Role of chlorine dioxide in NDMA formation from oxidation of model amines**Wenhui Gan¹, Tom Bond², Xin Yang^{1*}, Paul Westerhoff³**

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1 **Abstract.**

2 N-nitrosodimethylamine (NDMA) is an emerging disinfection by-product, and we show
3 that use of chlorine dioxide (ClO_2) has the potential to increase NDMA formation in waters
4 containing precursors with hydrazine moieties. NDMA formation was measured after
5 oxidation of 13 amines by monochloramine, ClO_2 and pre-treatment with ClO_2 followed by
6 post-monochloramination. Daminozide, a plant growth regulator, was found to yield
7 $5.01 \pm 0.96\%$ NDMA upon reaction with ClO_2 , although no NDMA was recorded during
8 chloramination. The reaction rate was estimated to be $\sim 0.0085 \text{ s}^{-1}$ and based upon our
9 identification by mass spectrometry spectra of intermediates the reaction likely proceeds via
10 the hydrolytic release of unsymmetrical dimethylhydrazine (UDMH), with the hydrazine
11 structure a key intermediate in NDMA formation. The presence of UDMH was confirmed by
12 gas chromatography–mass spectrometry (GC-MS) analysis. For 10 of the 13 compounds,
13 ClO_2 pre-oxidation reduced NDMA yields compared with monochloramination alone, which
14 is explained by our measured release of DMA. This work shows potential pre-oxidation
15 strategies to control NDMA formation may not impact all organic precursors uniformly, so
16 differences might be source specific depending upon occurrence of different precursors in
17 source waters. For example, daminozide is a plant regulator so drinking water that intakes
18 heavily influenced by upstream agricultural runoff could be at risk.

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24 **TOC/Abstract Art.**

39 Introduction.

40 N-nitrosodimethylamine (NDMA) is acutely carcinogenic, with a concentration of only
41 $0.7 \text{ ng}\cdot\text{L}^{-1}$ associated with a 10^{-6} lifetime cancer risk level¹. California has issued a
42 notification level of $10 \text{ ng}\cdot\text{L}^{-1}$ for NDMA in drinking waters and the United States
43 Environmental Protection Agency (USEPA) included it in Contaminant Candidate List 3, for
44 pollutants which may be considered for future regulation^{2,3}. Concern about NDMA has been
45 heightened by the increasing prevalence of polluted sources being used to produce drinking
46 water. For example, waters affected by wastewater effluents frequently produce higher
47 NDMA concentrations⁴.

48 In order to minimize risks associated with NDMA, it is imperative we improve our
49 knowledge of NDMA precursors and the pathways by which they generate NDMA. Previous
50 work suggested that DMA and monochloramine reacted to form unsymmetrical
51 dimethylhydrazine (UDMH), which could then be oxidized to NDMA⁵. Subsequently,
52 chlorinated unsymmetrical dimethylhydrazine (Cl-UDMH) was suggested as an important
53 intermediate after nucleophilic attack of DMA on dichloramine⁶. However, whereas molar
54 yields of NDMA from chloramination of DMA are low ($\sim 1\text{-}2\%$ ^{7,8}), it has been demonstrated
55 that some tertiary amines are far more potent precursors (i.e., higher molar yields upon
56 chloramination). NDMA yields from chloramination of specific tertiary amines like
57 methadone and ranitidine were over 50% ^{9,10}. Various mechanisms, including nucleophilic
58 substitution¹¹ and chlorine transfer followed by DMA release⁸ have been proposed to explain
59 NDMA formation from tertiary amines such as ranitidine. It has also been highlighted that
60 both monochloramine and dichloramine may play important roles in NDMA formation, for
61 example, from ranitidine and N,N-dimethyl-isopropylamine, respectively⁹.

Besides chloramines, oxidation of water samples by chlorine dioxide (ClO_2) can also form NDMA^{12, 13}. A small number of amines have been identified which can generate low yields of NDMA during oxidation by ClO_2 , for example, ranitidine and dimethylaniline (NDMA yields 0.055 and 0.016 % mol/mol, respectively)¹⁴. DMA does not have a high NDMA yield from reaction with ClO_2 ¹⁵. ClO_2 is a selective oxidant due to its ability to abstract one electron¹⁶. This means mechanisms which generate NDMA are likely to be different from application of chloramination. ClO_2 is applied for control of color, taste and odor¹⁷. And it is used as either a primary or secondary disinfectant, in the former case typically followed by secondary disinfectant, like chlorine and chloramine, to provide a distribution system residual¹⁸. As a secondary disinfectant, formation of NDMA has been observed in surface water after ClO_2 treatment¹². As a primary disinfectant, ClO_2 pretreatment followed by chloramination has exhibited inconsistent results for NDMA formation. Lee et al. reported that ClO_2 pretreatment of surface waters dramatically decreased NDMA formation¹⁵, whereas Shah et al. found that ClO_2 did not effectively reduce NDMA formation, and even increased NDMA in certain waters impacted by wastewater¹³. This indicates that pre-oxidation with ClO_2 can either deactivate specific precursors or convert them into more potent forms, depending on their identity. Further, Selbes and co-workers reported that NDMA yields of model tertiary amines after pre-oxidation with ClO_2 became similar to that from DMA i.e. that yields decreased for precursors more reactive than DMA and increased for the less potent precursors¹⁹. This suggests NDMA formation proceeded through the intermediate release of DMA. Nevertheless, the underlying oxidation mechanism responsible for the conflicting observations regarding influence of ClO_2 pretreatment on NDMA formation remains unclear.

Considering industrial and agricultural chemicals represent an important pool of NDMA precursors in surface waters, the aim of the present study was to assess the effect of ClO_2 on

NDMA formation through testing the NDMA formation potential (NDMA-FP) from amine precursors, with and without post-oxidation by chloramines. Model compounds were chosen to cover a variety amount of structures, including pharmaceuticals, personal care products (PPCPs), agricultural products and industrial contaminants with DMA functional groups. Model compounds with hydrazine moieties were also chosen as they had similar structures as NDMA. The occurrence of these compounds in surface water has been shown to be in the range of several ng/L to tens of $\mu\text{g/L}^{20, 21}$. For comparison, NDMA-FP with chloramination was also determined. The impact of ClO_2 dose, contact time and pH were also examined for selected precursors. Finally, the influence of a reactive precursor on NDMA-FP in authentic wastewater samples was estimated.

Materials and methods.

Reagents. Thirteen model compounds which possess a variety of chemical functionality were investigated (Figure 1), ranitidine was purchased from Alfa Aesar (USA), with the others obtained from J&K (China). Stock solutions (1 mM) of each model compound were prepared in either ultrapure water or acetonitrile. UDMH was obtained from Sigma (USA). Mixed nitrosamine calibration standards were purchased from Supelco (USA) and d6-NDMA was bought from Cambridge Isotope Laboratories (USA). Acetonitrile of HPLC grade was purchased from Merck (Germany). Dichloromethane was obtained from J&K (China). Resprep EPA Method 521 solid phase extraction (SPE) cartridges (6 mL/2 g) from Restek (USA) were used to pre-concentrate NDMA before analysis.

Monochloramine stock solutions were prepared daily by mixing equal volumes of diluted sodium hypochlorite (NaOCl) (Sigma, USA) and ammonium chloride solution at a molar ratio of 0.8:1 at pH 8. As with previous studies into oxidation by ClO_2 , ClO_2 solution

was prepared daily from gaseous ClO_2 by slowly adding dilute H_2SO_4 to a sodium chlorite (NaClO_2) solution using a set of glass gas diffusion bottle reactors, according to the standard method²². Consecutively, the resulting gas was collected and pumped through saturated NaOCl_2 solution and then collected into ice cold ultrapure water to produce a ClO_2 solution. Concentrations of ClO_2 and monochloramine were determined by the N-N-diethyl-p-phenylene diamine (DPD) – ferrous ammonium sulfate (FAS) titration method^{18, 22}.

Experimental procedures. All experiments were undertaken in duplicate and pH levels were controlled using phosphate buffer. When ClO_2 was used as sole oxidant, NDMA formation potentials (NDMA-FPs) were tested with ClO_2 in excess and a 5-day reaction time, following previous studies⁸. Each model compound was diluted to 2 μM , except for benzalkonium chloride and polyDADMAC, which were diluted to 2 $\text{mg}\cdot\text{L}^{-1}$, at pH 7 in 1 L amber bottles. ClO_2 was added at 0.2 mM before being left in the dark for 5 days at room temperature ($22\pm 1^\circ\text{C}$), before residual ClO_2 was quenched by sodium thiosulfate. A series of experiments with monochloramine as the oxidant were also conducted using the same concentrations and contact times as the ClO_2 tests. When ClO_2 was used for pre-oxidation, 20 μM ClO_2 was applied to 2 μM model compound at pH 7. After 15 min, residual ClO_2 was measured (Table S1) and quenched by adding a stoichiometric amount of sodium thiosulfate solution, based on following equation:

The removal of ClO_2 was confirmed using the DPD-FAS method. Afterwards, monochloramine solution (0.2 mM) was added for NDMA-FP tests as described above. Residual chloramine concentrations in every sample were confirmed after 5-day reaction.

Further testing for NDMA formation and dimethylamine (DMA) release was conducted with ClO_2 and/or monochloramine for the more reactive organic precursors. Tests used higher

precursor concentrations of 0.1 mM with NDMA being directly analyzed without solid phase extraction (SPE). When ClO_2 was used as the sole oxidant doses varied from 0.2 to 2 mM and reaction times from 10 seconds to 5 days. When ClO_2 was used as a pre-oxidant, the applied doses were the same, with a reaction time of 15 min. After residual chlorine dioxide was quenched, samples were reacted with 2 mM monochloramine for 5 days as described above.

The influent and effluent samples from a municipal wastewater treatment plant in South China were collected and the detailed treatment processes are described in Text S2 in the supporting information. The concentrations of daminozide were analyzed. The formation potential of NDMA from influent wastewater was also investigated by reacting with 2 mM chlorine dioxide for 5 days at pH 7.

Analytical methods. NDMA was concentrated by a factor of 500 by SPE prior to analysis using Ultra Performance Liquid Chromatography tandem mass spectrometry (UPLC/MS/MS) based on the method of Ripollés and co-workers²³. In brief, NDMA samples (500 mL) were spiked with 500 ng·L⁻¹ d6-NDMA as internal standard and concentrated by SPE extraction. 15 mL dichloromethane was used to elute NDMA before samples were further concentrated to 1 mL using a rotary evaporator at 30°C²⁴. For NDMA analysis without SPE extraction, samples were directly sent to UPLC/MS/MS. The detection limit of the method (SPE-UPLC/MS/MS) was 0.67 nM. Relative recoveries of NDMA, once corrected using the internal standard, ranged from 94 to 102%. DMA was quantified by gas chromatography-mass spectrometry (GC-MS) after derivation with benzenesulphonyl chloride (BSC) solution based on the method of Wang et al²¹. The detection limit for DMA was 2.2 nM. Additional details of the NDMA and DMA analysis are supplied as Text S1 in the Supporting Information (SI). Daminozide in wastewater samples was analyzed by UPLC/MS/MS after being concentrated on SPE (please see the SI).

Analysis of UDMH was based on the method of Rutschmann et al²⁵, with pentafluorobenzoyl chloride (PFB-Cl) as the derivatization agent and using GC-MS for quantification. Quantification of UDMH was carried out by selected ion monitoring (SIM) using the molecular ion (M⁺) at m/z 448 and fragment ions at m/z 181, 195, and 253. Details of UDMH analysis are supplied in the SI.

Results and discussion

NDMA formation during oxidation with chlorine dioxide. Six of the 13 precursors formed detectable levels ($\geq 0.034\%$ mol/mol) of NDMA during oxidation with chlorine dioxide (Table 1 and Figure S1). DMA formed no detectable NDMA during ClO₂ oxidation (Table 1). NDMA yields from TMA, DMBzA and DMPD were around 0.1% in each case, while tetracycline and DMDC produced $0.31 \pm 0.01\%$ and $0.48 \pm 0.01\%$, respectively (Table 1). Padhye and coworkers reported NDMA formation from direct reaction between ClO₂ and DMDC, albeit at a lower yield (0.004%)²⁶, than the one in the current study. This difference may be explained by the longer reaction time of 5 days (rather than 24 h) and higher ClO₂ dose of 0.2 mM (rather than 0.1 mM) used in the current study. Also, tetracycline was observed as a NDMA precursor during ClO₂ oxidation¹⁴. Since reaction between DMA and ClO₂ did not generate detectable levels of NDMA, this indicates that DMA was not an important intermediate in NDMA formation during oxidation of the other precursors by ClO₂. Daminozide was the most potent precursor, having a molar NDMA yield of $5.01 \pm 0.96\%$. To our knowledge this is the first time such high NDMA yields have been reported from reactions between amines and ClO₂.

Daminozide contains a hydrazine ((R₁R₂)N-N(R₃R₄)) functionality (Figure 1), which means that there is no requirement for an external nitrogen source during NDMA formation,

as is the case for the other precursors. Daminozide is analogous to 1, 1-dimethylhydrazine (UDMH) in this respect. It is interesting to note that high yields of NDMA from ozonation of both these compounds have been reported: 55% and 80% from daminozide and UDMH respectively²⁷. It is also relevant that there are multiple analytical methods for quantification of daminozide which rely upon hydrolysis of daminozide to UDMH followed by derivatization of the latter²⁸.

NDMA formation pathways during oxidation of daminozide with chlorine dioxide.

Since the mechanism which leads to NDMA formation from reaction between daminozide and ClO_2 is unresolved, the relevant pathways were investigated further. Aqueous reactions involving ClO_2 may proceed through one-electron abstraction with chlorite release²⁹, instead of oxidative substitution or addition, as can occur with chlorine or chloramines³⁰. For daminozide, the most likely sites for initial reaction with ClO_2 are the two nitrogen lone pairs. Thus, a mechanism is proposed as one possible pathway in which initial electron abstraction precedes release of either DMA or UDMH by hydrolysis (Figure 2). Further, since no NDMA was detected during reaction between DMA and ClO_2 (Table 1), it was likely that UDMH, rather than DMA, was the key intermediate in NDMA formation. Moreover, UDMH formation was confirmed by using GC-MS during reaction between daminozide and ClO_2 (Figure S2 and S3). UDMH yields as functions of oxidant dose during 5 min exposure of daminozide to ClO_2 (Figure S4) and at constant ClO_2 dose of 5:1 at variable contact times of up to 60 min (Figure S5) were also investigated. The detected UDMH release from daminozide ranged from 0.2 to 0.6% at ClO_2 to daminozide molar ratios from 1:0.1 to 1:1 and 5 min contact time. At higher ClO_2 doses, levels of UDMH decreased and it was barely detected when the dose increased to 10:1, possibly due to rapid reaction with ClO_2 (Figure S4). Furthermore, UDMH release from daminozide was observed to increase during the first 10-min of reaction between daminozide and ClO_2 , at a constant ClO_2 dose of 5:1, and

thereafter decrease rapidly (Figure S5). These data are in agreement with the hypothesis that UDMH release from daminozide is likely to be the rate-limiting step in NDMA formation.

The behavior of daminozide and UDMH under relevant oxidation scenarios was directly compared in order to investigate whether NDMA formation can be explained by release of the latter from the former. NDMA yields from oxidation of daminozide steadily increased from $1.22 \pm 0.06\%$ at a ClO_2 dose of 2:1 to $3.61 \pm 0.10\%$ at a ClO_2 dose of 20:1 after 5-day reaction (Figure 3a). Equivalent experiments with UDMH as a precursor exhibited a similar pattern: from NDMA formation of $1.10 \pm 0.03\%$ at a ClO_2 dose of 2:1 to $3.42 \pm 0.04\%$ at a dose of 20:1 (Figure 3a). Furthermore, a linear relation with $R^2=1.00$ was observed between NDMA formation from UDMH and daminozide, when these two precursors were oxidized by ClO_2 under the same reaction conditions (Figure 4). This supports the hypothesis that NDMA formation from daminozide proceeds via oxidation of UDMH. It should also be noted that NDMA yields from UDMH were consistently about 95% of those from daminozide at ClO_2 pre-oxidation doses of 2:1 to 20:1 (Figure 3a), which indicated other minor formation pathways also contribute. Another notable feature of NDMA formation from oxidation of daminozide with ClO_2 was its rapid formation kinetics, with a 0.0085 s^{-1} estimated pseudo-first order reaction rate constant (k) (Table S2 and Figure S6). The estimate of k was based on the following kinetic model developed by Shen and co-workers³¹ by fitting NDMA conversion curve of daminozide with ClO_2 oxidation: $Y = \frac{\theta}{1 + 10^{k \cdot (\text{Lag} - t)}}$, where Y is the NDMA molar conversion at given reaction time (t); θ is the maximum molar conversion obtained at kinetic testing; Lag is the time required to achieve 50% of the ultimate molar conversion.

To complement these results, DMA “release” following oxidation of daminozide was quantified (Figure 5). While no DMA was detected from chloramination of daminozide, low yields were observed during oxidation by ClO_2 from $1.86 \pm 0.05\%$ at a ClO_2 dose of 2:1 to

0.03±0.01% at a dose of 20:1. The decreased DMA release with increasing ClO₂ dose could be due to the transformation to the pathway of UDMH release. These DMA yields cannot account for the observed NDMA formation during ClO₂ oxidation of daminozide.

Figure 3c displays the effect of pH on NDMA formation from daminozide from reaction with ClO₂. The highest formation occurred at pH 6 and 7. After a 3-day reaction time, NDMA yields were 3.24±0.14% and 3.50±0.11% respectively at pH 6 and 7, while only 0.80±0.06% and 2.07±0.04% was recorded at pH 5 and 8, respectively.

It was previously noted that ClO₂ reacted faster with deprotonated amines than protonated ones, therefore pH may affect NDMA-FPs resulting from reaction with ClO₂^{15, 19}. Further, Lee et al¹⁵ noted apparent rate constants for oxidation of amines by ClO₂ vary with pH, since deprotonated amines react more strongly with ClO₂. Therefore, rate constants of tested amines reached a stable maximum at pH values above the amine's pK_a. Although the DMA moiety of daminozide has a pK_a of 2.8³², NDMA formation from reaction between ClO₂ and daminozide reached a peak at pH 6-7 (Figure 3c). Therefore, this indicates that the initial reaction between daminozide and ClO₂ was not the rate-determining step in NDMA formation. Instead, as UDMH has a pK_a value of 7.21³³, it's reasonable that oxidation of UDMH by ClO₂ reached higher efficiency at circumneutral pH and that this step is relevant to the overall NDMA yield. Equivalent experiments to assess the impact of pH were undertaken with UDMH and these displayed a similar pattern with daminozide, with NDMA yields of 1.72±0.14%, 3.04±0.10%, 3.32±0.05% and 1.94±0.04%% at pH 5, 6, 7 and 8 respectively (Figure 3c). This indirectly indicated that UDMH was the important intermediate from daminozide to react with ClO₂ to form NDMA. DMA formation from oxidation of daminozide by ClO₂ was low at all pH levels (Figure 3d). In contrast to NDMA formation from this precursor, DMA increased with pH, to a maximum of 0.15±0.05% at pH 8 (Figure 3d), which indicates base catalyzed hydrolysis of daminozide releases DMA.

NDMA formation during oxidation by monochloramine. The NDMA yields during chloramination from this study are comparable with those reported previously (Table 1). In particular, those from DMBzA, DMDC, DMAI, BAC, ranitidine and polyDADMAC agree well with previous literature^{15, 34-36} (Table 1). Conversely, daminozide did not form a detectable amount of NDMA during chloramination, a contrast to its behavior during reaction with ClO_2 .

To compare with data from daminozide, NDMA formation from oxidation of UDMH by NH_2Cl was also investigated. Yields were low and varied from $0.30 \pm 0.02\%$ to $0.50 \pm 0.03\%$ at molar NH_2Cl doses of 2:1 – 20:1 (Figure 3b). These data provide further evidence that ClO_2 , rather than NH_2Cl , was the oxidant largely responsible for NDMA formation from both daminozide and UDMH.

NDMA formation during oxidation by chlorine dioxide-monochloramine. NDMA formation from ten out of 13 precursors was reduced upon ClO_2 pre-oxidation, relative to yields from chloramination alone. For example, reductions in NDMA formation of 94%, 73%, 68% and 67% for DMAP, DMDC, DMBzA and ranitidine, respectively (Table 1). Moreover, NDMA formation from the quaternary amine polymer BAC was reduced by 21% and that from DMAI was reduced by 29%. Pretreatment using ClO_2 caused a small increase in the NDMA yield from DMPD, from $0.3 \pm 0.02\%$ to $0.5 \pm 0.02\%$. Only for daminozide did ClO_2 pre-oxidation enhance NDMA formation, as $5.04 \pm 0.21\%$ was measured during oxidation by $\text{ClO}_2\text{--NH}_2\text{Cl}$, while no NDMA was formed from monochloramination alone. ClO_2 pretreatment was also observed to effectively reduce NDMA formation from ranitidine, DMBzA and DMDC in previous studies^{15, 19}. In addition, enhanced NDMA conversion from reaction between daminozide and ClO_2 was reported by Selbes and co-workers, relative to that during chloramination. However, the increased NDMA conversion was attributed to

DMA release from daminozide¹⁹, rather than the pathway via UDMH proposed in this study. Moreover, NDMA formation from oxidation of daminozide by ClO₂ alone (without post-oxidation by chloramines) was not evaluated in the earlier study.

It has been proposed in literature that NDMA precursors can be decomposed to either DMA or oxidation products containing a DMA functional group during pre-oxidation with ClO₂, which resulted in NDMA-FPs similar to that of DMA after post-chloramination¹⁹. This explanation is consistent with the effect of ClO₂ pre-oxidation on DMDC and DMAP, which reduced NDMA-FP yields by 75% and >95%, respectively (Table 1). The NDMA-FP reduction of polyDADMAC was more likely due to the degradation to monomers by ClO₂, rather than conversion to DMA or TMA, because NDMA yield after pre-oxidation with ClO₂ was far less than that from DMA or TMA, namely $0.04 \pm 0.01\%$. Previous studies found that polyDADMAC monomers are less reactive than the quaternary polymer and consequently have with much lower NDMA-FP^{35, 37}. However, Park et al reported that ClO₂ pretreatment didn't significantly reduce NDMA-FP from polyDADMAC³⁸. Differences in experimental conditions account for these differences. In our study, NDMA-FP was measured after 5-days, whereas NDMA-FP was tested only after 1-day in the earlier study³⁸.

Ranitidine, DMAI and daminozide were selected for further experiments to study the effect of ClO₂ pretreatment considering their relatively high NDMA-FPs during ClO₂-NH₂Cl and the contrasting effect of ClO₂ pretreatment on these precursors.

Increasing ClO₂ dose during pre-oxidation of daminozide by ClO₂-NH₂Cl enhanced NDMA formation: from $1.02 \pm 0.04\%$ to $3.50 \pm 0.01\%$, as the ClO₂ dose increased from 0.2 mM to 2 mM of ClO₂ (Figure 5). Liberation of DMA from daminozide followed the opposite pattern, as it decreased from $1.86 \pm 0.04\%$ at a ClO₂ dose of 0.2 mM to 0.03% at a ClO₂ dose of 2 mM (Figure 5). Therefore, release of DMA cannot account for the considerable

enhancement of NDMA yields with increased ClO_2 pre-oxidation doses. The behavior of UDMH when oxidized by $\text{ClO}_2\text{-NH}_2\text{Cl}$ was directly compared with that of daminozide. UDMH was observed to follow a similar trend to daminozide, as NDMA yields increased with larger ClO_2 pre-oxidant doses and yields from the two precursors were always within 0.3% of each other under the various ClO_2 pre-oxidation doses.

Results from experiments with ranitidine at various ClO_2 pre-oxidation doses showed that higher ClO_2 doses enhanced the reduction of NDMA-FP, relative to the amount produced by chloramination alone (Figure S7). The reductions in NDMA-FP at ClO_2 doses of 0.2, 0.5, 1 and 2 mM were 54%, 93%, 95% and 98%, respectively. This illustrates higher ClO_2 pre-oxidation doses enhanced the reduction of NDMA. We quantified DMA release during the experiments. Release of DMA from ranitidine after pre-oxidation increased with increasing ClO_2 doses, from $0.83 \pm 0.15\%$ at 0.2 mM ClO_2 to $1.96 \pm 0.09\%$ at 2 mM ClO_2 (Figure S7). Therefore, the lower NDMA yield from ranitidine following ClO_2 pre-oxidation can be explained by with cleavage of DMA and/or TMA from the furan moiety.

Equivalent experiments with DMAI (Figure S7) showed ClO_2 pretreatment reduced NDMA formation, by 45% at a ClO_2 dose of 2:1. However, increasing the ClO_2 dose resulted in no additional reduction in NDMA-FP yield. Meanwhile, stable DMA yields (about 8%) from DMAI was observed as the ClO_2 doses from 5:1 to 20:1 (Figure S7). This implies that liberation of DMA was facile from this precursor and did not increase at the higher ClO_2 pre-oxidation doses used. As with ranitidine the observed decrease in NDMA formation can be explained by liberation of a less reactive precursor fragment, i.e. DMA and/or TMA.

Implications for water treatment. ClO_2 as a primary disinfectant is effective to inactivate majority of tertiary amines¹⁵. However, as highlighted by the high yields of NDMA reported in the current study from daminozide, deployment of ClO_2 as a primary or pre-

oxidant during water treatment has the potential to enhance NDMA formation in waters containing precursors with hydrazine moieties. Its application was restricted to non-food crops in 1989 in the USA³⁹ due to concern about the possible carcinogenic effects arising from exposure to it and its degradation product UDMH⁴⁰. Nonetheless, daminozide is still manufactured⁴¹ and applied as a plant growth regulator²⁵, with regulatory approval in the EU, Australia, USA, and China for use on non-food crops or ornamentals^{42, 43}. Although contamination of German groundwaters by daminozide was considered unlikely²⁷, the continued use of daminozide means its transport into surface waters remains a possibility, especially in areas of heavy use. Additional information about the occurrence of daminozide in surface waters and, more broadly, the potential for NDMA formation from chlorine dioxide treatment of surface waters containing daminozide and/or other precursors with hydrazine moieties is needed.

Since hydrazine and its derivatives are used in agriculture, as pesticides and fungicides, in boiler feed water treatment and pharmaceutical production⁴⁴, precursors with hydrazine moieties are possible to be found in surface water or soil, like the pesticide maleic hydrazide⁴⁵. A study held in Iran with collected water samples from Karoon river detected a hydrazine concentration of 0.4 μM ⁴⁶. Because available occurrence data of daminozide in water is limited, daminozide concentrations were analyzed in samples collected from a Chinese wastewater treatment plant. The concentration of daminozide was 124.77 ± 9.86 ng/L in the influent and was 103.38 ± 7.78 ng/L in the effluent. Furthermore, ClO_2 oxidation (2 mM) was applied on filtered influent and the 5-day NDMA-FP was 71.18 ± 5.07 ng/L (Table S3). Based on the NDMA yield from daminozide of 5.01% (Table 1), daminozide was estimated to account for ~15% of the NDMA-FP from ClO_2 oxidation. More sampling is required to fully evaluate the importance of daminozide as an NDMA precursor across a diverse range of surface water types and oxidation scenarios. This study also demonstrated that NDMA

formation from oxidation of daminozide with ClO_2 is distinct from that typically occurring during the chloramination of wastewater impacted waters. Oxidation of daminozide by ClO_2 is fast, with significant NDMA formation within 10 min, and with highest yields at pH 6-7. In contrast, NDMA formation from wastewater-impacted waters chloramination is slow, continuing through distribution systems and with highest yields around pH 8⁴⁷. Therefore, disinfecting at lower pH, as suggested previously as a strategy for NDMA mitigation, would maximize NDMA formation resulting from oxidation of hydrazine-containing precursors by ClO_2 .

Similarly, the high yields of NDMA reported from oxidization of UDMH and daminozide by ozone suggest its deployment as a pre-oxidant would also be counterproductive for NDMA control in waters containing precursors with hydrazine moieties²⁷. Daminozide represents a class of NDMA precursors that react differently to pre-oxidation than other identified precursors. Consequently, site-specific variations in the effectiveness of pre-oxidation at water treatment plants, or in the use of chlorine dioxide to treat stormwater or wastewater, are anticipated. Alternative precursor control strategies, such as sorption by activated carbon or pre-oxidation with free chlorine, are predicted to be more effective in these situations.

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Supporting information

Details of analytical methods and additional figures are included. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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547 **Table 1.** Molar yields of NDMA from model precursors in this study and literature.

Precursor	This study				Reference
	ClO ₂	NH ₂ Cl	ClO ₂ -NH ₂ Cl	Previous studies	
	NDMA yield(% mol/mol)				
DMA	ND	0.71 (±0.08)	0.87(±0.06)	0.24 ^a	5
				1.2 ^a	48
				3.0 ^a	15
TMA	0.11 (±0.01)	0.59 (±0.01)	0.21 (±0.03)	1.2 ^a	15
				1.9 ^a	34
DMBzA	0.10 (±0.02)	83.47 (±0.34)	27.45 (±0.47)	83.8 ^a	34
DMDC	0.48 (±0.01)	2.15 (±0.03)	0.60 (±0.04)	2 ^a	15
DMPD	0.13 (±0.01)	0.34 (±0.02)	0.67 (±0.02)	0.04 ^b	49
DMS	ND	1.08 (±0.10)	0.40 (±0.05)	52 ^b	49
DMAI	ND	5.61 (±0.13)	5.02 (±0.04)	6 ^a	15
DMAP	ND	11.96 (±0.21)	0.71 (±0.01)	4.2 ^a	15
BAC*	ND	0.27 (±0.01)	0.20 (±0.01)	0.26 ^a	35
Ranitidine	ND	65.66 (±1.72)	21.50 (±0.83)	40.2 ^a	7
				62.9 ^a	36
				82.7 ^a	31
Tetracycline	0.31 (±0.01)	0.54 (±0.04)	0.28 (±0.03)	1.2 ^a	9
PolyDADMAC*	ND	0.10 (±0.01)	0.04 (±0.01)	0.19 ^a	35
Daminozide	5.01 (±0.96)	ND	5.04 (±0.21)	55 ^b	27
	3.61 (±0.10)*		3.50 (±0.01)*		
UDMH	3.38 (±0.03)*	0.47 (±0.04)*	2.44 (±0.05)*	0.51 ^a	50

548 The values show the average±standard deviation for each yield. ND = not detectable, yields < 0.034%.
549 ClO₂: 0.2 mM ClO₂ + 2 μM precursor; ClO₂-NH₂Cl: 20 μM ClO₂ + 2 μM precursor for 15 min followed
550 by 5-day reaction with 0.2 mM NH₂Cl; NH₂Cl: 0.2 mM NH₂Cl + 2 μM precursor.
551 ^a NDMA molar conversion upon chloramination
552 ^b NDMA molar conversion upon ozonation
553 *data was collected with initial precursors level (1 mM) reacting with 2 mM ClO₂.
554

555

Figure 1. Structures of model compounds.

Figure 2. Proposed NDMA formation mechanism from daminozide by ClO_2 .

Figure 3. NDMA formation during oxidation of daminozide and UDMH by ClO₂ and NH₂Cl at pH 7 and 5-day reaction with the variation of oxidant to precursor molar ratios (a-b) ([daminozide] or [UDMH] =0.1 mM, ClO₂ and NH₂Cl varied from 0.2 to 2 mM.) and pH (c-d) ([daminozide] or [UDMH] =0.1 mM, [ClO₂] = 1 mM).

Figure 4. Linear relationship between NDMA formation from ClO_2 oxidation of daminozide and UDMH: 100 μM daminozide/UDMH, 0.2–2 mM ClO_2 for 5 days.

Figure 5. NDMA formation from ClO₂-NH₂Cl oxidation of daminozide and UDMH (left) and DMA formation after ClO₂ pretreatment of daminozide (right). Oxidation conditions = 0.2–2 mM ClO₂ followed by 2 mM NH₂Cl for 5 days.