

***N*-Nitrosodimethylamine Formation from Anthropogenic Nitrogenous Compounds during Preozonation and Post-chloramination with Characteristic Low Treatment Dose**

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Abstract

One effective option to minimize *N*-nitrosodimethylamine (NDMA) in finished drinking water is to identify and control its precursors. However, previous works to identify significant precursors use formation potential (FP) test using high dose to assure the maximum NDMA formation rather than the NDMA formation in finished waters. In this study, we applied characteristic low treatment doses of ozone (O₃)-to-dissolved organic carbon (DOC) of target compounds of 0.8 mg/mg and NH₂Cl of 2.5 ± 0.2 mg Cl₂/L to evaluate the NDMAFP yields of organic compounds bearing *N,N*-dimethylamine (DMA) and *N,N*-dimethylhydrazine (DMH) during preozonation and post-chloramination. The results in pH buffered Milli-Q water showed a significant decrease from ≤52% to non-detectable levels in the O₃-NDMAFP yields of O₃-reactive precursors (i.e., DMH-like compounds) after preozonation and post-chloramination. Similarly, a significant decrease from 0.5–12% to nonquantifiable levels was observed for the NH₂Cl-NDMAFP yields of NH₂Cl-reactive precursors; however, the NH₂Cl-NDMAFP yields of *N,N*-dimethylbenzylamine (DMBzA)-like compounds only decreased from ~110 to ≤43%, suggesting that these compounds could contribute to NH₂Cl-NDMAFPs even after preozonation. The effect of matrix in sewage-effluent and lake water samples varied and was specific for precursors; for example, the O₃-NDMAFP yield of 1,1,1',1'-tetramethyl-4,4'-(methylene-di-*p*-phenylene) disemicarbazide (TMDS), an important O₃-reactive NDMA precursor, did not significantly decrease when tested in sewage-effluent samples. Based on the previous occurrence concentration of TMDS in sewage samples, we estimated an NDMAFP of ~315 ng/L. This estimate exceeds the guidance concentrations of NDMA (3–100 ng/L), highlighting the importance of TMDS and its related compounds for NDMA formation.

Keywords: *N*-nitrosamine, NDMA, *N,N*-dimethylamine, *N,N*-dimethylhydrazine, semicarbazide, ozone, chloramine

1 Introduction

N-Nitrosodimethylamine (NDMA), a probable human carcinogen (International Agency for Cancer Research 1999; Richardson et al. 2007), is formed during water treatment by the reaction of chloramine (mainly monochloramine, NH_2Cl) or ozone (O_3) with organic compounds bearing *N,N*-dimethylamine (DMA) or *N,N*-dimethylhydrazine (DMH). (Mitch and Sedlak 2002; Schmidt and Brauch 2008; Padhye et al. 2011; Kosaka et al. 2014b). Once formed, NDMA is usually difficult to remove by most conventional- and advanced-water treatments (e.g., powdered- or granular-activated carbon, ozonation, UV irradiation/ H_2O_2) (Sharpless and Linden 2003; Lee et al. 2007b; Sacher et al. 2008; Mitch et al. 2009; McCurry et al. 2016, 2017). Although UV irradiation can effectively remove NDMA, the UV dose required to achieve an acceptable NDMA level for finished drinking water cost considerably (McCurry et al. 2016, 2017). These limitations warrant source control strategies to eliminate NDMA precursors during water treatment.

To effectively apply source control strategies, the potent NDMA precursors must be identified. One method for such identification is target analysis. Several studies (Mitch and Sedlak 2002, 2004; Schmidt and Brauch 2008; Kosaka et al. 2009, 2014b; Hinneh et al. 2019) have used target analysis to identify potent NDMA precursors by evaluating the NDMA formation potential (FP) yield (henceforth denoted as “NDMAFP yield”) of anthropogenic compounds bearing DMA or DMH. However, these studies often involve elevated oxidant doses of NH_2Cl or O_3 which assures the maximum NDMA rather than the NDMA formed when a realistic (much lower) treatment dose is applied. For example, Mitch and Sedlak (2004) demonstrated that *N,N*-dimethylaniline (DMA_n) formed significantly high NDMA ~155, 000 ng/L using high chloramination dose compared with <6 ng/L when using a condition simulating treatment plants (Mitch and Sedlak 2004). The authors attributed the large difference to both the amount of NH_2Cl (7 versus 140 mg Cl_2/L) and the contact

time (4 h versus 10 days, respectively). Similarly, in our previous work, DMA_n formed NDMA ~1,000 ng/L during chloramination for a comparable amount of NH₂Cl (Hinne et al. 2019). In the preceded examples, under FP conditions with high oxidant dose, NDMA could exceed its guidance or notification values (3–100 ng/L) (Ontario Ministry of the Environment 2002; Massachusetts Department of Environmental Protection 2004; California Office of Environmental Health Hazard Assessment 2006; Health Canada 2010; National Health and Medical Research Council 2011; United States Environmental Protection Agency 2016; California State Water Boards 2020; Ministry of Health, Labour and Welfare, Water Supply Division, Health Service Bureau CCL). These examples implicate that certain anthropogenic nitrogenous compound such as DMA_n might be improperly labeled as major NDMA precursors.

Furthermore, studies (Lee et al. 2007a; Shah et al. 2012) have shown that ozone applied upstream of drinking water or wastewater treatment trains can control NDMA formation during post-chloramination. However, although ozone has high reactivity with nitrogenous compounds (e.g., amines) and may deactivate the NH₂Cl-reactive sites of these precursors, preozonation may also release NH₂Cl-reactive precursors like DMA, leading to downstream NDMA formation upon chloramination (Lee et al. 2007a). For example, *N,N*-dimethylethanolamine was shown to form products other than DMA that could lead to NDMA formation (Lee et al. 2007a), and sewage impacted by compounds bearing DMH or DMA (e.g., *N,N*-dimethylsulfamide in the presence of bromide ion) could form considerable NDMA during ozonation (Oya et al. 2008; Schmidt and Brauch 2008; Kosaka et al. 2009, 2014c; Marti et al. 2015). Thus, to effectively apply ozone for preoxidation to minimize NDMA formation during post-chloramination, more information about the NDMA formation from precursors bearing DMH or DMA during preozonation and post-chloramination is needed. Several precursors bearing DMA have been shown to have high

NDMAFP yields during chloramination (Mitch and Sedlak 2002, 2004; Hinneh et al. 2019). However, ranitidine (RNTD), which is the most preponderant of these precursors by its high NDMAFP yield, was previously shown to not significantly contribute to the pool of NDMA precursors in real wastewater samples (Zeng and Mitch 2015; Zeng et al. 2016). On the other hand, other compounds have been shown to contribute to NDMA formation at wastewater treatment plants using ozone. Earlier studies reported certain compounds related to clothing, such as 1,1,1',1'-tetramethyl-4,4'-(methylene-di-*p*-phenylene) disemicarbazide (TMDS) (Kosaka et al. 2009, 2014c) and commercial dyes like methyl orange (Oya et al. 2008), as playing a role in NDMA formation at sewage treatment plants applying ozone. In addition, TMDS, including its isomer and some tentatively identified DMH-related compounds such as PubChem chemical identifier (PCCID) 20088012 or 53651166, were recently detected in sewage samples (Hinneh et al. 2022). However, the reactivity of these precursors towards NDMA formation under low oxidant-dose conditions remains poorly understood.

The objective of our work was to systematically examine the NDMAFP yields of anthropogenic nitrogenous compounds during preozonation and post-chloramination. By using low dosage of O₃ and NH₂Cl, we attempted to show the pertinent structures of NDMA precursors relevant for NDMA formation during preozonation and post-chloramination. Considering the practical aspect of our work, we generally selected the target compounds either because of their previous detection in wastewater (e.g., TMDS) (Kosaka et al. 2009; Hinneh et al. 2022) or their possibility of being present in the environment (e.g., anamorelin, ANAM) (Wakabayashi et al. 2021) (see Section 2). In addition, because water matrix components such as natural organic matter (NOM) can either inhibit or enhance the NDMA yields of precursors (Selbes et al. 2013; Marti et al. 2015), we

examined the effect of water matrices, using sewage effluent and lake water, on the NDMAFP yields of identified precursors.

2 Materials and methods

2.1 Reagents and Solutions

All reagents and standard solutions were of analytical grade ($\geq 95\%$) except *tert*-butyl alcohol, *t*-BuOH, (40%). A list of the standard solutions of all chemicals, their purities, and manufacturers or suppliers is provided in Table S1 in the Supporting Information (SI). Aqueous solutions were prepared in Milli-Q water produced from Milli-Q Plus System (Millipore, Billerica, MA, USA).

2.2 Selection and Categorization of Anthropogenic Nitrogenous Compounds

Twenty-four anthropogenic nitrogenous compounds, 15 of which are evaluated in this study for the first time, were selected as target compounds. The remaining nine compounds are known precursors of NDMA during ozonation or chloramination. The compounds are categorized into five groups (Fig. 1): 1) DMA-like compounds (Group I), 2) *N,N*-dimethylbenzylamine (DMBzA)-like (Groups II), 3) DMH-like (Group III), 4) dye-related (Group IV), and 5) organophosphates with DMA (Group V). Target compounds, including DMBzA-like (e.g., L-Moses), were selected because of their availability by chemical suppliers or manufacturers. Note that, for DMH-like compounds, we selected compounds with a similar structure to PCCID 20088012 or 53651166 (e.g., ANAM), an agonist of ghrelin, used to treat cancer cachexia and anorexia) (Wakabayashi et al. 2021) and with a possibility of being released to environmental waters.

2.3 Preparation of Ozone and Chloramine

Ozone. Ozone (O_3) stock solution was prepared daily by bubbling ozone, generated from an ozone generator (AZH-3S, Hamamatsu Vegetable, Japan) using pure oxygen gas, into 250 mL of Milli-

Q water in a reactor in an ice bath. The ozone stock solution typically ranged from 10–24 mg O₃/L (0.2–0.5 mM). Once prepared, the ozone solution was immediately used by diluting to the appropriate reaction concentration in samples of each target compound. **Chloramine.** Monochloramine (NH₂Cl) stock solution was prepared following the procedures employed in previous study (Hinne et al. 2019) with slight modifications. Briefly, ~ 2,000 mg Cl₂/L (i.e., NH₂Cl) was prepared daily by reacting an aliquot of 100 mM ammonium chloride (at pH 8.5) and an aliquot of ~4,000 mg Cl₂/L of sodium hypochlorite in a molar ratio of NH₄Cl: OCl⁻ = 1.2 (Schreiber and Mitch 2005). The reaction solution was stocked at 4 °C for 30 min, and it was used shortly after.

2.4 Ozonation or Chloramination of Target Compounds

2.4.1 Single-Step Oxidation

The single-step oxidation experiments were conducted to determine the maximum levels of NDMAFP yields during either ozonation or chloramination (Fig. 2A). For the **ozonation** experiments, 200–1000 mL amber glass bottles or conical flasks covered with aluminum foil were used. The reactions were initiated by bubbling 10 mg O₃/L (in gas phase at 1 L/min) directly into 1 or 10 µM of target compound in Milli-Q water at pH 7 (5 mM phosphate buffer) at 20 °C for 20 min. The concentrations of target compounds varied because of differences in their solubilities in Milli-Q water, though 10 µM was typically used. After 20 min, a small amount of 6 g/L of sodium thiosulfate (Na₂S₂O₃) was added to stop the reaction. These conditions were previously shown to be sufficient to evaluate the maximum NDMAFP yields of compounds (Hinne et al. 2022). **Chloramination** experiments were performed in similar bottles or flasks as those used for ozonation following procedures from our previous study with a few modifications (Hinne et al. 2019). Notably, the conventional FP test for evaluating NDMA formation, as described by Mitch

et al. (Mitch et al. 2003), typically involves the use of 140 mg Cl_2/L (2.0 mM). However, because of the low residual NH_2Cl after 24 h for some compounds (e.g., RNTD or BOP reagent: data not shown) in our preliminary investigation, this approach was generally not employed here. Instead, NH_2Cl is added at 100-fold DOC of target compounds (24–372 mg Cl_2/L) for 24 h. This dosing procedure was previously validated as sufficient for evaluating the NDMAFP yields of varied compounds (Hinne et al. 2019). However, for DMBzA-like compounds (e.g., 4-(dimethylaminomethyl) phenol, 4-DMAMP), such dose was insufficient, and a higher dose of 140 mg Cl_2/L was sufficient (see Section S3 and Fig. S4). Stock solutions (in methanol) of target compounds were diluted in Milli-Q water to make aqueous stock solutions before addition to each reactor flask. However, in a few cases, methanol stock was added directly. But methanol in solution was always $\leq 0.1\%$.

2.4.2 Sequential Oxidation

The sequential-oxidation experiments were conducted to evaluate the impact of preozonation on the NDMAFP yields of target compounds during post-chloramination using two experimental set-ups (Fig 2B,C). In the first set-up (Fig. 2B), NDMAFP yields of target compounds were assessed using high dose of ozone and a lower dose of chloramine: a target compound (1 μM) was added to a reactor flask, and ozone was added to the reactor flask. For this evaluation, chloramine dose was lower compared to those employed for single-step oxidation. After 20 min of preozonation, the sample was kept in the dark for 24 h to remove residual dissolved ozone. Next, 1 mL of sample was withdrawn for NDMA concentration measurement. Post-chloramination was then conducted by introducing chloramine into the reactor flask. After an additional 24 h, the reaction was stopped by adding small amount of $\text{Na}_2\text{S}_2\text{O}_3$ (6 g/L). And NDMA concentration was measured. It is noted that volumes of samples after preozonation were corrected by adding 1 mL of Milli-Q water before

post-chloramination, and dilution factors were accounted for NDMA concentration calculations. In the second set-up (Fig. 2C), NDMAFP yields were assessed using lower dose of both ozone and chloramine. Target compounds (1 μ M) were spiked in 50 mL conical flasks covered with aluminum foil. Ozone was added from preformed stock solution (10–24 mg O₃/L = 0.2–0.5 mM). Preozonation was initiated by adding 0.8 mg O₃/mg DOC of target compounds at pH 7 (5 mM phosphate buffer) and 20 °C. After 24 h in the dark at 20 °C, a 1 mL sample was withdrawn for NDMA concentration measurement. Post-chloramination was performed by adding 2.5 ± 0.2 mg Cl₂/L for 24 h. The reaction was then quenched by adding small amount of Na₂S₂O₃ (6 g/L). It is noted that the O₃-to-DOC ratio of 0.8 mg/mg was selected because it aligns with the typical dosing concentration (0.25–1.5 mg O₃/mg DOC of wastewater) (Zimmermann et al. 2011; Lee et al. 2013; Sgroi et al. 2014) observed in wastewater treatment to abate trace organic micropollutants. It is further noted that one case involving a modified O₃-to-DOC ratio increased from 0.8 (0.2–0.3 mg O₃/L) to 1.75 (0.4–0.7 mg O₃/L) was employed to examine the impact of preozonation concentration on the NDMAFP yields of DMBzA-like compounds (Fig. 4). The concentration of chloramine was adopted from Shen and Andrews (Shen and Andrews 2011), satisfying requirements for chloraminated distribution systems. The volumes of samples after preozonation were corrected by adding 1 mL of Milli-Q water before chloramination, and dilution factors were accounted for in NDMA concentration calculations.

2.5 Procedures to Examine the Effect of Water Matrices on NDMAFP Yields of Precursors

Samples of sewage effluent and lake water were respectively collected from a major sewage treatment plant and lake in the Western part of Japan and immediately filtered with 0.7 μ m GF/F glass microfiber filter paper (Whatman, Illinois, USA) upon arrival at our laboratory. The samples were then stored at 4 °C until use. The DOCs and pHs of sewage effluent and lake-water samples

were 9.57 mg C/L and ~7.0 and 1.40 mg C/L and 7.6, respectively. The NDMA of the raw sewage-effluent and lake-water samples (i.e., samples not subjected to reaction with O₃ or NH₂Cl) and samples reacted with O₃ or NH₂Cl were < 2 µg/L (the limit of quantification, LOQ). The actual raw NDMA in sewage-effluent samples, after solid-phase extraction (SPE) (see Section S2) (Hinneht et al. 2022), was 6.73 ng/L. The NDMA in the sewage-effluent samples after reaction with O₃ or NH₂Cl was the same (26 ng/L). The actual raw NDMA in lake water was not measured because it was expected to be very low. Sewage effluents were dosed according to procedure previously described for low-dose conditions: O₃-to-DOC (mg/mg) = 0.8 (7.7 mg O₃/L). Lake water was dosed with 0.5 and 2.0 mg O₃/L, which are typical O₃ concentrations used in drinking water treatment. NH₂Cl concentration was kept the same 2.5 ± 0.2 mg Cl₂/L.

3 Analytical Methods

The actual concentrations of chlorine and chloramine stocks were measured using DPD colorimetric method (4500-Cl G), and the concentration of ozone stock was measured using the Indigo method (Bader and Hoigné 1981). All measurements were achieved by a US-Vis spectrophotometer (UV-mini-1240, Shimadzu, Kyoto, Japan). NDMA was quantified according to previous work using LC-MS/MS (Hinneht et al. 2019) with slight modifications. Briefly, we measured NDMA and NDMA-d₆ by LC-MS/MS analysis. An ACQUITY UPLC BEH C₁₈ analytical column (Waters Corporation, USA) was used for LC separation on a Shimadzu prominence 20 A UPLC system (Shimadzu, Kyoto, Japan) interfaced to a triple quadrupole mass spectrometer (4000 QTRAP, SCIEX, USA). The mobile phases A and B were MQW (0.1% formic acid) and acetonitrile, respectively. The gradient condition was modified as follows: B: 5% (0 min)→ 5% (5.0 min)→ 95% (5.5 min)→ 95% (8.5 min)→ 5% (9.0 min)→ 5% (14.0 min). See Section S2 on NDMA measurement, extraction, and recovery.

4 Results and discussion

4.1 NDMA Formation during Ozonation or Chloramination in pH Buffered Milli-Q Water using High-Oxidant Dose

Table 1 shows the maximum NDMAFP yields of the 24 target compounds in pH buffered Milli-Q water under single-step oxidation by ozone or chloramine after 20 min or 24 h, respectively. Compounds with NDMAFP yields ≥ 0.5 and 0.3% (limit of quantification, LOQ) are considered as NDMA precursors during ozonation and chloramination, respectively. The NDMAFP yields of 15 of the target compounds are reported here for the first time: eight are NH_2Cl -reactive precursors of NDMA (NDMAFP yields: ≥ 0.3 –110%), and only four are ozone (O_3)-reactive precursors of NDMA (>0.5 –52%). To confirm whether the experimental conditions applied for the NDMAFP tests were sufficient for the oxidation reactions, we compared the results for the nine known precursors from our study to those of previous works. As shown in Table 1, our results agree well with previous works albeit some experimental differences.

The NH_2Cl -reactive precursors were DMA-like or DMBzA-like compounds. DMA-like compounds, including dye-related and organophosphates with DMA, formed relatively high NDMAFP yields (>0.3 –12%), and DMBzA-like formed the highest NDMAFP yields (up to 110%). The large difference in NDMAFP yields could be attributed to the structure of the precursors. For example, Selbes et al. (2013) demonstrated that the structural backbones of the tertiary amines, including the stability of the leaving groups, influence and relate to the NDMAFP yields (Selbes et al. 2013). In addition, previous studies showed that a few subsets of tertiary amine precursors with β -aromatic moiety adjacent the DMA functional group (e.g., DMBzA-like compounds) have remarkably higher NDMAFP yields compared to other precursors because of their reactive structural backbone (Shen and Andrews 2011; Le Roux et al. 2012; Spahr et al. 2017). The O_3 -

reactive precursors were the DMH-like compounds, and they formed the highest NDMAFP yields (up to 52%). The lone pair of electrons on the nitrogen atom in the DMH-like structures make them very susceptible for an ozone attack, which strongly influences their NDMAFP yields (von Sonntag and von Gunten 2015; Lim et al. 2016). However, the presence of electron donating or withdrawing group adjacent DMH moiety in their structures may enhance or inhibit their NDMAFP yields (Lim et al. 2016). It is noteworthy that DMH-like compounds have slow reactivity with NH_2Cl , which may explain their low NDMAFP yields (≤ 0.3 (LOQ)–1.1%) after chloramination. These discussions implicated the importance of the structural backbone of precursors on their NDMAFP yields. Thus, the target compounds in groups I–V are discussed here mainly based on their structural backbones. Henceforth, NDMAFP yield from reaction with O_3 or NH_2Cl is denoted as " O_3 -NDMAFP yield" or " NH_2Cl -NDMAFP yield", respectively.

Group I (DMA-like compounds): The NH_2Cl -NDMAFP yields of DMA and DMiPA were 12 and 0.5%, respectively. As shown in Table 1, the NH_2Cl -NDMAFP yield of DMA is consistent with previous study (0.6%) albeit the experimental difference (Hinneh et al. 2019). The formation of NDMA from DMA is proposed to follow second-order kinetics (Schreiber and Mitch 2006; Zhang et al. 2015), and the slight decrease in NH_2Cl -NDMAFP yield observed in this study could be attributed to the reduced DMA concentration from 100 to 10 μM . DMiPA formed higher NH_2Cl -NDMAFP yields compared to DMA likely due to the presence of the more stable and effective branched isopropyl leaving group adjacent to its DMA moiety compared to the methyl group in DMA (Chen and Young 2008). No detectable O_3 -NDMAFP yield was formed by DMA.

Group II (DMBzA-like compounds): RNTD and DMBzA formed NH_2Cl -NDMAFP yields of 74 and 77%, respectively. 4-(dimethylaminomethyl) phenol (4-DMAMP) formed the highest NH_2Cl -NDMAFP yield at 110%, and it is reported here as a new potent NDMA precursor during

chloramination. The respective NH₂Cl-NDMAFP yields of 4-amino-*N,N*-dimethylbenzene (4-DMAMA), *N,N*-dimethyl-1-phenylethylamine (*N,N*-DMPEA), and L-Moses were 21, 43, and 0.4%, highlighting the significance of *N,N*-dimethyl- α -arylamines to form substantial NH₂Cl-NDMAFP yields. Previous studies underscored the role of a β -aromatic substituent to the DMA moiety of these compounds for their high NDMAFP yields (Kemper et al. 2010; Gan et al. 2015; Spahr et al. 2017). The formation mechanisms of NDMA for these compounds involve initial substitution reactions of RNTD derivatives with NH₂Cl followed by a series of steps, including a rate-limiting nitrosation step (Liu et al. 2014) or the presence of aminyl radical from oxidation of organic amines, and *N*-peroxyl radicals from aqueous O₂ reactions (Spahr et al. 2017). However, L-Moses formed the lowest NH₂Cl-NDMAFP yield (0.4%) even after 5-day of chloramination (see Section S3). One explanation for such low NH₂Cl-NDMAFP yield is the inhibitory effect of the bulky substituent (Kodamatani et al. 2021). No detectable O₃-NDMAFP yields were observed for DMBzA and most DMBzA-like compounds.

Group III (DMH-like compounds) : 1,1,2'-trimethylhydrazine (TMH) formed the highest O₃-NDMAFP yield at 52%, exceeding TMDS (20%) and DMH (30%). The O₃-NDMAFP yield of TMH was notably higher compared to tetramethyl-2-tetrazene (TMT) (11%) and 2,2-dimethylhydrazinecarboxylic acid methyl ester (DHME) (5.7%). Additionally, ANAM, *N*-(3-aminophenyl)-*N,N*-dimethylsulfamide (3AP-DMS), *N,N*-4-trimethylbenzene-1-sulfonohydrazine (TMBSH), and 1-(dimethylamino)-3-phenylthiourea (DMPTSC) yielded O₃-NDMAFP <limit of quantification (LOQ) (0.3), 0.5, 2.8, and 2.9%, respectively. Previous studies on DMH-like compounds such as daminozide and DMH indicated that O₃ attacks the nitrogen atoms in their structures, and that the primary amine of DMH and the amide nitrogen of daminozide are the primary O₃-attack sites. While O₃ reacts readily with deprotonated or neutral nitrogen in amines,

hydrazines, and hydrazides (Lee et al. 2007a; Lim et al. 2016), the presence of adjacent functional groups (e.g., carbonyl or carboxyl groups) can direct O₃ reactivity with nitrogen atoms. The latter reason could likely explain the difference of O₃-NDMAFP yields among DMH-like compounds. The electron-withdrawing groups (EWG) (e.g., carbonyl) in TMDS, DMHE, TMBSH, DMPTSC, and ANAM can reduce electron density on the amide nitrogen, diminishing O₃ reactivity and leading to lower O₃-NDMAFP yields. Among the compounds with EWG, TMDS likely formed higher O₃-NDMAFP yield because of its additional DMH moiety (Kosaka et al. 2014c). The previous rationale also applies to NDMAFP yield for TMT. Dacarbazine (DTIC) form nonquantifiable O₃-NDMAFP yield (<LOQ: 0.3%), agreeing with the results of a previous study (Marti et al. 2015) (Table 1). Notably, the additional electron-donating methyl group on TMH, which increases electron density on the primary nitrogen, likely contributed to its higher reactivity with ozone (von Sonntag and von Gunten 2015). ANAM contains the TMH functional group and, although not yielding quantifiable NDMA, may release TMH through acidic- or basic-amide hydrolysis, subsequently forming NDMA during oxidation (Padhye et al. 2013). As shown in Figs. S2 and S3, after hydrolysis, ANAM can form up to 3 µg/L of NDMAFP during ozonation. Some DMH-like compounds (e.g., TMT and TMDS) formed detectable and quantifiable NH₂Cl-NDMAFP yields up to 0.6%, potentially due to the release of DMA (Mitch and Sedlak 2002; Schreiber and Mitch 2006).

Groups IV and V (Dye-related compounds and organophosphates with DMA): Dye-related compounds in Group IV, such as *N,N*-dimethyl-*p*-phenylenediamine (DMPD) and *N,N,N',N'*-tetramethyl-1,4-phenyldiamine (TMPD), yielded NH₂Cl-NDMAFP at 0.3 and 1.1%, respectively. The higher yield from TMPD could be attributed to the presence of an additional DMA group. Among the organophosphates with DMA moiety in Group V, hexamethylphosphoamide (HMPA)

displayed the highest NDMAFP yield at 3.5%, followed by bis-(dimethylamino)chlorophosphin (Bis-TMPCl) at 0.6%. As previously mentioned, most tertiary- and quaternary-amine precursors formed NDMA via DMA (NDMAFP yield: 0.5%). And considering the groups of DMA per HMPA, HMPA should form ~1.5%, which differs from the experimental value (3.5%). This suggests that other intermediates or even HMPA itself may contribute to its NH₂Cl-NDMAFP yield. No efforts were made here to explain this mechanism because preozonation completely deactivates the reactive sites of HMPA, leading to non-detectable NDMA (Fig. 3). Bis-TMPCl formed 0.6%, and no NDMA was detected for tris(dimethylamino)phosphine (HMPT) and BOP reagent. Note that both dye-related and organophosphates with DMA moiety did not generally form detectable O₃-NDMAFP yields (data not shown).

Overall, the NDMAFP yield of all target compounds, especially those of DMBzA-like and DMH-like, was oxidant-specific (see Fig. S5). DMH-like compounds are O₃-reactive, and DMBzA-like compounds are NH₂Cl-reactive precursors. Furthermore, the NDMAFP yields of O₃-reactive compounds (e.g., TMDS) via chloramination is not zero albeit very low, implicating that they are moderate precursors of NDMA upon chloramination.

4.2 NDMA Formation during Preozonation and Chloramination in pH Buffered Milli-Q Water using Low-Oxidant Dose

The impact of preozonation on the NDMAFP yields of target compounds during chloramination was examined using two experimental set-ups under sequential oxidation (Fig 2B,C). To be consistent, the term post-chloramination is used to describe the chloramination that follows preozonation. Table 1 shows the results for the first set-up using high dosage for preozonation (10 mg/L O₃ at 1L/min in gas phase for 20 min) and lower dosage for post-chloramination (2.5 ± 0.2 mg Cl₂/L for 24 h). Fig. 3 shows the results for the second set-up using lower dosage for both

preozonation (O_3 :DOC of target compound = 0.8 mg/mg; 0.2–0.3 mg O_3 /L for 24 h) and for post-chloramination (2.5 ± 0.2 mg Cl_2 /L for 24 h). It is noted that the NH_2Cl -NDMAFP yield was determined as the difference between the O_3 - NH_2Cl -NDMAFP yield (i.e., the total NDMAFP yield after preozonation and post-chloramination) and the Pre- O_3 -NDMAFP yield (i.e., O_3 -NDMAFP yield after preozonation). Determining the NH_2Cl -NDMAFP yield this way provides the overall impact of preozonation on the NDMAFP yields of the parent precursors before post-chloramination rather than the NH_2Cl -NDMAFP yields of byproduct (s) formed after preozonation. As shown for the first set-up in Table 1, the NDMAFP yields for all target compounds, excluding DMH-like compounds in Group II, were either not detected or <LOQ (3.0%) after post-chloramination. This confirmed that NH_2Cl -reactive precursors (e.g., DMA-like or DMBzA-like compounds) form little to no NDMA during ozonation even with high dose. Consequently, the subsequent discussion primarily centers on the DMH-like compounds in Group II with NDMAFP yields from <LOQ (3.0) to 39%.

Among the DMH-like compounds, TMH, DMH, and TMDS formed the highest O_3 -NDMAFP yields at 39, 19, and 17%, respectively. DHME, TMBSH and DMPTSC formed relatively low and comparable O_3 -NDMAFP yields at 5.1, 6.3, and 4.3%, respectively. However, DTIC, 3AP-DMS, and ANAM formed NDMAFP yields <LOQ (3.0%). It is noted that the reduction in the O_3 -NDMAFP yields of DMH-like compounds in this first set-up compared to that during single-step ozonation (Table 1) is likely attributed to the lower concentration of target compounds (1 vs. 10 μM , respectively). 1 μM target compound was selected for these experiments based on the solubilities of compounds and to represent a slightly lower concentration of target compound under low-oxidant dosage. Nevertheless, the O_3 -NDMAFP yield of DMPTSC increased 1.5 times, and the O_3 -NDMAFP yield of TMBSH also increased albeit the high standard deviation (Table 1). One

explanation for this increase is that the prolonged time (24 h) allowed for the complete depletion of the residual dissolved O₃ may have contributed to more reaction with O₃, thereby increasing their NDMAFP yields.

After post-chloramination, only DMH-like and DMBzA-like compounds formed NH₂Cl-NDMAFP yields. Four compounds (TMH, TMBSH, 4-DMAMA, and 4-DMAMP) formed NH₂Cl-NDMAFP yields at 2.6, 0.1, 3.0, and 3.0% respectively. The two DMH-like compounds (TMH and TMBSH) likely formed NH₂Cl-NDMAFP yields due to the release of DMA during preozonation and a further reaction of DMA with NH₂Cl during post-chloramination (Lee et al. 2007a). DMBzA-like compounds have been demonstrated to typically form NDMA through pathways that are different from the DMA pathway (Liu et al. 2014; Spahr et al. 2017). Hence, it is unlikely that a release of DMA and its further reaction with NH₂Cl ensued NDMA formation during post-chloramination of DMBzA-like compounds. However, the presence of NH₂Cl-NDMAFP yields after post-chloramination of 4-DMAMA and 4-DMAMP suggests that their NH₂Cl-reactive sites were likely not completely deactivated by preozonation. On the other hand, the absence of NH₂Cl-NDMAFP yields from DMBzA and RNTD implies the destruction of their reactive sites during preozonation. These results agree with a previous study (Selbes et al. 2014), demonstrating significant reduction in NH₂Cl-NDMAFP yields for DMBzA and RNTD during preozonation and post-chloramination compared to direct or single-step chloramination.

As shown for the second set-up in Fig. 3, the NDMAFP yields of all compounds, especially those of DMH-like compounds, were significantly reduced or not detected after preozonation. DMBzA-like compounds formed O₃-NDMAFP yields $\leq$ LOQ (3.0%). The marked reduction in O₃-NDMAFP yields of DMH-like compounds is likely due to the substantially lower O₃ concentration (0.2–0.3 mg O₃/L) employed here compared to direct or single-step ozonation in Table 1 (10 mg/L

in gas phase at 1 L/min for 20 min). Another explanation for such low O₃-NDMAFP yields DMH-like compounds is the scavenging of O₃ by the presence of coexisting byproducts during preozonation. However, it remains unclear which byproducts were formed during preozonation. Therefore, it is needed to determine which byproducts are formed during preozonation to better understand why DMH-like compounds formed low O₃-NDMAFP yields. Nonetheless, such determination was not made in the present study because we attempted to show only the potential changes in NDMAFP yields due to preozonation with low dose rather than to elucidate the byproducts.

After post-chloramination, the NH₂Cl-NDMAFP yields was significantly high for only DMBzA-like compounds: DMBzA (43%), RNTD (66%), 4-DMAMA (1.4), 4-DMAMP (3.0%), and *N,N*-DMPEA (8.0%). These results implicated that preozonation with low dose only partially deactivated NH₂Cl-reactive sites in these compounds while restricting NDMAFP yields for most compounds (compared to high dose in direct or single-step chloramination in Table 1). To confirm the partial effect of preozonation on the NH₂Cl-NDMAFP yields of DMBzA-like compound, another experiment was conducted by increasing the O₃-to-DOC ratio from 0.8 (0.2–0.3 mg O₃/L) to 1.75 (0.4–0.7 mg O₃/L). Fig. 4 shows the result of this experiment and confirms the decreasing trend in the NH₂Cl-NDMAFP yields of all target compounds after preozonation.

DMA-like, organophosphate with DMA, and dye-related compounds likely form NDMA through DMA reaction with NH₂Cl or O₃ (Lee et al. 2007a; Padhye et al. 2011). Given this reasoning and with the likely partial deactivation of the NH₂Cl-reactive sites of target compounds due to the low ozone dose, we expected the NH₂Cl-NDMAFP yields of these compounds to increase after post-chloramination. However, such increases were not observed in this study. One plausible explanation is that the hydroxyl radical (•OH) generated from ozone decomposition (Shokoohi et

al. 2023) contributed to the breakdown of formed NDMA. Previous studies (Lee et al. 2007a; Padhye et al. 2011) reported that the NH_2Cl -NDMAFP yields of DMA and tertiary amines which form NDMA through DMA consistently decreased with increasing ozone dose. This decrease was attributed to the decomposition of NDMA by $\cdot\text{OH}$ released during preozonation. However, it must be stated that this assumption of $\cdot\text{OH}$ decomposition of NDMA is kinetically problematic because NDMA reacts slowly with $\cdot\text{OH}$ ($k = 4.5 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$) (Lee et al. 2007a; Padhye et al. 2011). Nonetheless, in the current study, preozonated samples were allowed to sit for 24 h to ensure complete depletion of residual dissolved O_3 to non-detectable levels. This extended reaction time may have therefore contributed to the decomposition of formed NDMA by $\cdot\text{OH}$.

As summarized in Fig. S6A,B and C in the SI, these results suggest that preozonation with low-oxidant dose significantly decreases the NDMAFP yields of O_3 -reactive precursors (i.e., DMH-like) and to some degree the NDMAFP yields of NH_2Cl -reactive precursors (DMBzA-like compounds). However, considerable amounts of NH_2Cl -NDMAFP yields from 1.4 to 43% still form after post-chloramination of DMBzA-like compounds. This implies that, even when DMH-like compounds are absent from wastewater, DMBzA-like compounds could still serve as important precursors of NDMA during chloramination when ozone is applied for preoxidation.

4.3 Effect of Water Matrices on NDMAFP Yields of Precursors

Ten NDMA precursors (TMDS, TMBSH, TMH, RNTD, DMBzA, 4-DMAMP, 4-DMAMA, *N,N*-DMPEA, DMPD, and HMPA) were selected to evaluate the effect of co-existing water matrices on NDMAFP yields of precursors. Both DMH-like (i.e., TMDS, TMBSH, TMH) and DMBzA-like compounds (i.e., DMBzA, 4-DMAMP, 4-DMAMA, *N,N*-DMPEA) were selected because of their high NDMAFP yields upon ozonation or chloramination or preozonation and post-chloramination. In contrast, the dye-related compound (i.e., DMPD) and organophosphate with

DMA (i.e., HMPA) were selected to provide a diverse class of NDMA precursors. Additionally, compounds such as TMDS and HMPA were selected owing to their previous detections in wastewater. As previously mentioned, RNTD does not contribute to the pool of NDMA precursors in real wastewater samples. However, because RNTD has a similar reactivity to DMBzA-like compounds, it was selected here for comparison purposes. For the experiments, 1 μM of each precursor was spiked into samples of sewage effluent or lake water. The reactions for the sewage-effluent samples were then initiated by adding 7.7 mg O_3/L , and those for the lake-water samples were initiated by adding 0.5 or 2.0 mg O_3/L which are typical for drinking water treatment. See Material and methods for details on the experimental conditions.

4.3.1 Effect of Sewage Effluent on the NDMAFP Yields of Precursors

As shown in Fig. 5, the O_3 -NDMAFP yields of all precursors after preozonation ranged from 4 to 43% in the sewage-effluent samples. DMH-like compounds formed the highest O_3 -NDMAFP yields during preozonation: TMH (43%), TMDS (19%), and TMBSH (16%). The high NDMAFP yields of DMH-like compounds in sewage effluent compared to pH buffered Milli-Q water (<LOQ: 3.0%) (Fig. 3) is likely associated with the higher ozone dose added to sewage-effluent samples. DMBzA-like compounds and others only formed O_3 -NDMAFP yields to a marginal extent (~4%). This result agrees well with what was observed in the pH buffered Mill-Q water samples. Importantly, no increase was observed in NDMAFP yields of any of the precursors after post-chloramination. In other words, all precursors did not form NH_2Cl -NDMAFP yield.

These results suggest that preozonation likely deactivated the NH_2Cl -reactive sites of NH_2Cl -reactive precursors with high NH_2Cl -NDMAFP yields, specifically the DMBzA-like compounds. It further indicates that there was probably no release of NH_2Cl -reactive precursors (e.g., DMA) from DMH-like compounds during preozonation. It is important to note that residual NH_2Cl

remained in the sewage-effluent samples after 24 h of chloramination, but there was no residual dichloramine (NHCl_2) present (see Table S2). NHCl_2 is formed from NH_2Cl through a pH-dependent disproportionation reaction and is the more reactive species for NDMA formation during chloramination (Schreiber and Mitch 2006; Huang et al. 2018). The absence of NHCl_2 , which could have interacted with the components of sewage-effluent matrix such as natural organic matter (NOM), might explain the lack of NH_2Cl -NDMAFP yield after post-chloramination of DMBzA-like samples (see summary in Fig. S6).

4.3.2 Effect of Lake Water on the NDMAFP Yields of Precursors

The O_3 -NDMAFP yields of all precursors in the lake-water samples ranged from 4 to 5.8% at 0.5 mg O_3/L and from 4 to 33% at 2.0 mg O_3/L (Fig. 5). Similar to sewage-effluent samples, DMH-like compounds formed the highest O_3 -NDMAFP yields in lake-water samples. The O_3 -NDMAFP yield of TMH was the highest at 0.5 mg O_3/L (5.8%) and at 2.0 mg O_3/L (33%). In comparison, the O_3 -NDMAFP yield of TMDS was <LOQ (3.0) and 5.2% at 0.5 and 2.0 mg O_3/L , respectively. O_3 -NDMAFP yields of TMBSH was <LOQ (3.0%) at both ozone concentrations. However, the intensity of the peak areas of NDMA in the TMBSH sample was observed to increase when ozone was increased from 0.5 to 2.0 mg O_3/L (data not shown). Except for DMH-like compounds, the O_3 -NDMAFP yields of other precursors was ~4%. It is noted that these results were comparable to those in pH buffered Milli-Q water (Figs. 4 and S1). These results suggest that, although preozonation with low-oxidant dose can significantly reduce NDMAFP yields of DMH-like compounds, the low ozone demand in the lake water (data not shown) indicates that ozone is readily available to react with precursors which may form considerable O_3 -NDMAFP yields. Furthermore, it confirms that increasing the ozone concentration generally enhances the O_3 -NDMAFP yields of DMH-like compounds.

In contrast to the results of preozonation, both DMH-like and DMBzA-like compounds formed NH_2Cl -NDMAFP yields after post-chloramination (Fig. 5). For DMH-like compounds, the NH_2Cl -NDMAFP yields of TMH were the highest: 4.1 and 1.8% at 0.5 and 2.0 mg O_3/L , respectively. Only a marginal amount of NH_2Cl -NDMAFP yields were observed for both TMDS (0.8 and 0.7% at 0.5 and 2.0 mg O_3/L , respectively) and TMBSH (0.4 and 1.8% at 0.5 and 2.0 mg O_3/L , , respectively). These results confirm the release of NH_2Cl -reactive precursors from DMH-like compounds during preozonation. It is noteworthy that, although the NH_2Cl -NDMAFP yields of DMH-like compounds after post-chloramination were low, these reactions were not limited by the absence of NH_2Cl . This is because the residual NH_2Cl levels after 24 h of reaction was ~ 2.0 mg Cl_2/L at both ozone concentrations (see Tables S2A and B). For DMBzA-like compounds, the NH_2Cl -NDMAFP yields of *N,N*-DMPEA was 0.4 and 7.0% at 0.5 and 2.0 mg O_3/L , respectively. On the other hand, no NH_2Cl -NDMAFP yield was observed for 4-DMAMA and 4-DMAMP upon post-chloramination. These results implicate the complex impact of components of lake-water matrix on the NDMAFP yields of DMBzA-like compounds during preozonation and post-chloramination under low-oxidant dosage. It shows that preozonation of lake-water samples with low dose could not completely deactivate the NH_2Cl -reactive sites of *N,N*-DMPEA. However, it likely deactivated the NH_2Cl -reactive sites of 4-DMAMA and 4-DMAMP.

4.4 Implication for Water and Wastewater Treatment

As summarized in Fig. 6, the prioritization of DMH-like compounds as NDMA precursors shifts from high (Fig. 6A) to low (Fig. 6B) when using low-oxidant dosage during preozonation and post-chloramination. However, as demonstrated in Fig. 5, DMH-like compounds could form considerable amount of O_3 -NDMAFP yields during post-chloramination in sewage effluent even when low dose of ozone is used for preoxidation. For example, the O_3 -NDMAFP yield of TMDS

after preozonation using relatively lower-oxidant dose in sewage-effluent samples was 19%. This result was comparable to that in pH buffered Milli-Q water (O_3 -NDMAFP yield: 20%), suggesting that preozonation with low dose did not significantly impact the O_3 -NDMAFP yields of TMDS.

TMDS has been frequently detected in effluents at sewage treatment plants in Japan (Kosaka et al. 2009, 2014b). In addition, we recently quantified the concentration of TMDS in the influents at one sewage treatment plant in Japan to be 8.3 $\mu\text{g/L}$ (Hinneht et al. 2022). Moreover, TMDS and its related compounds have low removal after removal biological treatment including biofiltration (Kosaka et al. 2014b; Marti et al. 2017). Therefore, assuming no change in the concentration of TMDS because of its poor removal during conventional wastewater or sewage treatment, we estimated the NDMAFP as 315 ng/L if the O_3 -NDMAFP yield of TMDS remains 19%. This value exceeds the typical guidance value of NDMA (3–100 ng/L), highlighting the importance of TMDS and other DMH-like compounds as strong precursors of NDMA. TMDS and other DMH-like compounds showed no increase in the NDMAFP yields after post-chloramination of sewage effluent samples. This result implicated that their NH_2Cl -reactive sites were likely deactivated during preozonation and showed that they do not release NH_2Cl -reactive precursors upon preozonation in sewage effluent. It is important to note that, even in sewage plants not employing chloramine, NH_2Cl can still form because of the reaction of chlorine and ammonia when nitrification is not properly operated.

On the other hand, DMH-like compounds were shown in Fig. 5 to form NH_2Cl -NDMAFP yields during post-chloramination in lake water, suggesting that they could serve as important sources for the release of NH_2Cl -reactive precursors in water matrix with low ozone demand. Similarly, DMBzA-like compounds formed NH_2Cl -NDMAFP yields after post-chloramination in lake water using low dose of ozone for preozonation. The NH_2Cl -NDMAFP yields of *N,N*-DMPEA was

shown to increase with increasing ozone concentration. For example, compared to 0.4% NH_2Cl -NDMAFP yields at 0.5 mg O_3/L , higher O_3 concentration ~ 2.0 mg O_3/L during preozonation formed NH_2Cl -NDMAFP yield $\sim 7\%$ upon post-chloramination in lake-water sample of *N,N*-DMPEA. Using the NH_2Cl -NDMAFP yield of *N,N*-DMPEA, we attempted to estimate its contribution of NDMAFP during treatment of source waters. However, we did not find any data in the literature on the occurrence of *N,N*-DMPEA in environmental waters. Therefore, we assumed the accidentally discharge of *N,N*-DMPEA to environmental waters to estimate its NDMAFP. This assumption is based on a previous water quality accident in Japan in which hexamethylenetetramine (HMT) was accidentally release to into source waters (i.e., Tone River basin), resulting in the formation of formaldehyde during the disinfection stage of a drinking water treatment plant (Kobayashi et al. 2013; Kosaka et al. 2014a). The approximate concentration of HMT discharged was 0.144 mg C/L, so we surmised a similar concentration for *N,N*-DMPEA. Based on the NH_2Cl -NDMAFP yields of *N,N*-DMPEA in lake-water samples, the NDMAFP under this assumption was 5, 180 ng/L, which exceeds the guidance concentration of NDMA. This suggests that *N,N*-DMPEA and its related compounds could be important sources of NDMA during preozonation and post-chloramination. Although these illustrative examples may have overestimated the actual NDMA formed from these compounds because of the high target compound concentration used in this study, these assumptions which are based on actual occurrence concentrations demonstrate the potential risk of NDMA formation associated with these compounds.

5 Conclusion

This study systematically examined the NDMAFP yields of anthropogenic nitrogenous compounds during preozonation and post-chloramination. By using a characteristic low treatment

dosage of NH_2Cl or O_3 , we showed the pertinent structures of NDMA precursors relevant for NDMA formation during preozonation and post-chloramination. The results also reveal the varying impacts of preozonation with low-oxidant dose and components of water matrix on the NDMAFP yields of anthropogenic compounds in pH-buffered Milli-Q water, sewage effluent and lake water during post-chloramination. The main findings are summarized as follows:

1. The NDMAFP yield of all target compounds, especially those of DMBzA-like and DMH-likes, is oxidant-specific. DMH-like compounds are O_3 -reactive. Whereas, DMBzA-like compounds are NH_2Cl -reactive precursors.
2. In pH buffered Milli-Q water, a significant decrease from $\leq 52\%$ to non-detectable levels in the O_3 -NDMAFP yields of O_3 -reactive precursors (i.e., DMH-like compounds) after preozonation and post-chloramination. Similarly, a significant decrease from 0.5–12% to nonquantifiable levels was observed for the NH_2Cl -NDMAFP yields of NH_2Cl -reactive precursors. However, the NH_2Cl -NDMAFP yields of DMBzA-like compounds only decreased from ~ 110 to $\leq 43\%$, suggesting that these compounds could contribute to NH_2Cl -NDMAFPs even after preozonation.
3. The effect of matrix in sewage-effluent and lake water samples varied and was specific for precursors. The O_3 -NDMAFP yield of TMDS, an important O_3 -reactive NDMA precursor, did not significantly decrease when tested in sewage-effluent samples. Based on the previous occurrence concentration of TMDS in sewage samples, we estimated an NDMAFP of ~ 315 ng/L. This estimate exceeds the guidance concentrations of NDMA (3–100 ng/L), highlighting the importance of TMDS and its related compounds for NDMA formation.

6 Data availability statement

The authors declare that the data supporting the findings of this study are available within the paper and its Supplementary Information (SI) file. Should any raw data files be needed in another format, they are available from the corresponding author upon reasonable request.

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Statements and Declarations

Ethical Approval

Not Applicable

Consent to Participate

Not Applicable

Consent to Publish

Not Applicable

Authors Contribution

Klon D.C. Hinneh, Koji Kosaka and Shinya Echigo contributed to the study conception and design. Material preparation, data collection and analysis were performed by Klon D.C. Hinneh and Junki Okabe. Shinya Echigo and Sadahiko Itoh supervised and provided resources for the study. Koji Kosaka acquired funding for the study. The first draft of the manuscript was written by Klon D.C. Hinneh, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

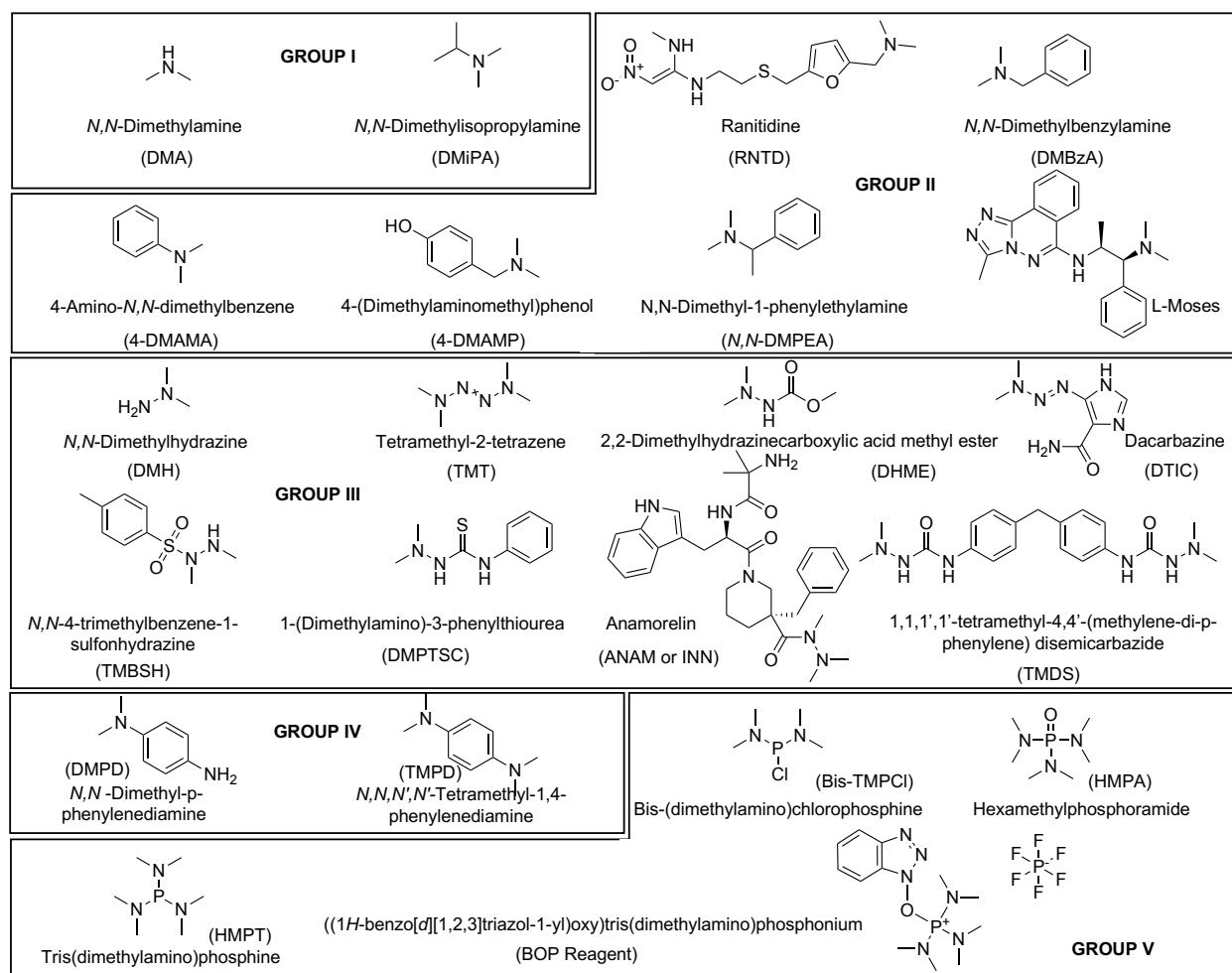
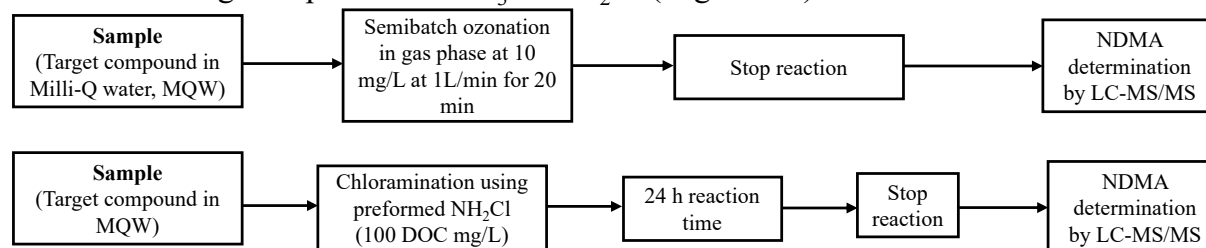
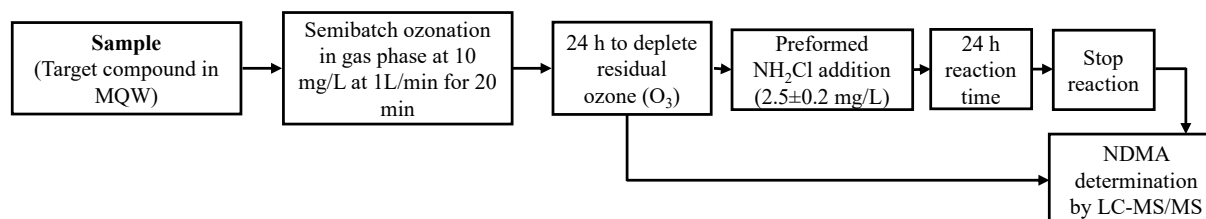


Fig. 1 Structures of target anthropogenic compounds. Group I are DMA-like compounds, Group II are DMBzA-like compounds, Group III are DMH-like compounds, Group IV are dye-related compounds, and Group V are organophosphates with DMA.

A. Direct or single-step oxidation: O₃ or NH₂Cl (High Dose)



B. Sequential oxidation by semibatch ozonation: Pre-O₃ / Post-NH₂Cl (Set-up 1 – High Dose)



C. Sequential oxidation by batch ozonation: Pre-O₃ / Post-NH₂Cl (Set-up 2 – Low Dose)

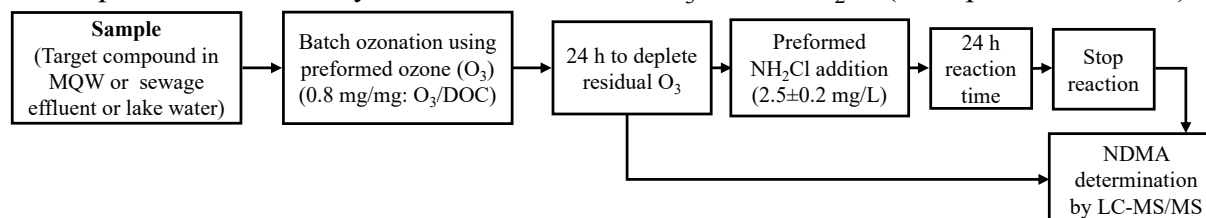


Fig. 2 Scheme of experimental set-ups in this study.

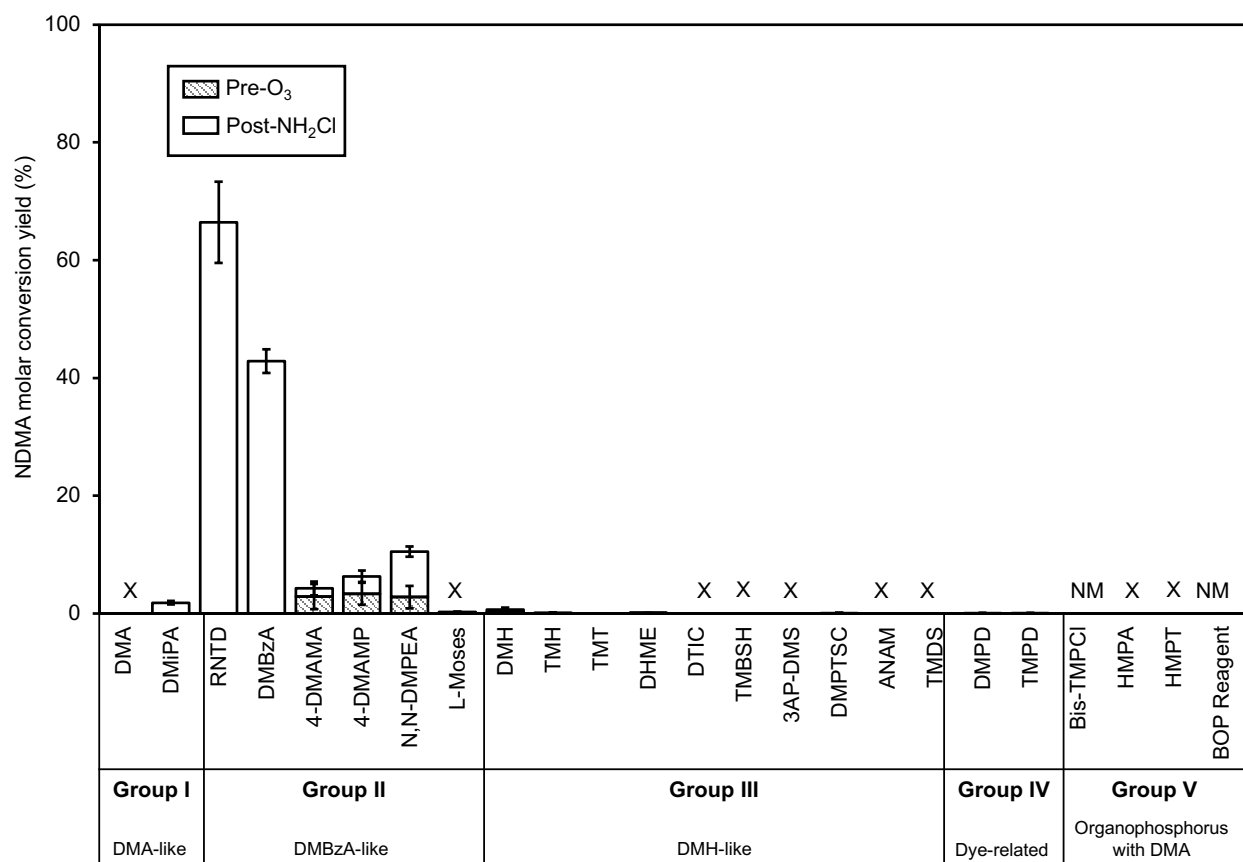


Fig. 3 NDMA molar conversion yields (i.e., NDMAFP yields) of 1 μ M target compounds in pH buffered Milli-Q water during preozonation with O₃-to-DOC of 0.8 mg/mg (0.2–0.3 mg O₃/L) and chloramination with NH₂Cl of 2.5 $\pm$ 0.2 mg Cl₂/L. Note that NH₂Cl-NDMAFP (i.e., Post-NH₂Cl-NDMAFP) yield was calculated as the difference between O₃-NH₂Cl-NDMAFP yield (i.e., NDMAFP yield after preozonation and post-chloramination) and the Pre-O₃-NDMAFP yield (i.e., O₃-NDMAFP yield after preozonation). NDMAFP yields are mean and standard deviations after duplicate measurements. X means not detected, NM means not measured, and black spaces indicate <LOQ (2 μ g/L: 3.0% at 1 μ M target compound).

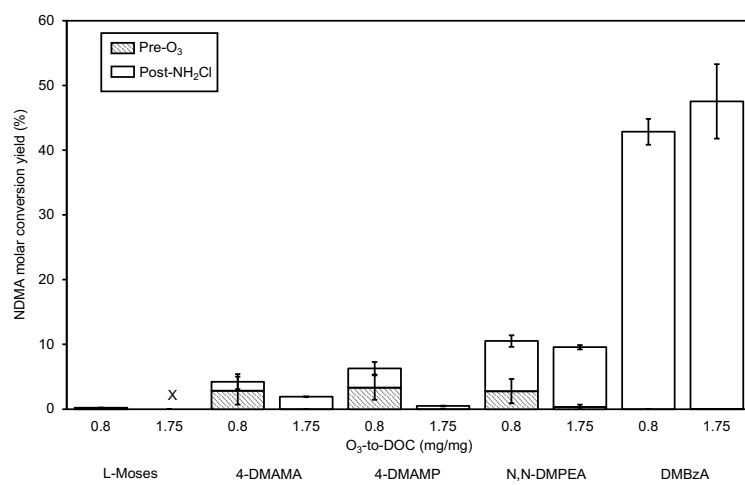


Fig. 4 NDMA molar conversion yields (i.e., NDMAFP yield) of 1 μ M DMBzA-like compounds in pH buffered Milli-Q water during preozonation with O₃-to-DOC of 0.8 (0.2–0.3 mg O₃/L) versus 1.75 (0.4–0.7 mg O₃/L) followed by chloramination with NH₂Cl of 2.5 ± 0.2 mg Cl₂/L. NDMAFP yields are mean and standard deviations after duplicate measurements. X means not detected.

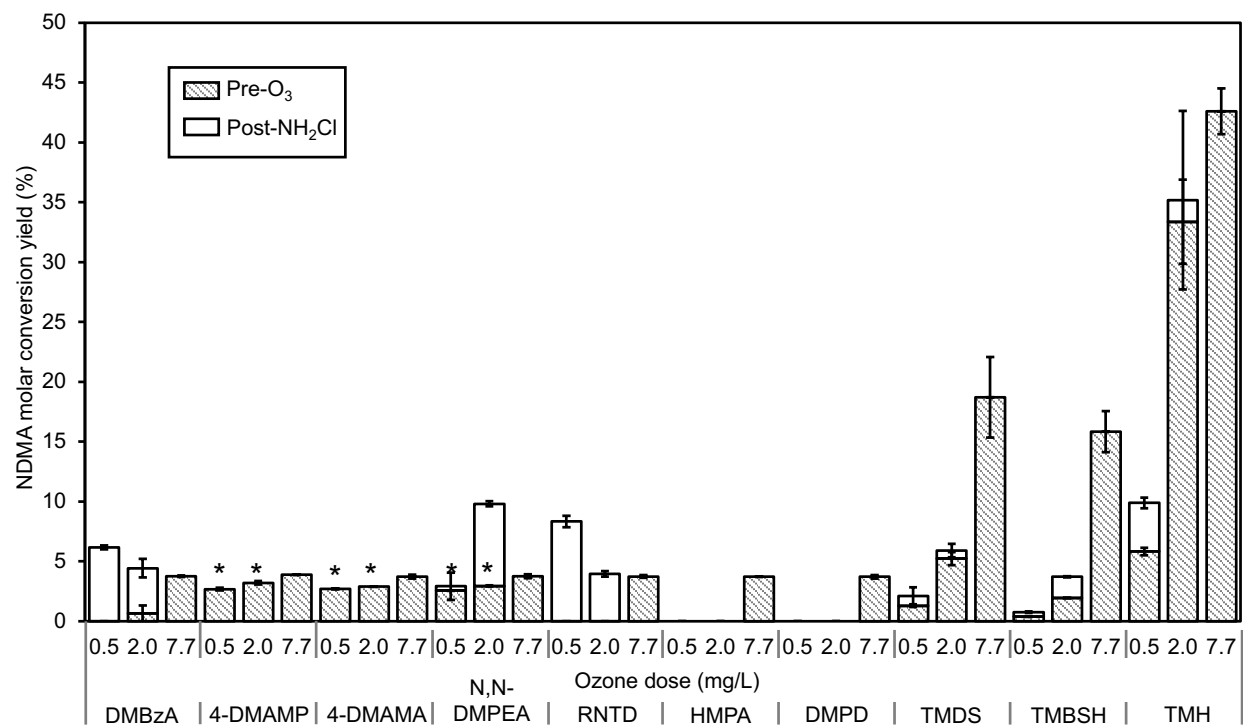


Fig. 5 NDMA molar conversion yields (i.e., NDMAFP yields) of 1 μ M of each precursor in lake water and sewage effluent during preozonation and post-chloramination. Lake water samples were dosed with 0.5 and 2.0 mg O₃/L, typically employed for drinking water treatment. And sewage effluent samples were dosed with O₃-to-DOC of 0.8 mg/mg (7.7 mg O₃/L). Post-chloramination for both samples were the same with NH₂Cl of 2.5 $\pm$ 0.2 mg Cl₂/L. *Note that pH buffered water was used because lake water sample was insufficient. Black spaces indicate <limit of quantification (LOQ) (2 μ g/L: 3.0% at 1 μ M target compound).

A. High Oxidant Dose

		NH ₂ Cl	
		High	Low
O ₃	High		DMH-like
	Low	DMBzA-like	DMA-like Org.-P w/DMA Dye-related

Priority from single-step oxidation
(O₃ or NH₂Cl)

B. Low Oxidant Dose

		NH ₂ Cl	
		High	Low
O ₃	High		
	Low	DMBzA-like	DMH-like DMA-like Org.-P w/DMA Dye-related

Priority from sequential oxidation
(Pre-O₃/Post-NH₂Cl)

General structures of NDMA precursors

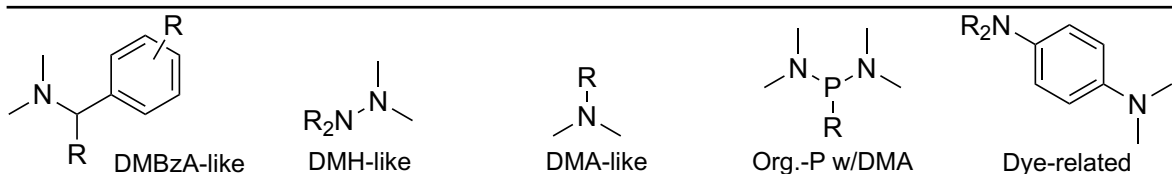


Fig. 6 The generalized importance of the structures of precursors from (A) single-step oxidation to (B) sequential oxidation by preozonation and post-chloramination in pH buffered Milli-Q water. Note the priority after sequential oxidation may be impacted by water matrix as was shown for DMH-like compound (e.g., TMSD) when tested in sewage-effluent samples (see Fig 5).

Table 1. NDMA molar conversion yields (i.e., NDMAFP yields) of target compounds in pH buffered Milli-Q water

NDMAFP yields (%) (±SD ^b)										
Classification of compounds	Target compound	Single-step oxidation				Sequential oxidation				Group
		This study		Referenced study		This study				
		O ₃	NH ₂ Cl	O ₃	NH ₂ Cl	Reference	Pre-O ₃	O ₃ -NH ₂ Cl	Post-NH ₂ Cl ^c	
DMA-like	DMA	X	0.50 (0.04)	<0.3	0.61 (0.03)	Marti et al., 2015 (O ₃); Hinneh et al., 2019 (NH ₂ Cl)	X	X	X	I
	DMiPA	–	12.2 (2.18)	–	9.3 (0.2)	Hinneh et al., 2019	X	X	X	
DMBzA-like	RNTD	–	74.5 (3.41)	–	51.3 (3.5) – 89.9	Hinneh et al., 2019, Shen and Andrews, 2011	X	X	X	II
	DMBzA	–	76.8 (0.03)	–	37.4 (4.2) – 83.8	Hinneh et al., 2019, Selbes et al., 2013	X	X	X	
	<i>4-DMAMA</i>	–	20.9 (0.3)	–	–	–	<LOQ	~3.0 (2.0)	~3.0 (2.0)	
	<i>4-DMAMP</i>	–	110 (12)	–	–	–	<LOQ	~3.0 (1.0)	~3.0 (1.0)	
	<i>N,N</i> -DMPEA	–	42.7 (3.8)	–	–	–	<LOQ	<LOQ	<LOQ	
	<i>L</i> -Moses (<i>L</i> -45)	–	0.37*	–	–	–	<LOQ	<LOQ	<LOQ	
DMH-like	TMH	52.1 (0.2)	<i>X</i>	–	–	–	38.9 (1.8)	41.5 (2.3)	2.57 (2.92)	III
	DMH	30.4 (4.4)	–	80	0.02	Schmidt and Brauch, 2008 (O ₃), Hinneh et al., 2019 (NH ₂ Cl)	18.8 (1.3)	18.4 (0.4)	X	

	TMT	11.0 (0.1)	0.30 (0.01)	19 (0.4)	0.39	Kosaka et al., 2014	–	–	–	
	DHME	5.70 (0.70)	<LOQ	8.0 (0.6)	0.071	Kosaka et al., 2014	5.1*	5.0*	X	
	DTIC	<LOQ	<LOQ	<0.3	<0.3	Marti et al., 2015	<LOQ	<LOQ	<LOQ	
	<i>TMBSH</i>	2.80 (0.13)	–	–	–	–	6.32 (2.62)	6.43 (2.53)	0.10 (3.00)	
	<i>3AP-DMS</i>	0.53 (0.14)	<LOQ	–	–	–	<LOQ	<LOQ	<LOQ	
	<i>DMPTSC</i>	2.92 (0.19)	<LOQ	–	–	–	4.33 (0.10)	4.28 (0.18)	X	
	<i>ANAM</i>	<LOQ	–	–	–	–	<LOQ	X	X	
	TMDS	20.4 (0.6)	0.62 (0.09)	23–27	0.7	Marti et al., 2015; Kosaka et al., 2009	17.0 (0.3)	17.0 (0.7)	X	
Dye-related	<i>DMPD</i>	<LOQ	0.34 (0.01)	0.043	–	Oya et al., 2008	X	X	X	IV
	<i>TMPD</i>	X	1.06 (0.02)	–	–	–	<LOQ	<LOQ	<LOQ	
Organophosphorus with DMA	<i>Bis-TMPCl</i>	–	0.55 (0.03)	–	–	–	–	–	–	V
	<i>HMPA</i>	–	3.50 (0.06)	–	–	–	X	X	X	
	<i>HMPT</i>	–	X	–	–	–	<LOQ	X	X	
	<i>BOP Reagent</i>	–	X	–	–	–	<LOQ	<LOQ	<LOQ	

^a % is NDMA molar conversion yield (i.e., NDMA formation potential (FP) yield), and it is [(mol of NDMA)/ (mol of target compounds)] multiply by 100; ^b SD is standard deviation from duplicate measurements; ^c Post-NH₂Cl is the NDMA formed from only NH₂Cl – it is calculated as the difference of O₃-NH₂Cl-NDMAFP yield and Pre-O₃-NDMAFP yield (i.e., O₃-NDMAFP after preozonation). Bolded number indicates maximum NDMA formed under the formation potential (FP) conditions. Asterisk (*) means a single measurement; Dash line (–) means not measured; X means not detected. LOQ is limit of quantification: 2 µg/L. For