Understanding *N*-nitrosodimethylamine (NDMA) formation during chloramination: Precursor characteristics, pathways and mitigation

상수 염소 처리 과정중에 형성되는 *N*−니트로소디메틸아민에 대한 이해: 전구체의 특징, 경로와 경감

Mingizem Gashaw Seid.[1,2] · Aseom Son[1] · Kangwoo Cho[3] · Seokwon Hong[1,2*]
민기[1,2] · 손아섬[1] · 조강우[3] · 홍석원[1,2*]

[1]*Center for Water Resource Cycle Research, Korea Institute of Science and Technology, Hwarangro 14 gil, Seongbuk-gu, Seoul 02792, Republic of Korea*
[2]*Division of Energy and Environment Technology, KIST-School, University of Science and Technology, Seoul 02792, Republic of Korea*
[3]*Division of Environmental Science and Engineering, Pohang University of Science and Technology (POSTECH), Pohang 37673, Republic of Korea*
[1]한국과학기술연구원, [2]과학기술연합대학원대학교, [3]포항공과대학교

ABSTRACT

N-nitrosodimethylamine (NDMA) is a class of disinfection byproducts and a frequently detected nitrosamine with carcinogenic potentials. This review summarizes NDMA precursors, their formation mechanisms in chloraminated water, and mitigation strategies. Understanding the formation mechanism and characteristics of precursors is essential for developing a mitigation strategy. Dimethylamine (DMA), the most widely studied NDMA precursor, has an NDMA molar yield up to 3%. In comparison, a subset of tertiary amines, e.g., pharmaceuticals, generate up to 90% upon chloramination. Potent NDMA precursors, are characterized by their negative partial charge, low planarity values and molecular weight, and high bond length and pK$_a$ values. A nucleophilic substitution of tertiary amine on chloramine is a key reason for the high NDMA yield from the most potent NDMA precursors. The distribution and fate of NDMA in surface water, aquifers, and its formation in the distribution system can be mitigated through two strategies: (1) degrading or/removing NDMA after its formation and (2) pre-treatment of its precursor's prior chloramination.

Key words: Chloramination, Mitigation, NDMA precursors, Nucleophilic substitution, Pre-treatment

주제어: 클로라민 처리, 경감, NDMA 전구체, 친핵성 치환, 전처리

1. Introduction

N-nitrosodimethylamine (NDMA) is a highly water-

soluble and frequently detected nitrosamine. NDMA is formed as a disinfection by-product (DBP) or reaches the subsurface as an impurity from industrial influents. In the past decades the level and frequency of NDMA detection increased alarmingly, with reported concentrations up to 105 μg/L in waste-impacted waters and drinking water distribution

facilities (Mitch et al., 2003). As the result, developed nations have surveyed and implemented maximum acceptable concentrations of NDMA (3~40 ng/L) in their guidelines for drinking water (Health Canada, 2011). The 10^{-6} lifetime excess cancer risk from drinking water consumption for NDMA has been reported at 0.7 ng/L. Numerous studies have investigated NDMA formation based on widely used chlorine disinfectants (Le Roux et al., 2011; Shen and Andrews, 2011; West et al., 2016) and ozone (Lim et al., 2016; Marti et al., 2015; Oya et al., 2008). However, some strong oxidants, i.e., KMnO$_4$ (Andrzejewski and Nawrocki, 2007), UV irradiation (Soltermann et al., 2013), and peroxycarboxylic acids (West et al., 2016), are also associated with NDMA formation during water and wastewater treatment. Activated carbon materials that are used in drinking water and wastewater treatment processes can also catalyze amine precursors to yield NDMA under relevant conditions (Padhye et al., 2011). Typically, chloramination is blamed for NDMA formation which is largely dependent on source water quality characteristics. Recent findings indicated that NDMA can be also formed via ozonation with a high yield, which becomes a great concern in treatment of waters containing a subset of *N, N*-dimethylamino or -dimethylhydrazine compounds (Lim et al., 2016). In this review however, only NDMA formation upon chloramination was discussed. Thus, the main objective of this review is to offer a comprehensive overview of NDMA formation during chloramination with a particular focus on the source and chemical characteristics of precursors and their formation mechanisms. In parallel, mitigation strategies i.e. drinking water and wastewater treatment process towards NDMA removal and pre-treatment prior chloramination for NDMA abatements were discussed.

2. Source and chemical characteristics of NDMA precursors

Several studies have explored nitrogen containing substances as model precursors of NDMA formation, and the significant sources of NDMA precursors can be classified as follows: (i) *amine-based macro constituents* : specifically pharmaceuticals and personal care products, agricultural chemicals, and chelating agents with DMA moieties (Bond et al., 2017; Selbes et al., 2012); (ii) *source waters* : any potential load from effluent-impacted waters, i.e., sewage and wastewater treatment effluent, agricultural or storm water runoff, and eutrophic waters (Zeng et al., 2016); (iii) *natural or wastewater- derived organic matter* : dissolved organic nitrogen, intracellular organic matter extracted from cyanobacteria, and some plants and soluble microbial products (Dotson et al., 2009); (iv) *wastewater treatment materials* : amine functional and/or nitrogen-containing surface groups of carbon nanotubes (Verdugo et al., 2014) or polymeric resins, polyelectrolytes, and quaternary polymers and membranes (Flowers and Singer, 2013; Park et al., 2009); and (v) *water distribution and storage construction materials* : rubber seals, gaskets, pipelines, and corrosion byproducts (Teefy et al., 2014). Therefore, NDMA may form upon chloramination of a source water containing substances classified above or be accumulated as impurities during disinfection of wastewater effluent-impacted water and, in some cases, during water treatment. Moreover, water treatment materials can leach NDMA precursor constituents and form more NDMA during chloramination. Concurrently, activated carbon and carbon nanomaterials can catalyze trace levels of amines to generate NDMA and its potential precursors in the water treatment processes.

Dimethylamine (DMA) has been widely studied as the most effective precursor of NDMA formation with a yield up to 3% (Le Roux et al., 2012). The NDMA yield from the most widespread phenylurea herbicides is usually less than 1% (Le Roux et al., 2011). In comparison, pharmaceuticals and personal care products can result in relatively higher molar yield during chloramination. Particularly, a sub set of *N,N*-dimethyl-α-arylamines, such as ranitidine, are characterized by higher (up to 90 %) molar yields of NDMA (Shen and Andrews, 2011). Chloramination of most tertiary or certain quaternary amines can produce NDMA through dealkylation reactions to yield DMA as the primary intermediate (Mitch and Schreiber, 2008). Therefore, for these compounds, yields for NDMA formation would be comparable or less than that of DMA (~ 3%). NDMA formation potential (NDMA FP) of selected precursors are summarized in Tables 1 and 2.

Table 1. NDMA formation from selected precursors (Bei et al., 2016; Bond et al., 2017; Hanigan et al., 2015; Le Roux, et al., 2011; Selbes et al., 2012; Shen and Andrews, 2011). Molar yields were calculated based upon the initial precursor concentration

NDMA precursors[1]	Molar yield (%)	NDMA precursors[2]	Molar yield (%)
Dimethylamine	2.3	DMP30	18.4
Diltiazem	2.4	Mannich	11.4
Doxepin	2.3	Doxylamine	8.9
Trimethylamine	1.9	Minocycline	8.2
Tetracycline	1.2	Ziram	6.7
Amitriptyline	1.2	N,N-dimethyltertbutylamine	6.2
Carbinoxamine	1.2	Sumatriptan	6.1
Tramadol	0.6	Chlorphenamine	5.4
Mifepristone	0.4	Nizatidine	4.9
Isoproturon	0.3	Insosine Pranobex	0.4
Diuron	0.15	Promethazine	2.8

NDMA formation potential conditions :
  • Precursors concentrations : 0.025 - 100 μM and for Mannich, 0.44 mg/L
  • NH_2Cl concentrations: 10 mg/L as Cl_2 - 4 mM
 • Contact time: 1 - 7 days at pH 7.0 - 8.5 and temperature of 20 - 25 ℃.

[1]NDMA precursors with an NDMA molar yield comparable to or less than from DMA.
[2]NDMA precursors with relatively higher NDMA molar yields than from DMA.

Table 2. NDMA formation from potent precursors, their structures, and molecular descriptors (Bond et al., 2017; Hanigan et al., 2015; Le Roux, et al., 2011; Selbes et al., 2012; Shen and Andrews, 2011). Molar yields were calculated based upon the initial precursor concentration

Potent NDMA precursors	Molar yield (%)	Partial charge	Planarity (°)	Bond length (Å)	pK_a
[1]Ranitidine	89.9	-0.439	122.6	1.455	8.4
[2]N,N-Dimethyl-isopropylamine	83.9	-0.522	123.0	1.471	10.1
[3]Rivastigmine	83.3	-0.409	123.2	1.467	8.4
[4]N,N-Dimethyl-benzylamine	83.5	-0.252	127.3	1.467	9.3
[5]5-(Dimethylaminomethyl)furfuryl alcohol	77.6	-0.384	122.6	1.454	8.7
[6]N,N-Dimethylthiophene-2-methylamine	74.9	-0.379	122.1	1.461	8.9
[7]Methadone	70.0	-0.385	127.7	1.473	8.3
[8]Conessine	42.3	-0.552	121.7	1.472	9.6
[9]N,N-Dimethyl-1-(1H-pyrrol-2 yl) methanamine	25.0	-0.424	121.3	1.465	9.6

Structure of potent precursors
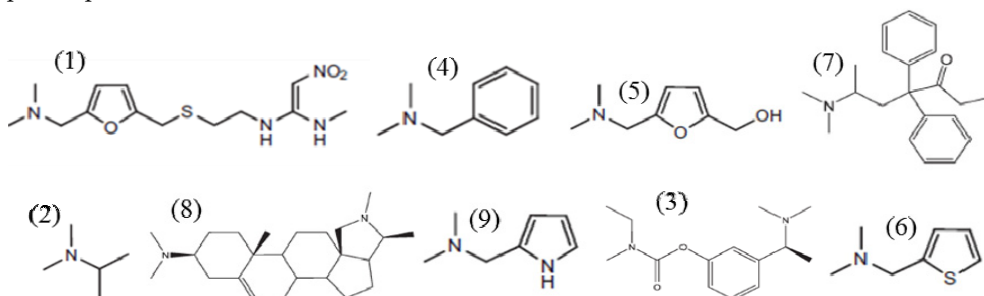
Previous work has indicated that certain chemical characteristics, such as polarity, molecular weight, and partial charge, can be used to understand the nature of NDMA precursors. A solid-phase extraction, resin fractionation technique, ultrafiltration molecular weight distribution, polarity rapid assessment method, and computational chemistry have been used as potential tools for isolating and characterizing NDMA precursors (Bond et al., 2017; Dotson et al., 2009; Liao et al., 2015). A study by Chen et al. (2014) demonstrated that NDMA precursors were more to have a non-polar moiety and positive change on DMA group, and have very low or high molecular weights. Liao et al. (2015) reported that the non-polar fraction, obtained from aquaculture-impacted lake water, primarily contributes to NDMA formation potential. Likewise, a partial change of the DMA nitrogen, polarity of the DMA moiety, bond length of $(CH_3)_2$N-R, and pK_a of the DMA nitrogen could be descriptors of NDMA precursors (Bond et al., 2017). Because these properties are related to the geometry of the DMA moiety, accessibility of the nitrogen lone pair for reaction, presence of electron-donating and/or -withdrawing groups, and speciation of precursors (Bond et al., 2017). For instance, Shen and Andrews (2012) found that the ultimate NDMA formation typically occurs at a pH approximately 1.2-1.6 unites lower than the pK_a of the precursor DMA nitrogen. Selbes et al. (2012) showed that the stability and electron distribution of the leaving group determined the molar yield of NDMA from most tertiary amines.
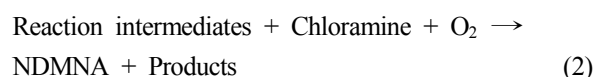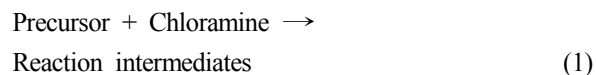
More recently, a study by Bond et al. (2017) defined the molecular properties of NDMA precursors using computational chemistry. The authors classified NDMA precursors based on chemical functionality as follows: (i) $(CH_3)_2$N-alkyl-R (i.e., ranitidine), (ii) $(CH_3)_2$N-aryl (i.e., *N,N*-Dimethylamine), (iii) $(CH_3)_2$N-C=$R_1(R_2)$ (i.e., Unsymmetrical dimethylhydrazine, UDMH), (iv) $(CH_3)_2$-N-hetroatom (i.e., UDMH), and (v) $(CH_3)_2N^+$-R_2 (i.e., tetramethylamine). Though there were no solid correlation between NDMA formation and any of the individual descriptors, the occurrence of electron-donating groups is a prerequisite for higher yielded precursors (Bond et al., 2017). For instance, NDMA precursors with electron-donating groups around the amine nitrogen have higher pK_a values, while electron-

withdrawing groups will increase acidity and decrease pK_a values. Furthermore, the presence of electron-withdrawing groups will reduce bond length, whereas electron-donating groups increases bond length (Bond et al., 2017). Collectively, tertiary and quaternary amines with the DMA moiety bounded to the -COR and -CSR groups had high partial charge and lower NDMA formation potential. Potent NDMA precursors with an acidic hydrogen and electron-donating group in α and β to the DMA are characterized by their negative partial charge, low planarity values, and high bond length / pK_a values (Bond et al., 2017).

3. NDMA formation mechanisms upon chloramination

Most of the findings on NDMA formation demonstrated that NDMA could be formed via the following primary pathways; (i) the HOCl enhanced nitrosation pathway and (ii) nucleophilic attack of DMA moiety on chloramine (Schreiber and Mitch, 2006; Mitch et al., 2003). Since the co-existence of nitrite and free chlorine in drinking water is unusual, the general importance of the nitrosation pathway appears to be limited. However, the nitrosation pathway could be descriptive during chlorination of wastewater effluents, particularly in treatment plants associated with partial nitrification (Shah and Mitch, 2012).

Most of the previous studies proposed that nucleophilic substitution rather than chlorine transfer is the main NDMA formation mechanism. The multi-step formation mechanism (Liu et al., 2014; Schreiber and Mitch, 2006; Spahr et al., 2017), can be simplified to two-reaction steps as follows (Seid et al., 2018):

Precursor + Chloramine $\longrightarrow$
Reaction intermediates $\qquad\qquad$ (1)

Reaction intermediates + Chloramine + O_2 $\longrightarrow$
NDMNA + Products $\qquad\qquad$ (2)

In these reactions, it is assumed that NH_2Cl and $NHCl_2$ can generate reaction intermediates i.e., the dimethylhydrazine-type compound via nucleophilic substitution. After nucleophilic initiation, multiple reaction steps including
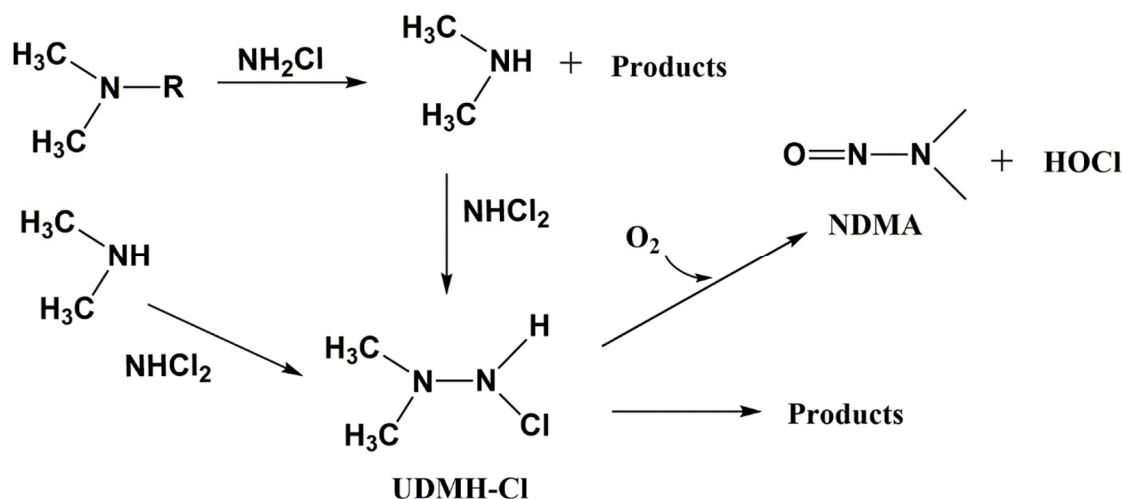
Fig. 1. Proposed NDMA formation pathways from DMA and tertiary or quaternary alkylamines during chloramination (adopted from Schreiber and Mitch, 2006).
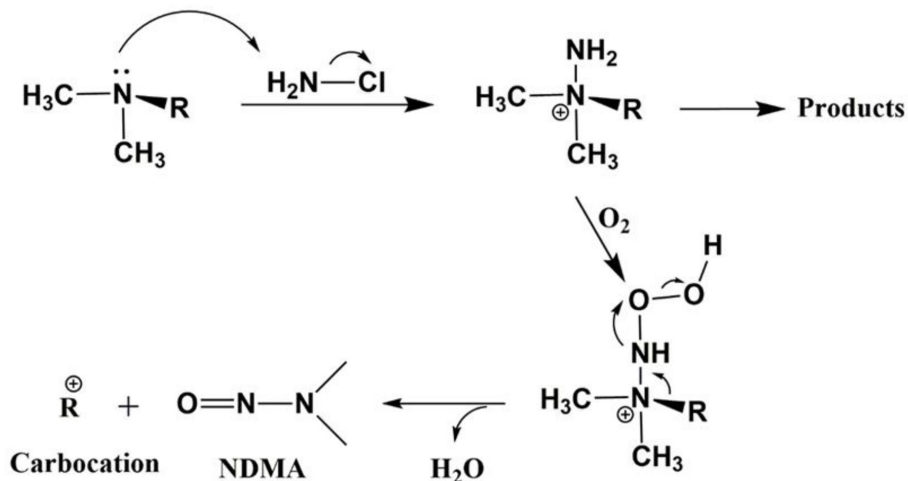

Fig. 2. Proposed NDMA formation pathways from tertiary amines during chloramination (adopted from Le Roux, et al., 2012).

radical intermediates generation, a subsequent oxidation and nitroso group formation, and further decomposition, could be involved in eq. (2) (Le Roux et al., 2012; Seid et al., 2018; Spahr et al., 2017). A UDMH-Cl pathway (Fig. 1.) could be incorporated with NOM (natural organic matter) and, for tertiary or quaternary amines, NDMA could be formed via dealkylation reaction to produce DMA as the primary intermediate that forms NDMA in the subsequent oxidation (Schreiber and Mitch, 2006; Mitch and Schreiber, 2008). However, UDMH alone generated very low NDMA during chloramination (i.e., <0.01 %). Thus, for higher molar yield precursors, UDMH may not to be a major intermediate leading to NDMA formation (Le Roux

et al., 2012).

A study by Le Roux et al. (2012) provided evidence that a chlorine transfer cannot explain the high yields of NDMA during chloramination of tertiary amines, whereas nucleophilic substitution is the main reaction occurring on the DMA group of tertiary amines (Fig. 2.). For example, during chloramination of ranitidine, a chlorine transfer leads to a chlorinated and/or hydroxylated analog of ranitidine, thioethyl-N-methyl-2-nitroethene-1,1-diamine group, and dimethyl-aminomethyl furfuryl alcohol, while nucleophilic substitution leads to the dimethylhydrazine-type compound. Later, the positive charge on the nitrogen atom of the DMA group reduces the pK_a of hydrogen on the NH_2 moiety.

The resulting highly reactive NH^- intermediate reacts with dissolved oxygen to generate a nitroso group of NDMA. In this case, the formation of stable carbocation would account for the high NDMA yield from a subset of amines, such as ranitidine (Le Roux et al., 2012). However, based on a density functional theory model, Tanju Karanfil and coworkers proposed a four-step formation mechanism for NDMA from tertiary amines (Liu et al., 2014). This mechanism corroborates the pathway proposed by Le Roux et al. (2012) and suggests that the NDMA yield for tertiary amines is determined by the nitrosation reaction, which is the rate-limiting step (Liu et al., 2014).

A recent study by von Gunten and coworkers demonstrated that the nitrosation step is not necessary for NDMA formation and *N*-centered radicals are principal reaction intermediates during the chloramination of *N,N*-dimethylamine- methylfurane moieties (Spahr et al., 2017). Likewise, this mechanism initiated by nucleophilic substitution forms the dimethylhydrazine-type compound (Fig. 3.). In comparison, the one −electron oxidation of the dimethylhydrazine-type compound by NH_2Cl generates aminyl radicals (products and $H_2N\bullet$). Later, N-centered aminyl radicals can be oxygenated by molecular oxygen to amino-peroxyl radicals (products and $H_2N-O-O\bullet$). In this case the stoichiometric consumption of O_2 is dependent on the extent of short-lived aminyl radicals (Spahr et al., 2017). Once aminyl radicals form, coupling the two N-peroxyl radicals could generate tetroxide species. Subsequent decomposition of tetroxide species leads to NDMA, stable carbocation, and hydrogen peroxide. In comparison, reactions of $H_2N\bullet$ with aqueous O_2 would lead to the formation of $H_2N-O-O\bullet$ and transform to unidentified products (Spahr et al., 2017). Collectively, a direct nucleophilic substitution on the DMA moiety of NDMA precursor explains the high NDMA yields from tertiary amines. The resulting formation yield is highly dependent on the stability of carbocation and accumulation of amino-peroxyl radicals.
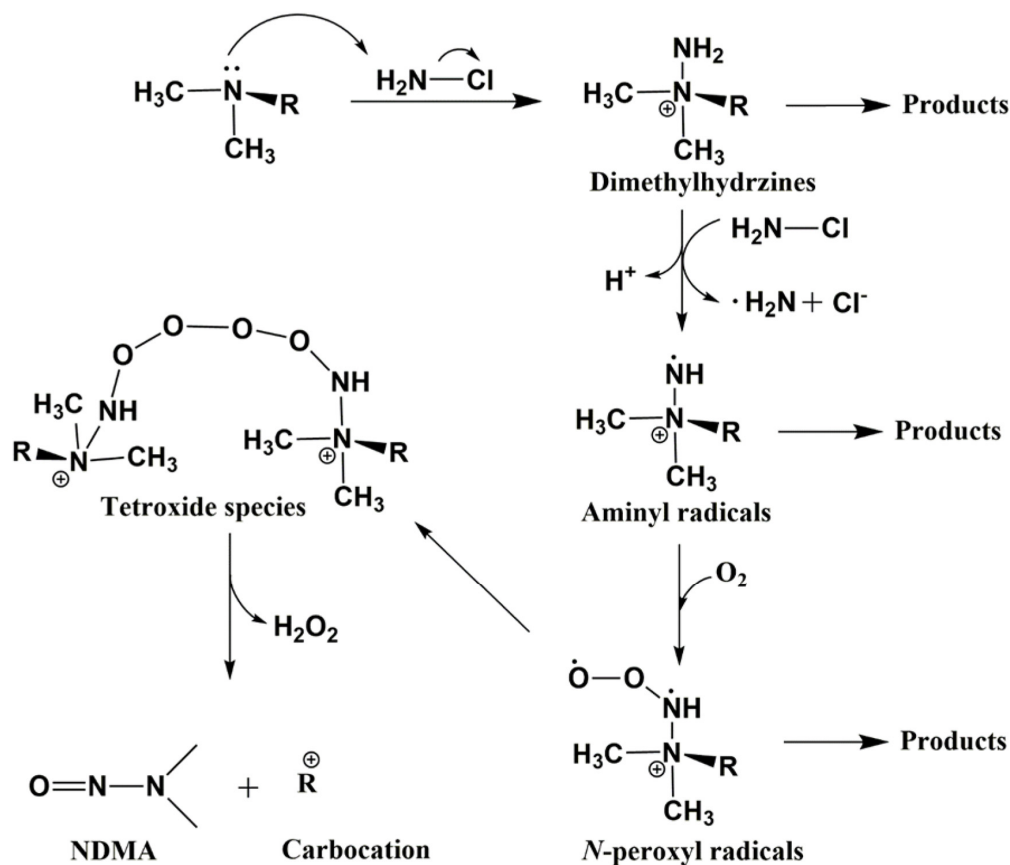

Fig. 3. Proposed NDMA formation pathways from tertiary amines during chloramination (adopted from Spahr et al., 2017).

4. Mitigation strategies for NDMA formation control

The current level of NDMA in surface waters and aquifers as well as its formation in distribution systems can be mitigated through two strategies: (1) degrading or/removing NDMA after its formation and (2) deactivating or removing its precursors during water treatment before chloramination. NDMA is likely to be removed during coagulation, lime softening, and sand filtration treatment processes (Ho et al., 2011; Sedlak et al., 2005). However, zero-valent and noble metal catalysts can effectively reduce NDMA (Huo et al., 2018). In situ and ex situ bioremediation studies have revealed that a variety of microorganism in undefined microcosms or in pure cultures are capable of cometabolizing NDMA (Fournier et al., 2006). UV treatment has been identified as an efficient method for destructing NDMA in aquatic environments, and particularly in groundwater (Lee et al., 2005). NDMA can also be attenuated by electrochemical remediation, adsorption on microporous materials,

semiconductor photocatalysis, and advanced oxidation processes, such as ferrate, ozone, UV and/or H_2O_2, Fenton, and radiolysis (Chaplin et al., 2009; Hiramoto et al., 2002; Lee et al., 2008). More recently, several studies have demonstrated the rejection of NDMA via membrane application (Fujioka et al., 2013). In summary, NDMA can be reduced, adsorbed, oxidized, or rejected depending on specific techniques, with a promising efficacy. NDMA generally transforms to DMA, formaldehyde and methylamine, and inorganic nitrogen species, as shown in Fig. 4. In some cases, the regeneration of NDMA from oxidized products or concurrent formation of regulated DBPs may be the limitation for NDMA removal methods (Chaplin et al., 2009; Lee et al., 2007; Xu et al., 2010).

The effectiveness of NDMA removal method depends on the several characteristics of source water quality such as dissolved oxygen (DO), bromide, nitrite, and NOM. For instance NDMA can be easily oxidized to DMA and nitrite by UV and/or gamma ray irradiation, however irradiation of nitrite-containing waters in combination with secondary
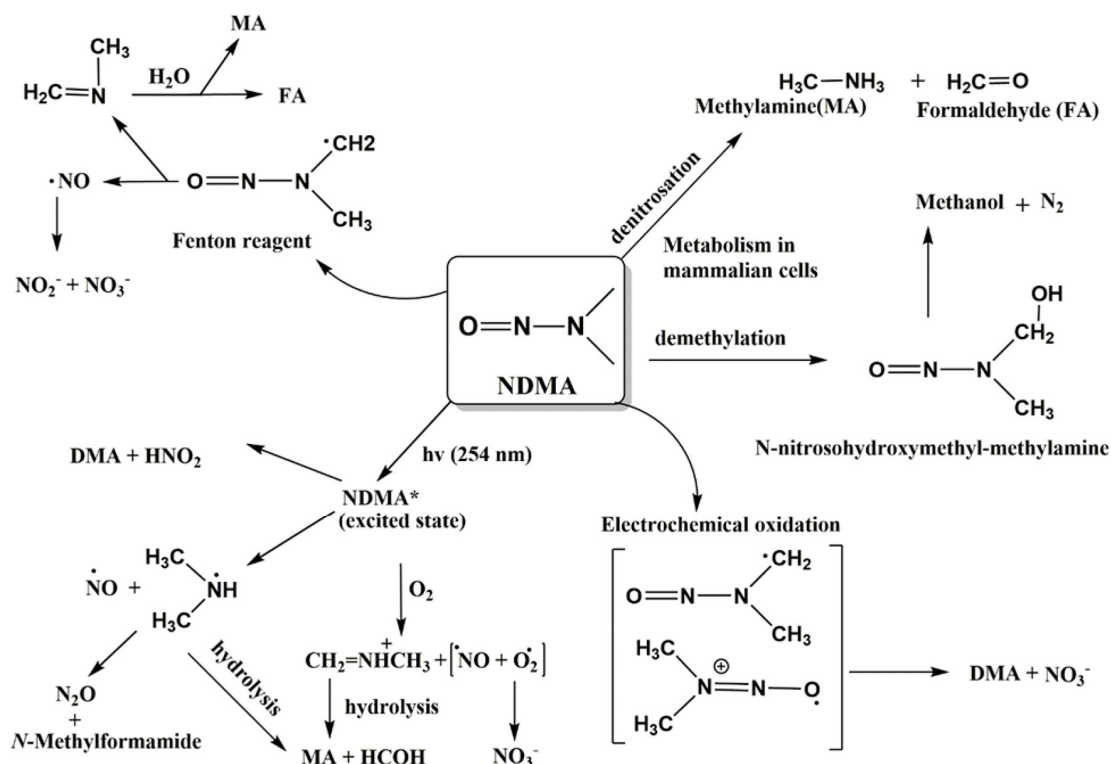
Fig. 4. Possible NDMA degradation pathway by Fenton, UV photolysis, electrochemical oxidation, and microcosms cometabolic process (adopted from Chaplin et al., 2009; Fournier et al., 2006; Hiramoto et al., 2002; Lee et al., 2005).

amines or their chlorinated analogs often leads to NDMA and other toxic byproducts (Soltermann et al., 2013; Xu et al., 2010). The presence of NOM inhibits the photodegradation of NDMA in drinking water, while DO enhances the degradation rate under acidic or neutral pH (Xu et al., 2009). In addition, DO, copper, and bisulfide surrogates affect the performance of catalytic reduction of NDMA via metallic catalysts (Frierdich et al., 2009; Han et al., 2017). Also ozone-based NDMA removal methods are catalyzed by bromide and lead to bromate formation (Lee et al., 2007). Furthermore, the presence of background ions (e.g. HCO_3^-) are also reported to reduce the effectiveness of OH^--induced NDMA removal (Lee et al., 2007).

Pre-treatment prior to chloramination has been reported as an effective tool for mitigating NDMA formation. NDMA precursors can be deactivated or removed using a wide variety of strategies, including biological activated carbon or river bank filtration, membrane rejection, adsorption on microporous materials, bio or catalytic reduction, natural attenuation, and chemical oxidation. However, chemical oxidants (chlorine, ozone, chlorine dioxide, permanganate, ferrate, and hydrogen peroxide) and UV irradiation has been employed widely. Lee et al. (2008) reported a 46~84% reduction on the NDMA FP after pre-oxidation of secondary and tertiary amines with ferrate (IV). Pre-chlorination reduced NDMA formation from selected precursors by 10~50%, while pre-chlorination of quaternary amine polymers showed almost no effect on overall NDMA formation (Selbes et al., 2014). NDMA FP from doxylamine in the presence or absence of NH_2Cl can be halved after UV treatment. However, a dose of 50 mg/L H_2O_2 increased NDMA FP by more than 30% (Farré et al., 2012). Ozonation at 6 mg/L removed approximately 90% of NDMA FPs for all selected amine-based pharmaceuticals (Wang et al., 2015). In contrast, some oxidized byproducts had higher NDMA FPs than the parent compound after oxidation with Cl_2, ClO_2, and $KMnO_4$ (Wang et al., 2015). Collectively, a significant or complete deactivation of potent NDMA precursors can be archived when pre-oxidants react with precursor's amine moieties. For instance, a recent study found that the chlorine transfer to acetamidine and/or thioether moiety does not contribute significantly to NDMA FP reduction from ranitidine, while

an ozone or chlorine reaction with the tertiary amine and furan moieties removed NDMA FP effectively (Jeon et al., 2016).

The effectiveness of pre-oxidation to eliminate the key structural moieties of NDMA precursors depend on structure of precursors and boundary conditions, such as pH, contact time, temperature, NOM, and background ions (i.e., NH_3, NO_2^-, Br^-). Nevertheless, selecting a pre-oxidant and its application should be assessed carefully, as some pre-oxidants can generate NDMA and other DBPs from precursors or daughter analogs formed during the oxidation process. Ozonation is generally effective for destroying NDMA potent precursors, however, a source of water containing specific compounds e.g. *N,N*-dimethylhydrazine moieties generate a high yield of NDMA upon ozonation (Lim et al., 2016). Pre-ozonation of selected polymers and dyes led to the increase NDMA FP (Selbes et al., 2014). In contrast, pre-ozonation was effective for the reduction of NDMA FP from a specific potent precursors i.e. ranitidine (Selbes et al., 2014; Wang et al., 2015). Pre-ozonation of polyamine-impacted waters at low exposures was ineffective on NDMA reduction, while NDMA formation was increased during warm seasons from ozone pretreated waters with a relevant exposure (McCurry et al., 2015). On the other hand, with a specific ozone demand per dissolved surrogates or nitrite, pre-ozonation eliminated NDMA FP from a pharmaceuticals-containing wastewater effluent (Jeon et al., 2016).

On the other hand, chlorine significantly reduces NDMA FP, excluding water samples with high ammonia and nitrite concentrations (Jeon et al., 2016). Ammonia could affect the specification of chloramine, in which NDMA can be directly formed upon chloramination (Mitch and Sedlak, 2002). Pre-chlorination of nitrite-containing waters might increase NDMA formation via nitrosation (Shah et al., 2012). In addition, pre-ozonation of bromide-impacted water can increase NDMA FP with or without a subsequent chloramination (Luh and Mariñas, 2012; Von Gunten et al., 2010).

Pre-chlorination pH, NOM, and temperature have been related to the precursors specification and abatement during oxidation process (McCurry et al., 2015; Selbes et al., 2014; Shen and Andrews, 2013). For instance, at lower

pre-chlorination temperature, NDMA FP was increased in polymer-impacted waters with subsequent chloramination (McCurry et al., 2015). An increase in pre-chlorination pH has resulted either a decrease or increase in NDMA FP depending on precursor type; pre-chlorination of wastewater-impacted water at pH 8 was efficient in the reduction of NDMA FP, while there is no significant variation in polymer-impacted water (McCurry et al., 2015). NDMA FP from ranitidine was effectively deactivated at lower pre-chlorination pH, while increasing pH from 5.5 to 9.5 enhanced NDMA FP from a sub-set of N,N-dimethyl-α-arylamines (Selbes et al., 2014). In the case of poly(diallyldimethylammonium chloride) there was no apparent change in NDMA FP with the variation of pre-chlorination pH (Selbes et al., 2014). On the other hand, a short pre-chlorination of pharmaceuticals impacted in real water matrix can enhance NDMA FP, however, prolonged chlorine exposure might destroy NOM fractions and inhibit further formation of NDMA via NOM-pharmaceuticals interaction (Shen and Andrews, 2013).

5. Conclusions

Chloramination has been primarily blamed for NDMA formation during water treatment and biofouling mitigation processes. This review described the formation mechanism of NDMA during DMA and selected tertiary amines. The nucleophilic substitution mechanism is likely a key step responsible for NDMA formation from tertiary amines. The formation of a stable carbocation in the benzylic position and N-centered radicals are responsible for the high NDMA yields observed from tertiary amines. Potent NDMA precursors, with an acidic hydrogen and electron- donating group α and β to the DMA, are characterized by their negative partial charge, low planarity values, and high bond length and pKa values. In addition, non-polar fraction and low molecular weight precursors contribute the largest to NDMA formation potential. Furthermore, NDMA formation potential from potent precursors can be determined using physical and chemical treatment methods. Pre-oxidation prior to chloramination is promising strategy to control NDMA formation during the disinfection process.

References

Andrzejewski, P., Nawrocki, J. (2007). N-nitrosodimethylamine formation during treatment with strong oxidants of dimethylamine containing water, Water Sci. Technol., 56, 125-131.

Bei, E., Liao, X., Meng, X., Li, S., Wang, J., Sheng, D., Chao, M., Chen, Z., Zhang, X., Chen, C. (2016). Identification of nitrosamine precursors from urban drainage during storm events: A case study in southern China, Chemosphere, 160, 323-331.

Bond, T., Simperler, A., Graham, N., Ling, L., Gan, W., Yang, X., Templeton, M.R. (2017). Defining the molecular properties of N-nitrosodimethylamine (NDMA) precursors using computational chemistry, Environ. Sci. Water Res. Technol., 3, 502-512.

Chaplin, B.P., Schrader, G., Farrell, J. (2009). Electrochemical oxidation of N-nitrosodimethylamine with boron-doped diamond film electrodes, Environ. Sci. Technol., 43, 8302-8307.

Chen, C., Leavey, S., Krasner, S.W., Suffet, I.H. (2014). Applying polarity rapid assessment method and ultrafiltration to characterize NDMA precursors in wastewater effluents, Water Res., 57, 115-126.

Dotson, A., Westerhoff, P., Krasner, S.W. (2009). Nitrogen enriched dissolved organic matter (DOM) isolates and their affinity to form emerging disinfection by-products, Water Sci. Technol., 60, 135-143.

Farré, M.J., Radjenovic, J., Gernjak, W. (2012). Assessment of degradation byproducts and NDMA formation potential during UV and UV/H_2O_2 treatment of doxylamine in the presence of monochloramine, Environ. Sci. Technol., 46, 12904-12912.

Flowers, R.C., Singer, P.C. (2013). Anion exchange resins as a source of nitrosamines and nitrosamine precursors, Environ. Sci. Technol., 47, 7365-7372.

Fournier, D., Hawari, J., Streger, S.H., McClay, K., Hatzinger, P.B. (2006). Biotransformation of N-nitrosodimethylamine by Pseudomonas mendocina KR1, Appl. Environ.

Microbiol., 72, 6693-6698.

Frierdich, A.J., Joseph, C.E., Strathmann, T.J. (2009). Catalytic reduction of N-nitrosodimethylamine with nanophase nickel-boron, Appl. Catal. B Environ., 90, 175-183.

Fujioka, T., Khan, S.J., McDonald, J.A., Roux, A., Poussade, Y., Drewes, J.E., Nghiem, L.D. (2013). N-nitrosamine rejection by nanofiltration and reverse osmosis membranes: The importance of membrane characteristics, Desalination, 316, 67-75.

Han, Y., Chen, Z. lin, Shen, J. min, Wang, J. he, Li, W. wei, Li, J., Wang, B. yuan, Tong, L. na. (2017). The role of Cu(II) in the reduction of N-nitrosodimethylamine with iron and zinc, Chemosphere, 167, 171-177.

Hanigan, D., Thurman, E.M., Ferrer, I., Zhao, Y., Andrews, S., Zhang, J., Herckes, P., Westerho, P. (2015). Methadone contributes to N-nitrosodimethylamine formation in surface waters and wastewaters during chloramination, Environ. Sci. Technol., Lett. 2, 151-157.

Health Canada. (2011). Guidelines for Canadian drinking water quality - Chlorine guideline technical document, N-nitrosodimethylamine. Water, Air and Climate Change Bureau, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Ontario. (Catalogue No H128-1/11-662E).

Hiramoto, K., Ryuno, Y., Kikugawa, K. (2002). Decomposition of N-nitrosamines, and concomitant release of nitric oxide by Fenton reagent under physiological conditions, Mutat. Res., 520, 103-111.

Ho, L., Grasset, C., Hoefel, D., Dixon, M.B., Leusch, F.D.L., Newcombe, G., Saint, C.P., Brookes, J.D. (2011). Assessing granular media filtration for the removal of chemical contaminants from wastewater, Water Res., 45, 3461-3472.

Huo, X., Liu, J., Strathmann, T.J. (2018). Ruthenium catalysts for reduction of N-nitrosamine water contaminants, Environ. Sci. Technol., 52, 4235-4243.

Jeon, D., Kim, J., Shin, J., Hidayat, Z.R., Na, S., Lee, Y. (2016). Transformation of ranitidine during water chlorination and ozonation: Moiety-specific reaction kinetics and elimination efficiency of NDMA formation potential, J. Hazard. Mater., 318, 802-809.

Le Roux, Julien, Gallard, H., Croué, J.P., Papot, S., Deborde, M. (2012). NDMA formation by chloramination of ranitidine: Kinetics and mechanism, Environ. Sci. Technol., 46, 11095-11103.

Le Roux, J., Gallard, H., Croué, J.P. (2011). Chloramination of nitrogenous contaminants (pharmaceuticals and pesticides): NDMA and halogenated DBPs formation,

Water Res., 45, 3164-3174.

Lee, C., Choi, W., Yoon, J. (2005). UV photolytic mechanism of N-nitrosodimethylamine in water: Roles of dissolved oxygen and solution pH, Environ. Sci. Technol., 39, 9702-9709.

Lee, C., Lee, Y., Schmidt, C., Yoon, J., Von Gunten, U. (2008). Oxidation of suspected N-nitrosodimethylamine (NDMA) precursors by ferrate (VI): Kinetics and effect on the NDMA formation potential of natural waters, Water Res., 42, 433-441.

Lee, C., Yoon, J., Von Gunten, U. (2007). Oxidative degradation of N-nitrosodimethylamine by conventional ozonation and the advanced oxidation process ozone/hydrogen peroxide, Water Res., 41, 581-590.

Liao, X., Bei, E., Li, S., Ouyang, Y., Wang, J., Chen, C., Zhang, X., Krasner, S.W., Suffet, I.H.M. (2015). Applying the polarity rapid assessment method to characterize nitrosamine precursors and to understand their removal by drinking water treatment processes, Water Res., 87, 292-298.

Lim, S., Lee, W., Na, S., Shin, J., Lee, Y. (2016). N-nitrosodimethylamine (NDMA) formation during ozonation of N,N-dimethylhydrazine compounds: Reaction kinetics, mechanisms, and implications for NDMA formation control, Water Res., 105, 119-128.

Liu, Y.D., Selbes, M., Zeng, C., Zhong, R., Karan, T. (2014). Formation mechanism of NDMA from ranitidine , trimethylamine, and other tertiary amines during chloramination : A computational study, Environ. Sci. Technol., 48, 8653-8663.

Luh, J., Mariñas, B.J. (2012). Bromide ion effect on N-nitrosodimethylamine formation by monochloramine, Environ. Sci. Technol., 46, 5085-5092.

Marti, E.J., Pisarenko, A.N., Peller, J.R., Dickenson, E.R. V. (2015). N-nitrosodimethylamine (NDMA) formation from the ozonation of model compounds, Water Res., 72, 262-270.

McCurry, D.L., Krasner, S.W., von Gunten, U., Mitch, W.A. (2015). Determinants of disinfectant pretreatment efficacy for nitrosamine control in chloraminated drinking water, Water Res., 84, 161-170.

Mitch, W.A., Schreiber, I.M. (2008). Degradation of tertiary alkylamines during chlorination/ chloramination : Implications for formation of aldehydes, nitriles, halonitroalkanes, and nitrosamines, Environ. Sci. Technol., 42, 4811-4817.

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

during chlorination, Environ. Sci. Technol., 36, 588-595.

Mitch, W.A., Sharp, J.O., Trussell, R.R., Valentine, R.L., Alvarez-Cohen, L., Sedlak, D.L. (2003). N-nitrosodimethylamine (NDMA) as a drinking water contaminant: A review, Environ. Eng. Sci., 20, 389-404.

Oya, M., Kosaka, K., Asami, M., Kunikane, S. (2008). Formation of N-nitrosodimethylamine (NDMA) by ozonation of dyes and related compounds, Chemosphere, 73, 1724-1730.

Padhye, L.P., Hertzberg, B., Yushin, G., Huang, C.H. (2011). N-nitrosamines formation from secondary amines by nitrogen fixation on the surface of activated carbon, Environ. Sci. Technol., 45, 8368-8376.

Park, S., Wei, S., Mizaikoff, B., Taylor, E., Favero, C., Huang, C., Park, S., Wei, S., Mizaikoff, B., Taylor, A.E. (2009). Degradation of amine-based water treatment polymers during chloramination as N- nitrosodimethylamine (NDMA) precursors, Environ. Sci. Technol., 43, 1360-1366.

Schreiber, I.M., Mitch, W.A. (2006). Nitrosamine formation pathway revisited : The importance of chloramine speciation and dissolved oxygen, Environ. Sci. Technol., 40, 6007-6014.

Sedlak, D.L., Deeb, R. a, Hawley, E.L., Mitch, W. a, Durbin, T.D., Mowbray, S., Carr, S. (2005). Sources and fate of nitrosodimethylamine and its precursors in municipal wastewater treatment plants, Water Environ. Res., 77, 32-9.

Seid, M.G., Cho, K., Lee, C., Park, H.M., Hong, S.W. (2018). Nitrite ion mitigates the formation of N-nitrosodimethylamine (NDMA) during chloramination of ranitidine, Sci. Total Environ., 633, 352-359.

Selbes, M., Kim, D., Ates, N., Karanfil, T. (2012). The roles of tertiary amine structure , background organic matter and chloramine species on NDMA formation, Water Res., 47, 945-953.

Selbes, M., Kim, D., Karanfil, T. (2014). The effect of pre-oxidation on NDMA formation and the influence of pH, Water Res., 66, 169-179.

Shah, A.D., Krasner, S.W., Lee, C.F.T., Von Gunten, U., Mitch, W.A. (2012). Trade-offs in disinfection byproduct formation associated with precursor preoxidation for control of N-nitrosodimethylamine formation, Environ. Sci. Technol., 46, 4809-4818.

Shen, R., Andrews, S.A. (2013). NDMA formation from amine-based pharmaceuticals- Impact from prechlorination and water matrix, Water Res., 47, 2446-2457.

Shen, R., Andrews, S.A. (2012). Formation of NDMA from ranitidine and sumatriptan : The role of pH, Water Res., 47, 802-810.

Shen, R., Andrews, S.A. (2011). Demonstration of 20 pharmaceuticals and personal care products (PPCPs) as nitrosamine precursors during chloramine disinfection, Water Res., 45, 944-952.

Soltermann, F., Lee, M., Canonica, S., von Gunten, U. (2013). Enhanced N-nitrosamine formation in pool water by UV irradiation of chlorinated secondary amines in the presence of monochloramine, Water Res., 47, 79-90.

Spahr, S., Cirpka, O.A., Hofstetter, T.B. (2017). Formation of N-nitrosodimethylamine during chloramination of secondary and tertiary amines: Role of molecular oxygen and radical intermediates, Environ. Sci. Technol., 51, 280-290.

Teefy, S., Chan, C.C., Wong, W., Work, L. (2014). NDMA formation from gaskets used in water storage tanks, J. Am. Water Works Assoc., 106, E408-E417.

Verdugo, E.M., Krause, C., Genskow, K., Han, Y., Baltrusaitis, J., Mattes, T.E., Valentine, R.L., Cwiertny, D.M. (2014). N-functionalized carbon nanotubes as a source and precursor of N-nitrosodimethylamine: Implications for environmental fate, transport, and toxicity, Environ. Sci. Technol., 48, 9279-9287.

Von Gunten, U., Salhi, E., Schmidt, C.K., Arnold, W.A. (2010). Kinetics and mechanisms of N-nitrosodimethylamine formation upon ozonation of N,N-dimethylsulfamide-containing waters: bromide catalysis, Environ. Sci. Technol., 44, 5762-8.

Wang, X., Yang, H., Zhou, B., Wang, X., Xie, Y. (2015). Effect of oxidation on amine-based pharmaceutical degradation and N-nitrosodimethylamine formation, Water Res., 87, 403-411.

West, D.M., Wu, Q., Donovan, A., Shi, H., Ma, Y., Jiang, H., Wang, J. (2016). N-nitrosamine formation by monochloramine, free chlorine, and peracetic acid disinfection with presence of amine precursors in drinking water system, Chemosphere, 153, 521-527.

Xu, B., Chen, Z., Qi, F., Ma, J., Wu, F. (2010). Inhibiting the regeneration of N-nitrosodimethylamine in drinking water by UV photolysis combined with ozonationby, J. Hazard. Mater., 177, 1167-1169.

Xu, B., Chen, Z., Qi, F., Shen, J., Wu, F. (2009). Factors influencing the photodegradation of N-nitrosodimethylamine in drinking water, Front. Environ. Sci. Eng. China, 3, 91-97.

Zeng, T., Glover, C.M., Marti, E.J., Woods-Chabane, G.C., Karanfil, T., Mitch, W.A., Dickenson, E.R. V. (2016). Relative importance of different water categories as sources of N-nitrosamine precursors, Environ. Sci. Technol., 50, 13239-13248.