Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/watres

# NDMA formation from amine-based pharmaceuticals – Impact from prechlorination and water matrix

*Ruqiao Shen**, *Susan A. Andrews*

*Department of Civil Engineering, University of Toronto, 35 St. George St., Toronto, Ontario, Canada M5S 1A4*

ARTICLE INFO

*Article history:*
Received 1 October 2012
Received in revised form
6 February 2013
Accepted 8 February 2013
Available online 17 February 2013

*Keywords:*
NDMA
Prechlorination
Ranitidine
Sumatriptan
NOM

ABSTRACT

The presence of N-nitrosodimethylamine (NDMA) in drinking water is most commonly associated with the chloramination of amine-based precursors. One option to control the NDMA formation is to remove the precursors via pre-oxidation, and prechlorination is among the most effective options in reducing NDMA formation. However, most of the findings to-date are based on single-precursor scenarios using the model precursor dimethylamine (DMA) and natural organic matter (NOM), while few studies have considered the potential interactions between water matrix components and the target precursors when investigating the prechlorination impact. Specifically, little is known for the behaviour of amine-based pharmaceuticals which have recently been reported to contribute to NDMA formation upon chloramination. This work demonstrates that prechlorination can affect both the ultimate NDMA conversion and the reaction kinetics from selected pharmaceuticals, and the nature and extent of the impact was compound-specific and matrix-specific. In the absence of NOM, the NDMA formation from most pharmaceuticals was reduced upon prechlorination, except for sumatriptan which showed a consistent increase in NDMA formation with increasing free chlorine contact time. In the presence of NOM, prechlorination was shown to enhance initial reactions by reducing the binding between NOM and pharmaceuticals, but prolonged prechlorination broke down NOM into smaller products which could then form new bonds with pharmaceuticals and thus inhibit their further conversion into NDMA.



## 1. Introduction

The presence of N-nitrosodimethylamine (NDMA) in drinking water has been commonly associated with the disinfection process, especially chloramination. NDMA is a highly mutagenic compound and a potential human carcinogen, with a $10^{-6}$ lifetime cancer risk associated with a drinking water concentration of 0.7 ng/L (EPA IRIS, 1993). The exposure to NDMA through drinking water has become a concern especially for utilities that apply chloramine as the secondary disinfectant. Health Canada has recently proposed a maximum acceptable concentration for NDMA of 40 ng/L in drinking water (Health Canada, 2010). USEPA also placed it on the drinking water contaminant candidate list 3 (CCL3) together with four other nitrosamines (USEPA, 2009). NDMA is currently regulated in drinking water in several provinces and states across North America, including Ontario (9 ng/L; MOE, 2003), Massachusetts (10 ng/L; MassDEP, 2004), and California (10 ng/L; OEHHA, 2006).

During drinking water treatment processes, NDMA is most commonly formed via the slow reaction between chloramines (especially dichloramine) and amine-based precursors (Schreiber and Mitch, 2006a). NDMA is also formed through a nitrosation mechanism at acidic pH (Choi and Valentine,

* *Corresponding author*. Tel.: +1 4169783141; fax: +1 4169783674.
E-mail addresses: shenruqiao@yahoo.com.cn (R. Shen), sandrews@civ.utoronto.ca (S.A. Andrews).
0043-1354/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.watres.2013.02.017

2003), but this mechanism is of less importance in drinking water due to the generally low nitrite concentrations and the neutral/basic pH. Moreover, ozonation can also lead to the formation of NDMA (Andrzejewski et al., 2008; Oya et al., 2008); an especially high yield was observed for dimethylsulfamide, a degradation product of the fungicide tolyfluanid (Schmidt and Brauch, 2008).

Early studies on NDMA typically used the model precursor dimethylamine (DMA; Gerecke and Sedlak, 2003) and natural organic matter (NOM; Chen and Valentine, 2007; Dotson et al., 2007; Gerecke and Sedlak, 2003; Mitch and Sedlak, 2004), however chloramination of these precursors typically gave low yields of NDMA and thus cannot always account for all of the precursors present in natural waters. More recently, higher levels of NDMA formation have been associated with wastewater-impacted surface water (Krasner, 2009; Schreiber and Mitch, 2006b; Shah et al., 2012), indicating the contribution from anthropogenic compounds. Several studies have linked NDMA formation to quaternary amines used in personal care products (Kemper et al., 2010), pharmaceuticals and pesticides (Le Roux et al., 2011, 2012a b; Shen and Andrews, 2011a,b), as well as some amine-based polymers and resins (Kohut and Andrews, 2003; Mitch and Sedlak, 2004; Najm and Trussell, 2001; Wilczak et al., 2003). Mitch and Schreiber (2008) have proposed that the NDMA formation from tertiary amines proceeds via a chlorine transfer reaction to release the DMA which is then subsequently oxidized to NDMA. However, NDMA formed from DMA alone cannot explain the high yields from some tertiary amines such as ranitidine. A recent study by Le Roux et al. (2012b) has proposed an alternative mechanism for NDMA formation from chloramination of ranitidine, which involves a direct substitution on the DMA group of ranitidine and can well explain its high yield of NDMA.

In practice, chloramine is usually used as the secondary disinfectant following primary disinfection (e.g., $Cl_2$, UV, and $O_3$). Moreover, instead of using preformed monochloramine, most utilities that perform chloramination typically apply free chlorine first, followed by the addition of ammonia to form chloramine on site. Compared with chloramine alone, the application of pre-oxidation may modify or destroy the precursors and release transformation products that may or may not react with the subsequent secondary disinfectant.

Generally, the application of preoxidation prior to chloramination has been reported to reduce the NDMA formation from DMA and NOM. Preoxidation processes have included prechlorination (Chen and Valentine, 2008; Charrois and Hrudey, 2007; Mitch et al., 2010), $O_3$ and $O_3/H_2O_2$ (Chen and Valentine, 2008; Pisarenko et al., 2012), $ClO_2$ (Lee et al., 2007), ferrate (Lee et al., 2008), and $KMnO_4$ (Chen and Valentine, 2008). Among all the options, ozone and chlorine were found to be most effective in reducing NDMA formation (Shah et al., 2012). However, oxidation of precursors does not necessarily lead to the reduction in NDMA formation. In some cases, prechlorination may increase NDMA formation at lower exposures due to insufficient oxidation (Chen and Valentine, 2008; Shah et al., 2012). It has also been observed that UV and $UV/H_2O_2$ pretreatment have increased the NDMA formation from amine-based polymers (e.g., polyDADMAC, epi-DMA), possibly due to the increased degradation of the polymers releasing more NDMA precursors (Harvey, 2009). More recently, Radjenovic et al. (2012) have reported that the oxidation products of the pharmaceutical tramadol by UV and $UV/H_2O_2$ have higher NDMA formation potentials (FPs) than the parent compound. Thus, the impact of preoxidation on the formation of NDMA requires further investigation.

Currently, most of the findings regarding the preoxidation impact have been based on DMA and NOM. Several studies used treated wastewater as a "precursor pool", but few specific compounds have been studied separately, especially pharmaceutical-based precursors. Moreover, very little information is available in terms of how the preoxidation process might affect the NDMA formation kinetics. This study investigates the impact of prechlorination on the NDMA formation from eight selected pharmaceuticals, especially the impact on their reaction kinetics. The eight pharmaceuticals were selected because of their relatively high NDMA FPs among the twenty pharmaceuticals and personal care products (PPCPs) tested in a previous study by the authors (Shen and Andrews, 2011a). This work also compares the prechlorination impact with and without the presence of NOM, and looks into how the interactions in between NOM, pharmaceuticals, and free chlorine could affect the NDMA formation from selected pharmaceuticals. Relatively high pharmaceutical concentrations (6.8–11.1 μg/L) compared with their expected environmental levels were applied in this study in order to be able to measure the differences in NDMA formation under different disinfection conditions. However, Shen and Andrews (2011b) demonstrated that the NDMA formation kinetics in a real water matrix was relatively independent of the initial pharmaceutical concentration because chloramine was present in large excess relative to the pharmaceutical concentrations; therefore similar reaction kinetics are expected for selected pharmaceuticals at their environmental levels. Findings from this work could be of particular concern for water reuse processes where much higher concentrations of pharmaceuticals might be subjected to chloramination.

## 2. Materials and methods

Chemical structures of the eight selected pharmaceuticals are illustrated in Fig. 1. The pharmaceuticals (25 nM of each) were dosed into selected water matrices (raw, not filtered) individually and subjected to different disinfection strategies. The chloramination experiments (preformed chloramine) were carried out under the same simulated distribution system (SDS) conditions as applied in Shen and Andrews (2011b). The sequential disinfection experiments (prechlorination followed by chloramination) employed modified SDS conditions, where a sodium hypochlorite (NaClO) solution was first added, followed by the addition of ammonia chloride ($NH_4Cl$) to form chloramine after a range of target free chlorine contact times (0.5–120 min). The resulting chloramine concentration at the point of $NH_4Cl$ addition was the same as that which was applied in the preformed chloramination experiments for each matrix (i.e., 2.5 ± 0.2 mg/L plus the 24 h chloramine demand for each matrix). The initial free chlorine dosage and the $NH_4Cl$ dosage for each matrix were determined via preliminary chlorine/chloramine demand tests (see details in Supporting Information). All of the other conditions remained