showed very low yields of NDEA. A similar structure is observed for metformin, which has the DMA group bound to an electron-withdrawing biguanide. Amitriptyline and escitalopram have a long alkyl carbon chain between the DMA group and the bulky aromatic system, and this weakens the electron-donating effect. In the case of tramadol, venlafaxine, and the four macrolide antibiotics (azithromycin, clarithromycin, erythromycin, and roxithromycin), they have complicated steric structures close the DMA group, which may hinder the chlorine transfer reaction.

The results were generally in good agreement with a previous study by Schmidt et al. (2006), as summarized in Table 2. Ranitidine gave a much higher yield of NDMA in the present study than reported in the literature, even with a shorter reaction time. However, there was not enough information available on the characteristics of the drinking water matrix used in the literature, and thus it was difficult to further compare the results and explain the discrepancy. Further studies would be needed to determine the potential impact from various water matrices relevant to drinking water.

### 3.2. *Nitrosamine-FP under SDS conditions*

SDS conditions are usually applied to mimic practical disinfection conditions common to water treatment plants and distribution systems. Nitrosamine-FP upon chloramination under the SDS conditions was determined for the eight pharmaceuticals which rendered an NDMA molar conversion higher than 1% under MFP conditions. The results are summarized and compared with MFP results in Fig. 3. No significant difference was observed regarding the NDMA molar conversion between the two sets of conditions (paired *t*-test, 95% confidence level). Under either condition, the relative amount of chloramine was in large excess relative to that of the pharmaceuticals (mg/L vs. μg/L), suggesting that the reaction is not limited by the availability of chloramine and that essentially complete reactions can be achieved under the SDS conditions. It also indicates that the eight pharmaceuticals are capable of forming NDMA under the practical chloramine disinfection conditions.

SDS tests for the eight target pharmaceuticals were also performed using a series of initial PPCP concentrations (Fig. 4). The NDMA molar conversion varied as the initial PPCP concentration changed, but no common pattern was observed. For ranitidine, chlorphenamine and doxylamine, the molar conversion was generally consistent, varying within ±30%; while for nizatidine, carbinoxamine, diltiazem and tetracycline, the molar conversion decreased slightly with increasing initial PPCP concentration; sumatriptan was the only compound showing consistently a slightly increasing molar conversion as the initial PPCP concentration increased. Under all the concentrations tested, chloramine was always in large excess, so the different trends in response to the change of initial PPCP concentrations might be related to their reaction kinetics. Thus, further kinetic studies are needed and may require case-by-case investigation.

These eight pharmaceuticals have been largely consumed in the market and some have been detected in surface waters. For example, ranitidine and nizatidine are widely used in North America to treat and prevent peptic ulcer disease and gastroesophageal reflux disease. Specifically, ranitidine has been detected in surface waters at various locations with concentrations in the tens of ng/L range (Kasprzyk-Hordern et al., 2008; Kolpin et al., 2002, 2004; Zuccato et al., 2005). Diltiazem is used to treat hypertension and some types of arrhythmia, with concentrations up to several hundred ng/L detected in some US and UK streams (Kasprzyk-Hordern et al., 2008; Kolpin et al., 2002, 2004). Tetracycline is a broad-spectrum antibiotic used against various bacterial infections, and has been frequently detected in many US and Canadian sites with concentrations up to 300 ng/L (Kolpin et al., 2002, 2004; Miao et al., 2004). In the present study, the lowest concentration tested was 100 ng/L for ranitidine, nizatidine, chlorphenamine, and doxylamine (Fig. 4). Ranitidine shows the

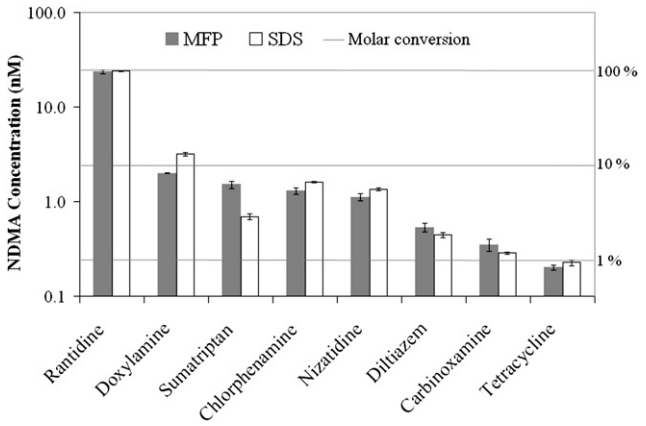


**Fig. 3 – Comparison of NDMA-FPs for selected PPCPs between the MFP and the SDS conditions (Tap water; initial concentration of PPCPs = 25 nM).**

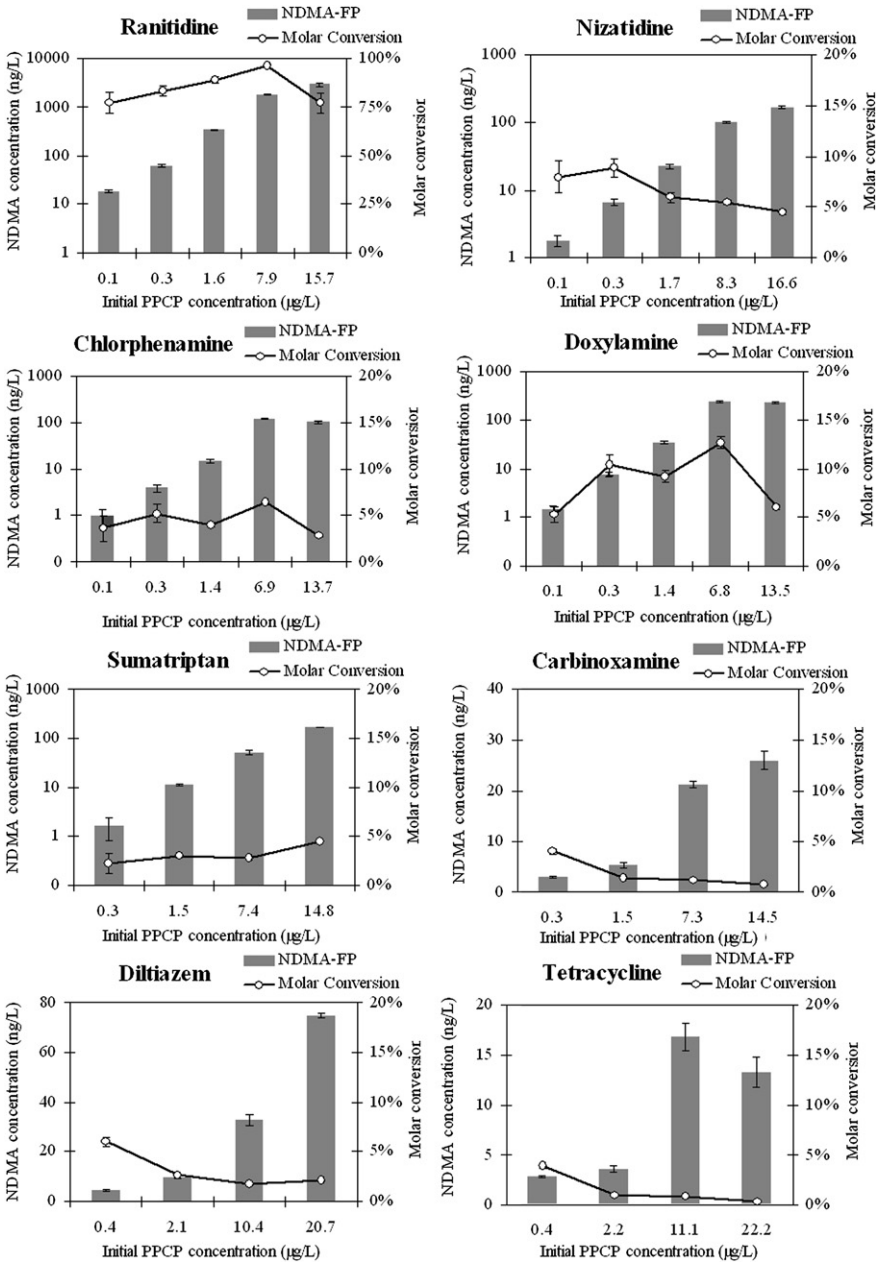


**Fig. 4 – NDMA-FPs and molar conversions for selected PPCPs at different initial concentrations (SDS conditions; tap water).**

strongest potential to form NDMA, with molar conversion higher than 77% at all the concentrations tested. Even at 100 ng/L, ranitidine can form 18.2 ± 1.2 ng/L of NDMA, which is beyond the current Ontario regulation of 9 ng/L and the California regulation of 10 ng/L. NDMA formed via the other three compounds at 100 ng/L were low, but still within the quantifiable range. As well, even though the majority of the selected PPCPs form low levels of NDMA, added together they may still pose a concern in terms of the overall formation of nitrosamines.

In real environments, PPCPs are usually present in the form of mixtures rather than as single compounds. A test was conducted to examine the potential effect of mixtures on the formation of NDMA via PPCPs. The eight pharmaceuticals were prepared in a mixture and subjected to chloramination under the SDS conditions. Although a slight antagonistic effect was observed in the mixture of pharmaceuticals, the NDMA-FP was reduced by less than 10–15% compared with the sum of NDMA concentrations produced from single compounds at the same concentration (Fig. 5).

Furthermore, it is worth noting that to better evaluate the NDMA-FP of pharmaceuticals, it will be necessary to take into consideration all the PPCP-derived species containing the DMA groups that may enter the drinking water treatment scheme. Pharmaceutical substances usually undergo metabolism within the human body and thus are excreted as a mixture of parent compounds together with the metabolites; also some pharmaceuticals are subjected to transformations

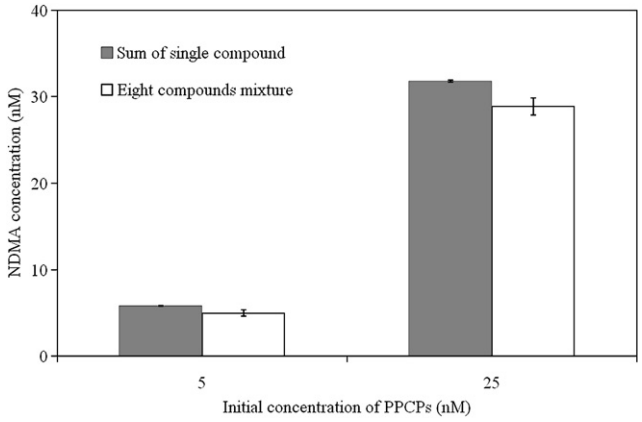


**Fig. 5 – NDMA-FPs for single PPCP vs. PPCP-mixture (Eight PPCPs: ranitidine, nizatidine, carbinoxamine, chlorphenamine, doxylamine, diltiazem, sumatriptan, and tetracycline) (SDS conditions; tap water).**

in the environment, resulting in the formation of different transformation products. However, as long as the DMA functional groups are components of the metabolites and/or transformation products, they may still contribute to the formation of NDMA when reacting with chloramines. Take ranitidine as an example, earlier pharmacokinetics and pharmacodynamics studies have indicated that 30–70% of ranitidine is excreted as the parent form (Jjemba, 2006), and its major metabolites in human body include N-oxide, S-oxide, and desmethylranitidine (Carey et al., 1981). In the aquatic environment, ranitidine is transformed into two major products under solar irradiation (Isidori et al., 2009). The S-oxide metabolite and both the solar irradiation products maintain the DMA groups in their structures. Moreover, removal of parent ranitidine in conventional wastewater treatment plants has been reported to vary between 0 and 89% in different seasons (Castiglioni et al., 2006), but no data is available in terms of the removal of its major metabolites. Currently, most occurrence studies have been only focused on the parent compounds but have not detected or reported the likely substantial amounts of their metabolites and transformation products. As a result, even though the concentration of the parent compound in the environment is low (ng/L level), altogether with its metabolites and transformation products, the overall nitrosamine formation potential may still be high and should be taken into consideration.

### 3.3. *Impact of $Cl_2$:N mass ratio*

Chlorine to ammonia nitrogen ($Cl_2$:N) mass ratio is an important factor for chloramine disinfection. It can determine the dominant chloramine species along with pH (6.5–8.5) typically encountered in drinking water disinfection (USEPA, 1999). Monochloramine is predominately formed when the applied ratio is less than 5:1; dichloramine starts to form as the ratio increases, yielding a mixture of monochloramine and dichloramine; breakpoint reaction occurs when the ratio is above 7.6:1, resulting in the formation of free chlorine and nitrogen trichloride.

Mitch et al. (2005) have reported that the occurrence of dichloramine can significantly enhance the NDMA formation via tertiary amines, regardless of its relatively minor fraction. In the present study, the potential impact from the $Cl_2$:N mass ratio was studied by exposing a mixture of eight pharmaceuticals to chloramines prepared at different $Cl_2$:N mass ratios. It was observed that the NDMA molar conversion increased as the ratio increased from 3:1 to 6.3:1, corresponding to an increasing fraction of dichloramine from approximately 10–40% in the dosed samples (Fig. 6).

For utilities applying chloramine disinfection, it is generally recommended to maintain the $Cl_2$:N mass ratio near to but below 5:1 to achieve the required residual and to avoid breakpoint reactions (USEPA, 1999). However, it is difficult to maintain a stable operating ratio, and a slight shift of the ratio above 5:1 might cause a spike of NDMA formation. Furthermore, monochloramine undergoes disproportionation to form some dichloramine over a period of a day or so (USEPA, 1999). Therefore, the chloramine residual towards the further end of the distribution system very likely includes a portion of

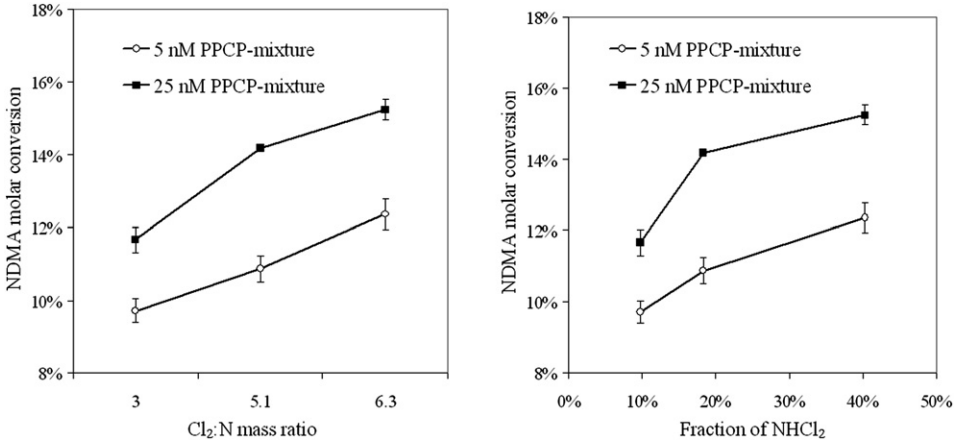


**Fig. 6 – Impact of $Cl_2$:N mass ratio (left) or the fraction of $NHCl_2$ (right) on the NDMA formation via selected PPCPs (Eight PPCPs in the mixture: ranitidine, nizatidine, carbinoxamine, chlorphenamine, doxylamine, diltiazem, sumatriptan, and tetracycline; SDS conditions; tap water).**

dichloramine. If there are any potential nitrosamine precursors present in the finished drinking water, such as trace level PPCPs, the prolonged formation of nitrosamines in the distribution system may cause a concern especially when water needs to be delivered over a long distance.

## 4. Conclusions

- All of the 20 selected PPCPs were able to form corresponding nitrosamines upon chloramine disinfection. Eight pharmaceuticals rendered molar conversions higher than 1%, showing the potential to form NDMA under practical disinfection conditions. Ranitidine showed a particularly strong potential to form NDMA, even at environmentally relevant concentrations. The molar yields of NDMA via ranitidine (0.1–15.7 μg/L) were higher than 77%.
- NDMA molar conversion increased with the $Cl_2$:N mass ratio, indicating an enhancement effect of dichloramine on the formation of NDMA via selected PPCPs. This may cause potential concern in the distribution system.
- Although the majority of these compounds gave yields of less than 1% molar conversion, when added together they may still contribute significantly to the formation of nitrosamines during chloramine disinfection.

Overall, results from the present study have suggested that PPCPs with substituted amine groups can serve as potential nitrosamine precursors during chloramine disinfection. Due to their trace level in source waters, it is not likely that PPCPs will account for the majority of nitrosamine precursors in drinking water. However, this study proves the possible connection between the transformation of PPCPs and the formation of nitrosamines during chloramination process. Further research would be needed to determine the possible impact from different water matrices. Kinetic studies are also required to investigate the possible reaction mechanisms involved. Moreover, metabolites and transformation products of some PPCPs may also pose the potential to form nitrosamines, thus the overall nitrosamine formation potential of PPCPs should consider the parent compounds, their metabolites, as well as the possible transformation products.

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