PAPER

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Low-level *N*-nitrosamine occurrence in disinfected drinking water and relationships with standard water quality indicators

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N-Nitrosodimethylamine (NDMA) is a probable human carcinogen that can be formed in drinking water treatment systems as a byproduct of chloramination and chlorination. Occurrence of NDMA and other *N*-nitrosamines in the United States has been previously assessed using a variety of techniques, but few studies have been able to distinguish between concentrations above and below suggested screening levels (*e.g.*, 0.7 ng L^{-1} for NDMA). This study evaluated the presence of NDMA and seven other *N*-nitrosamines in two drinking water distribution systems in the northeastern United States (*n* = 42 locations) and assessed factors influencing its occurrence. NDMA was present in 98% of water samples across both systems (MDL 0.15 ng L^{-1}) with higher concentrations in the system utilizing chloramination (0.39–1.32 ng L^{-1}) than the system utilizing chlorination (0.20–0.54 ng L^{-1}). Samples were collected before and after flushing taps, and higher concentrations of NDMA were observed in samples collected prior to flushing, suggesting increased formation due to temporary stagnation. *N*-Nitrosomorpholine was the only other *N*-nitrosamine detected in samples taken after tap flushing (5% detection rate; MDL 0.21 ng L^{-1}), though four additional nitrosamines were detected before flushing in at least one sample. Water quality parameters (*i.e.*, chlorine residual, dissolved organic carbon, total dissolved nitrogen, specific UV absorbance, pH, temperature, specific conductance) and other disinfection byproducts (trihalomethanes) were measured to assess correlations with NDMA occurrence, and NDMA concentrations were negatively correlated with residual chlorine in both distribution systems. These observations illustrate the potential prevalence of low-level nitrosamine occurrence in disinfected drinking water and provide a framework for system-specific understanding of NDMA occurrence, which can aid in prioritizing locations where further investigation may be needed to mitigate potential exposure risks.

Water impact

N-Nitrosamines present a health concern in drinking water due to their carcinogenic potency. This analysis of *N*-nitrosamines using sensitive analytical techniques demonstrated low-level occurrence of *N*-nitrosodimethylamine (NDMA) in 98% of sampled waters and found negative correlations between NDMA concentration and residual chlorine within different distribution systems. These findings inform future monitoring efforts by illustrating the potential prevalence of low-level nitrosamine occurrence and aiding in the prioritization of locations for further investigation of potential exposure risks.

Introduction

N-Nitrosamines are a class of organic contaminants that present a health concern in drinking water due to their carcinogenic potency.[1,2] These compounds can enter drinking water systems *via* direct contamination of source water or through formation as disinfection byproducts (DBPs).[3–5] *N*-Nitrosodimethylamine (NDMA), the most commonly detected nitrosamine in drinking water,[2,6,7] is listed in the United States Environmental Protection Agency's (USEPA) Integrated Risk Information System (IRIS) with a 10^{-6} lifetime excess cancer risk level of 0.7 ng L^{-1} (pptr).[8] Accurate assessments of the potential health risks posed by NDMA exposure rely on robust differentiation between measurements above and below this level of concern.[9]

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Surveys of nitrosamine occurrence in drinking water often focus on NDMA and other common *N*-nitrosamines (*N*-nitrosomethylethylamine (NMEA), *N*-nitrosodiethylamine (NDEA), *N*-nitrosodi-*n*-propylamine (NDPA), *N*-nitrosodi-*n*-butylamine (NDBA), *N*-nitrosopyrrolidine (NPYR), *N*-nitrosopiperidine (NPIP), *N*-nitrosomorpholine (NMOR), and *N*-nitrosodiphenylamine (NDPhA)). Results collected through the USEPA's Unregulated Contaminant Monitoring Rule 2 (UCMR2) in 2008–2010 showed an NDMA detection rate of 10% (of n = 18 098 total samples) across 1198 public water systems (method reporting limit (MRL) of 2 ng L^{-1}).[10] Five other nitrosamines were monitored but seldom detected (NMEA, NDEA, NDPA, NDBA, NPYR), despite sometimes forming under similar conditions as NDMA.[11] Smaller surveys have been conducted in various regions, including the United States and Canada,[3,12–17] Spain,[18] United Kingdom,[19] China,[20–22] and Japan,[23] with varied method detection limits (MDLs) and MRLs. Few studies have quantified NDMA below its IRIS 10^{-6} risk level (0.7 ng L^{-1}) (Table S1).[12,18,20] Furthermore, traditional sampling techniques for drinking water typically require a period of tap flushing to ensure that water is being drawn from the distribution system, rather than from water that has stagnated in household plumbing. While this approach ensures more consistent data collection (*i.e.*, less variation based on household-level dynamics), it may not be representative of true exposures at the tap, and further study is necessary to understand the effects of temporary stagnation on NDMA and other nitrosamines. Taken together, the limited number and scale of existing assessments, combined with sensitivity limitations and constraints of traditional sampling techniques, indicate further need for investigation of low-level occurrence in distribution systems.

A growing body of literature has highlighted several key factors driving NDMA formation in treated water systems: the use of chloramination for secondary disinfection,[2,5–7,14,24,25] contributions from wastewater effluent,[14,24–27] and the presence of high-yield amine precursors such as dimethylamine[24,28] and ranitidine.[29–31] Nevertheless, current understanding of NDMA precursors in these systems is unable to account for the total formation of NDMA in drinking water,[2,32–36] and examination of individual precursors or combinations of precursors across different utilities is impractical for evaluating overall NDMA formation. Additionally, variable disinfection practices (*e.g.*, the use of chlorination *vs.* chloramination for secondary disinfection) can affect the formation of NDMA in distribution systems.[2] The use of bulk parameters (*e.g.*, dissolved organic nitrogen (DON), dissolved organic carbon (DOC)) as surrogate measurements of unidentified NDMA precursors could obviate the need to identify specific precursors and has been investigated in some studies.[12,13,19,21,33,36–38] However, the interactions between these parameters within different treatment systems remains poorly understood, and a proxy that holds in one system may not in another. If routinely monitored water quality characteristics were able to predict NDMA

occurrence, researchers could use this information to prioritize locations for further investigation to mitigate potential NDMA exposure risks.

Past efforts to establish health-protective standards for nitrosamines have been constrained by practical quantitation limits (PQLs) that exceed health-relevant thresholds.[39–41] Currently, there are no enforceable US regulations for *N*-nitrosamines in drinking water, although USEPA has considered some potential regulation[42,43] and has specified a risk screening level of 0.11 ng L^{-1} for NDMA in tap water.[44] Some states have established suggested levels for NDMA in drinking water, such as California's public health goal of 3 ng L^{-1} (derived from an estimation of carcinogenic risk[39]) and Massachusetts's guideline value of 10 ng L^{-1} (bounded by PQL limitations[40]). As a class of unregulated DBPs, nitrosamine control must be considered in conjunction with impacts on regulated DBPs, such as trihalomethanes (THMs) and haloacetic acids (HAAs).[45–49] Since individual DBPs are uniquely influenced by the combination of disinfectant practices, organic matter content, and reaction conditions in a given treatment system, understanding the interrelated effects of these variables on nitrosamine levels is key to making regulatory decisions and DBP management.

The objectives of this study were to assess the occurrence of NDMA and seven other nitrosamines in treated drinking water systems at health-relevant levels (*i.e.*, the USEPA 10^{-6} risk level) and investigate the relationships between nitrosamine concentrations and other common water quality metrics. Drinking water samples were collected before and after flushing taps from two public water systems, one chlorinated and one chloraminated, in the northeastern United States and analyzed using solid phase extraction (SPE) and liquid chromatography with tandem mass spectrometry (LC-MS/MS). Measurements of other water quality parameters (*e.g.*, chlorine residual, organic matter content, THMs) were also obtained and evaluated with respect to the presence of NDMA to evaluate possible relationships in each system. These relationships were also used to derive a framework for system-specific understanding of NDMA occurrence based on routinely monitored water quality characteristics.

Materials and methods

Chemicals and reagents

A certified reference standard containing 2000 μg mL^{-1} each of nine *N*-nitrosamines (NDMA, NDBA, NDEA, NDPhA, NDPA, NMEA, NMOR, NPIP, and NPYR) was purchased from Sigma Aldrich. Isotopically labeled reference standards (^{15}N-NDMA and NDMA-d_6) were purchased from Cambridge Isotope Laboratories. Optima LC-MS grade methanol and formic acid, and gas chromatography (GC) grade dichloromethane (DCM) were obtained from Fisher Scientific. Ultrapure (18 MΩ) water was obtained using a MilliQ IQ 7000 system equipped with an LC-Pak purifier and 0.2 μm Millipak filter. Additional reagent information is in the SI (Text S1).

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Sample collection

Water samples were collected from drinking water distribution systems in northeastern Maine in June 2024 (Region 1, n = 21 locations; Fig. 1a) and in eastern Massachusetts in January and February 2025 (Region 2, n = 19 locations; Fig. 1b). Region 1 served a small (<3300), dispersed population, some of whom reside on tribal lands, while Region 2 served a large (>100 000), dense urban population. Individual sampling locations were selected through voluntary participation. Water sources (kitchen faucets, bathroom faucets, or external spigots) were flushed until a minimum of two measurement criteria (temperature, pH, specific conductance) were stable (±5%) for three consecutive readings using a YSI Professional Plus multiparameter instrument (average flush time: 9 ± 3 minutes). Samples of finished water were also taken from the drinking water treatment plants in each region (DWTP 1 and DWTP 2). DWTP 1 used chlorination for secondary disinfection, while DWTP 2 used chloramination. Both systems drew from surface water (see treatment overviews in Fig. S1). Field blanks were collected using ultrapure water.

Samples for N-nitrosamine analysis were collected in pre-combusted (450 °C for 8 h), 1 L amber glass bottles with PTFE-lined caps. Three samples were collected at every sampling location (n = 42 locations; 126 total samples). At each location in the distribution systems (n = 40) and for the finished water tap at DWTP 1, one sample was collected immediately upon initiation of tap flow ("pre-flush"), and two samples were collected upon completion of flushing ("post-flush"). The finished water in DWTP 2 was collected from a point of continuous flow; these samples were collected in triplicate and considered to be post-flush samples. Samples were dechlorinated upon collection with 100 mg L^{-1} of sodium thiosulfate and kept on ice during field collection. ^{15}N-NDMA was added at 20 ng L^{-1} to each sample within 24 hours as a recovery standard. Samples were stored at 4 °C and extracted within two months of collection; recovery was stable for at least 2 months (Fig. S2).

N-Nitrosamine extraction and pre-concentration

N-Nitrosamine analysis of water samples was performed using a modified version of EPA Method 521.[50,51] Samples (initial volume of 1 L) were extracted using an automated SPE system (Promochrom Technologies) with pre-packed activated charcoal cartridges (Restek) and 10 μm inline filters (see Table S2 for SPE method parameters). Cartridges were eluted with 15 mL of DCM, which was passed through a reservoir packed with sodium sulfate to remove excess water and subsequently concentrated via nitrogen evaporation. Laboratory blanks and fortified laboratory blanks (0.5 ng L^{-1} of all nitrosamines) were prepared in ultrapure water and included in every extraction batch. NDMA-d_6 was added as an internal standard (1 μg L^{-1}) to all extracts (1 mL final volume).

Analysis of N-nitrosamines with LC-QqQ-MS

Sample extracts were analyzed via liquid chromatography with triple quadrupole mass spectrometry (LC-QqQ-MS) using an atmospheric pressure chemical ionization (APCI) source in multiple reaction monitoring (MRM) mode (Agilent). Reverse-phase chromatographic separation was performed using a ZORBAX RRHD Eclipse Plus C18 column (2.1 × 50 mm, 1.8 μm) (Agilent). See Tables S3–S5 and Fig. S3 for method parameters and performance details.

N-Nitrosamine calibration standards (0.1 to 10 μg L^{-1}) and continuing calibration check standards (0.5 μg L^{-1}) were made using a certified reference standard and internal standard (NDMA-d_6) and were analyzed using a weighted linear regression ($1/x$) with Agilent MassHunter Quantitative Analysis software. MDLs were calculated using the average and standard deviation of method blanks (n = 26; 0.15 ng L^{-1} for NDMA; Table 1).[52] NDMA was detected above the lowest calibration standard (0.1 μg L^{-1}) in some laboratory blank extracts. Measurements below the MDL were included in statistical tests but excluded from the detection rate and reported concentration ranges. Mean recovery (n = 134; samples and field blanks) was 67 ± 9%.
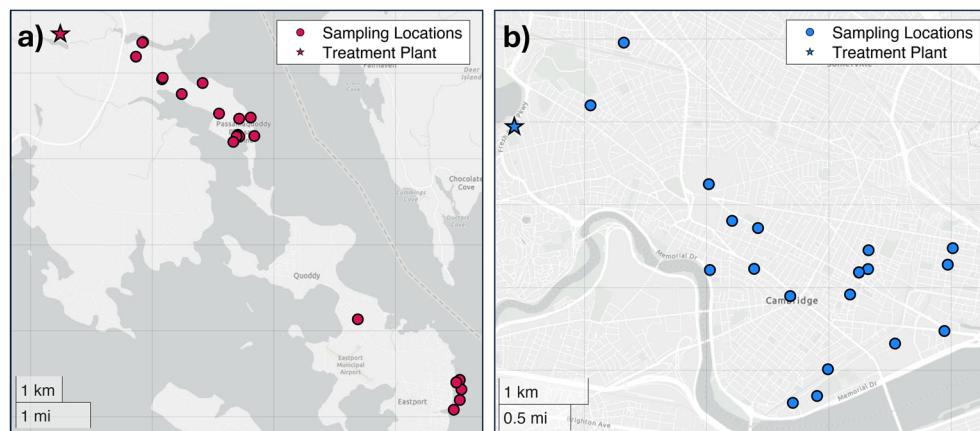
Fig. 1 Sampling locations and treatment plants in (a) Region 1 (Eastport, ME; n = 21) and (b) Region 2 (Cambridge, MA; n = 19). Points are radially offset to protect anonymity.

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Table 1 Detections of *N*-nitrosamines in water samples in Regions 1 and 2

		NDMA	NMOR	NMEA	NPYR	NDEA	NPIP	NDPA	NDBA
MDL (ng L^{-1})		0.15	0.21	0.18	0.40	0.13	0.10	0.10	2.0
EPA screening level (ng L^{-1})^a		0.11	12	0.71	37	0.17	8.2	11	2.7
Concentration range (ng L^{-1})^b	Region 1	ND–0.54	ND–0.29	ND	ND	ND	ND	ND	ND
	Region 2	0.39–1.32	ND–0.37	ND	ND	ND	ND	ND	ND
Detection rate^c	Region 1	95%	5%	0%	0%	0%	0%	0%	0%
	Region 2	100%	5%	0%	0%	0%	0%	0%	0%
	Overall	98%	5%	0%	0%	0%	0%	0%	0%

^{a} USEPA Regional Screening Level (RSL) table, tap water. ^{b} ND = not detected. ^{c} Detection rates (above MDL) were calculated based on the average of post-flush detections (out of $n = 22$ in Region 1; $n = 20$ in Region 2).

N,N-Dimethylformamide (DMF) was found to interfere with NDMA quantitation in some extracts (see Text S2 and Fig. S4 and S5 for further details). DMF was identified in sample extracts and unextracted water and quantified using calibration standards created from a pure reference material (see Table S6 for extract storage times). To distinguish this interference, collision energy and mobile phase composition were optimized to maximize separation of NDMA and DMF (as detailed in Text S2). Additionally, peak height was used to quantify NDMA concentrations in all extracts (Table S7 and Fig. S6).

Analysis of other water quality parameters

Samples for analysis of other water quality parameters (free and total chlorine, THMs, dissolved organic carbon (DOC), total dissolved nitrogen (TDN), specific ultraviolet absorbance (SUVA)) were collected and measured in accordance with standard procedures (see Text S3 and Table S8). Free chlorine measurements were taken in Region 1, which uses only sodium hypochlorite as a secondary disinfectant, while total chlorine measurements were taken in Region 2, which uses chloramination for secondary disinfection (*i.e.*, chlorine residual measurements were in alignment with EPA monitoring requirements[53]). Chlorine residual measurements may serve as a proxy for water age, as residuals are known to decay over time. Samples for THM analysis were spiked with internal standard (fluorobenzene) analyzed *via* purge and trap coupled to GC-flame ionization detection (FID) (Table S9). THMs are reported as total trihalomethanes (TTHMs; sum of bromodichloromethane, bromoform, chloroform, dibromochloromethane; LOD = 0.4 μg L^{-1}). Means and standard deviations are reported for triplicates. Distance was calculated as linear distance based on geographic coordinates (rather than pipeline distance travelled) to assess as an alternative proxy for water age (see Text S4 and Fig. S7 for details).

Results and discussion

N-Nitrosamine occurrence

NDMA was the most detected *N*-nitrosamine in this study, exhibiting a detection rate in post-flush samples of 95% in Region 1 and 100% in Region 2 (MDL 0.15 ng L^{-1}; Tables 1 and

S10–S11). Additionally, NMOR was detected in two post-flush samples in this study (one detection in each region's distribution system), while NMEA, NPYR, NDEA, NPIP, NDPA, and NDBA were not detected in any of these samples. Notably, a potential interferent was observed for NPYR in many samples, and a ubiquitous interferent was observed for NDBA; note that all reported nitrosamine concentrations represent true detections after accounting for known interference through comparison of MRM fragmentation patterns (see Text S5 and Fig. S8 for further details). Previous occurrence studies have found widely variable NDMA detection rates (10–100%) (Table S1), though NDMA has generally been the most prevalent nitrosamine in water samples.[2,6,7,12–14,17,18,21,22,54] Higher frequencies of detection may be partially attributable to lower reporting limits in some studies;[6] for example, if a higher detection threshold was applied to this study (*e.g.*, the MRL from UCMR2 (2 ng L^{-1})), the overall detection rate would decrease from 98% to 0%.

The average (post-flush) NDMA concentrations in Region 2 (0.39 ± 0.01 to 1.32 ± 0.07 ng L^{-1}) generally exceeded the levels found in Region 1 (ND to 0.54 ± 0.01 ng L^{-1}; Table 1). This difference may be partially attributed to Region 2's use of chloramination as a secondary disinfection step, which has been strongly linked to higher rates and amounts of NDMA occurrence compared to chlorination.[2,5–7,14,24,25] The mechanism of NDMA formation from chloramination is thought to occur *via* formation of an unsymmetrically substituted hydrazine derivative and subsequent oxidation; NDMA formation from chlorination under similar conditions is typically minor but may be enhanced by the presence of ammonia (*via* effective chloramination) or nitrite (*via* nitrosation).[2,5,24,28,55,56] Seasonal effects may have also influenced the differences in concentrations (Region 1 and 2 were sampled in summer and winter, respectively). Temporal changes may be attributed to temperature effects and source water quality, but the net effects vary between sites.[12,15,18,20,21] The maximum detected concentration of NDMA (1.32 ng L^{-1}) fell below the maxima of many previous studies (3.3–630 ng L^{-1}; Table S1), indicating lower susceptibility to NDMA formation in the systems studied here. Notably, 98% of samples exceeded the EPA's screening level of 0.11 ng L^{-1} for NDMA, and 38% exceeded the EPA's IRIS risk level. While the EPA's IRIS risk level of 0.7 ng L^{-1}

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for NDMA is based on a consideration of lifetime carcinogenic risk (*i.e.*, a 1-in-a-million increase), chronic low-dose exposure to nitrosamines is an understudied feature of nitrosamines' potential health risks. A large body of literature has established the potential carcinogenicity of nitrosamines in humans,[57] but more work is needed to assess these health effects at the low levels found in this study. Furthermore, cumulative risk to chronic low-dose exposures in mixtures is poorly understood.[58,59]

In both regions, there was a significant difference in NDMA concentrations between the pre- and post-flush samples from the distribution systems (Wilcoxon signed-rank test; Region 1 $p = 0.003$; Region 2 $p = 0.02$; Fig. 2a). Most locations ($n = 31$) exhibited a higher concentration in pre-flush samples than in the corresponding post-flush samples, indicating a decrease in NDMA after the flushing procedure (Fig. 2b). The pre-flush samples represent water that has undergone a period of temporary stagnation within the household plumbing system due to inactivity at the tap, which is released when the tap refreshed with flowing water from the distribution system (typically within 5–15 minutes). Stagnation can increase DBP formation,[60] among other effects on water quality,[61,62] though the magnitude of this effect would vary based on user behavior and plumbing design. Generally, stagnation contributes to a longer overall residence time between entering the distribution system and exiting at the point of use, which has been linked to greater occurrence of nitrosamines[6,7,12,17,63] and some other DBPs (*e.g.*, THMs).[64–66] Here, the concentrations of NDMA found in the distribution system (0.20 ± 0.01 to 0.54 ± 0.01 in Region 1; 0.64 ± 0.01 to 1.32 ± 0.07 in Region 2) exceeded the amount in the DWTP finished water in both regions (not detected in Region 1; 0.39 ± 0.04 ng L^{-1} in Region 2), indicating continued formation of NDMA after leaving the

treatment plant. This increase within the distribution system and household plumbing may be due to prolonged contact time between the chlorine residual and the organic matter in the water (*i.e.*, higher water age) and/or may be enhanced due to interactions with organic precursor material contained in biofilms on pipe walls.[67,68] Note that some studies observed an opposite effect with certain DBPs (*e.g.*, HAAs, haloacetonitriles, haloketones) at distribution system extremities, attributed to biodegradation, hydrolysis, and/or abiotic reduction.[65,69,70]

Additional nitrosamines were detected only in pre-flush samples (NDEA, NPIP, NDPA, NDBA) or had a higher detection rate in pre-flush samples (NMOR) (Fig. 3 and Tables S12–S14), consistent with stagnation promoting formation of additional nitrosamines. Longer residence times have been previously observed to correspond with greater occurrences of NMOR, NPYR, and NPIP in a distribution system, suggesting formation over time after disinfection.[13,63] In contrast, other studies suggested that NMOR may occur as an industrial byproduct rather than *via* disinfection, due to its presence in some influent waters and minimal change upon typical disinfection.[15,71,72] In this study, NMOR was not observed in finished water samples (*i.e.*, DWTP effluent), indicating that it formed only after entering the distribution system. Co-occurrence of multiple nitrosamines was uncommon, but some pre-flush samples ($n = 3$) contained three different nitrosamines. The levels of NDMA in these samples also fell in the upper quartile of each respective region (0.67 ng L^{-1} in Region 1; 1.4 and 2.4 ng L^{-1} in Region 2), suggesting that a longer residence time may promote the formation of multiple nitrosamines simultaneously. NDBA concentrations were also unexpectedly elevated in some pre-flush samples (6.1 and 15.3 ng L^{-1}; compared to screening level of 2.7 ng L^{-1}), though these samples did not correspond
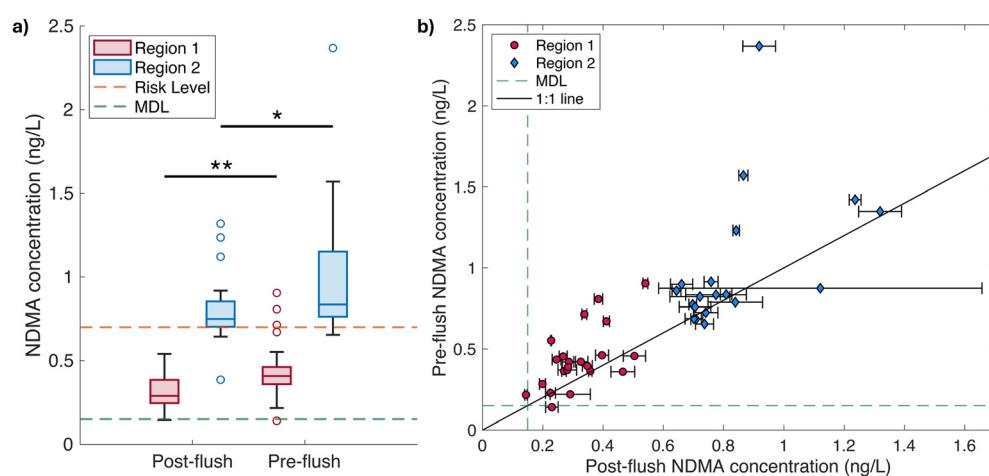
Fig. 2 Pre- and post-flush NDMA levels. (a) Concentration distributions of NDMA in the post-flush ($n = 2$ per location; averaged) and pre-flush ($n = 1$ per location) samples in the distribution systems and finished water of Region 1 ($n = 20$) and Region 2 ($n = 22$; finished water in Region 2 had no corresponding pre-flush sample because it was continuously flowing). Boxes indicate 25th, 50th, and 75th percentiles and whiskers extend to the maximum or minimum values within 1.5 times the interquartile range (IQR); outliers are marked as points. Significant differences *via* Wilcoxon rank-order test are marked with asterisks (**p-values < 0.01; *p-values < 0.05). (b) A comparison of NDMA in the pre-flush and post-flush samples at each location. Error bars denote the standard deviation of the post-flush samples ($n = 2$). A 1:1 line is shown for reference.
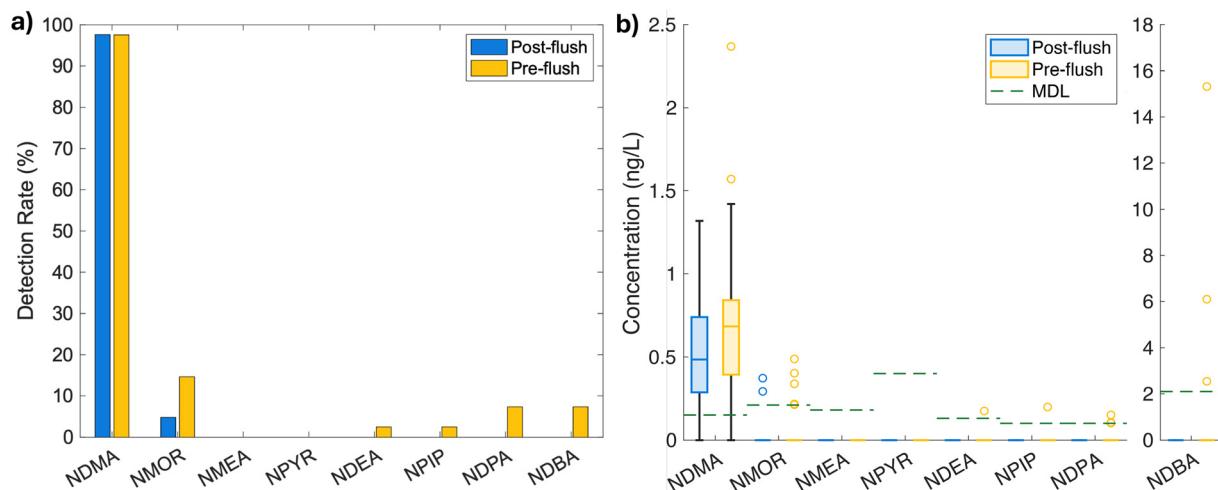
Fig. 3 Eight *N*-nitrosamine detections in drinking water (pre- and post-flush). Pre- and post-flush (a) detection rates and (b) measured concentrations for eight nitrosamines. Boxes indicate 25th, 50th, and 75th percentiles and whiskers extend to the maximum or minimum values within 1.5 times the interquartile range (IQR); outliers are marked as points. Non-detects are plotted at 0.

to elevated occurrence of other nitrosamines. Importantly, these findings demonstrate that samples collected using the standard tap flushing procedure may underrepresent the overall nitrosamine exposure of consumers.

Relationships with other water quality parameters

Additional water quality parameters were measured to evaluate the relationships with NDMA occurrence (Fig. 4a). Chlorine residuals were investigated as a proxy for water age, since disinfectant residuals are known to decrease over time after dosage due to reactions with organic matter and interactions with pipe walls.[66,73–75] The free chlorine residual in Region 1's distribution system was 0.05–0.51 mg L^{-1} as Cl$_2$, while the total chlorine residual in Region 2 was 1.88–2.58 mg L^{-1} as Cl$_2$; the highest chlorine residuals occurred in the DWTP finished water (0.94 and 2.81 mg L^{-1}, Regions 1 and 2, respectively). These measurements are not directly comparable between systems due to the unequal efficacy of these different disinfectants,[76,77] but each residual measurement represents the relative disinfectant effectiveness within each system.[53] In general, lower chlorine residuals within a system may be associated with higher water age and hence reflect an extended reaction time during which DBPs may continue to form and/or degrade within the distribution system. Both regions exhibited a strong and significant monotonic correlation between NDMA and chlorine residual (Fig. 4b; Region 1: $\rho = -0.81$, $p < 0.001$; Region 2: $\rho = -0.68$, $p = 0.001$). The negative correlation between NDMA and chlorine residual suggests a corresponding relationship between the rate of NDMA formation and the rate of chlorine decay in this system (neither utility in the study regions used re-chlorination stations during the sampling period). This trend aligns with previous observations that NDMA tends to increase with longer residence times,[6,7,12,17,63] similar to THMs,[66,74,78–80] and indicates that locations with more depleted chlorine residuals (relative to initial dosage) may represent areas of

higher water age where elevated concentrations of NDMA can be found. These findings highlight the importance of monitoring for NDMA at locations of maximum residence time (*e.g.*, as in UCMR2).

NDMA occurrence was also compared to occurrence of TTHMs, which are regularly monitored for compliance with regulations. TTHM concentrations were higher and spanned a broader range in Region 1 (13.8 ± 0.1 to 32.7 ± 0.2 μg L^{-1}) compared to Region 2 (4.4 ± 0.2 to 7.4 ± 0.1 μg L^{-1}) (Fig. 4a). This is consistent with previous findings that chloramination as a secondary disinfectant strategy is associated with lower amounts of TTHMs than chlorination.[48,81,82] There was a significant correlation between TTHMs and NDMA in Region 1 ($\rho = 0.68$, $p < 0.001$), indicating their co-occurrence in this chlorinated system, while no such relationship existed in Region 2 ($\rho = -0.27$, $p = 0.26$) (Fig. 4b). Brisson *et al.*, 2013 (ref. 12) observed a relationship between high levels of THMs and NDMA occurrence in a chloraminated system and Cai *et al.*, 2023 (ref. 21) noted a positive relationship between chloroform and NDMA in samples from distribution systems with varied secondary disinfectant strategies. These findings suggest that elevated THMs may indicate the presence of NDMA in some chlorinated or chloraminated systems, though this was not observed in the chloraminated system in this study (Region 2). This contrast underscores variation between systems, despite similar disinfection practices, and highlights an important regulatory challenge: differences in formation dynamics between regulated DBPs (*e.g.*, TTHMs) and unregulated DBPs (*e.g.*, *N*-nitrosamines) pose a challenge for potential control strategies that address the presence of all DBPs.[49]

The impact of organic matter concentrations, quantified as DOC, on NDMA formation was also explored. DOC was higher and more variable in Region 2 (1.52 ± 0.07 to 1.97 ± 0.08 mg L^{-1}; Fig. 4a) than in Region 1 (0.50 ± 0.04 to 0.65 ± 0.04 mg L^{-1}), indicating a larger potential pool of organic

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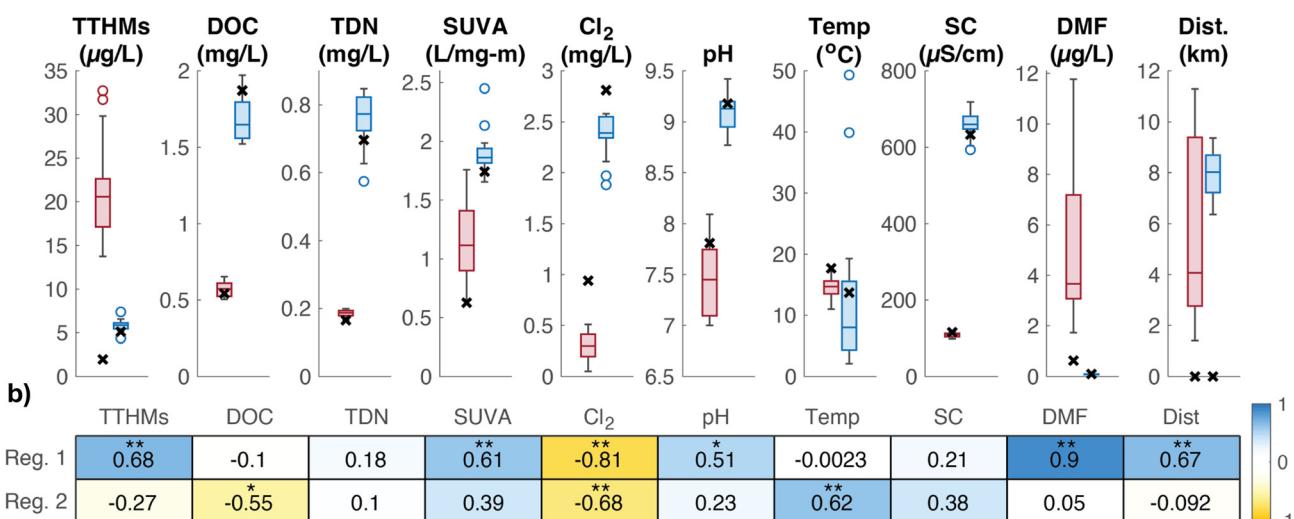
Fig. 4 Drinking water characteristics and relationship with NDMA levels. (a) Water quality parameters (TTHMs, DOC, TDN, SUVA, chlorine residual (Cl_2), pH, temperature (Temp), specific conductance (SC), recovery-adjusted DMF (DMF)) and linear geographic distance (Dist.) in treated water from the distribution systems in each region; DWTP finished water shown for comparison. Boxes indicate 25th, 50th, and 75th percentiles and whiskers extend within 1.5 times the interquartile range (IQR); outliers are marked as points. (b) Spearman correlations (ρ) between average (post-flush) NDMA concentrations and each water quality parameter. The color bar indicates correlation strength and asterisks denote significance (**p-value < 0.01, *p-value < 0.05).

precursor material. Region 1 displayed no significant relationship with DOC ($\rho = -0.10$, $p = 0.64$), while Region 2 displayed a significant negative correlation ($\rho = -0.55$, $p = 0.01$) (Fig. 4b). Previous studies have observed some weak associations between NDMA and DOC, though these relationships are presumed to be dependent on site-specific DOC chemistry.[2,12,13,20,27,33] The lack of correlation in Region 1 suggests that DOC is not adequately representative of NDMA precursor content in this system, and/or that other dynamics in this region overwhelm any discernible influence. The negative relationship between DOC and NDMA seen in Region 2 may indicate that a large fraction of this DOC pool was competitively reacting with chloramine species and reducing the amount of these species that remained available for reacting with NDMA precursors. This finding further supports the notion that DOC on its own is not sufficiently specific to represent NDMA precursor content.[32,83] Note that the ozonation step in Region 2's DWTP could have affected the composition of the DOC pool *via* a) oxidation of chloramine- and/or chlorine-reactive NDMA precursors,[83,84] thereby decreasing NDMA formation potential, and/or b) reaction with ozone-reactive precursors,[2] thereby increasing NDMA formation.

Another proxy for organic matter, SUVA, was slightly higher in Region 2 (1.7 to 2.4 L mg^{-1} m^{-1}; Fig. 4a) compared to Region 1 (0.65 to 1.8 L mg^{-1} m^{-1}), indicating a higher fraction of aromatic compounds in the DOC pool. A positive correlation between NDMA and SUVA was observed in Region 1 ($\rho = 0.61$, $p = 0.003$; Fig. 4b), in contrast with the absence

of a statistically significant relationship present in Region 2 ($\rho = 0.39$, $p = 0.09$). Similarly inconsistent results were present across prior studies, where some observed a correlation between NDMA and SUVA[12,13,22] while others did not.[20,32,85] These findings indicate that the effectiveness of SUVA as a representation of NDMA precursor content is not robust, as NDMA precursors could also come from aliphatic moieties. While it is possible that SUVA may represent NDMA precursors more effectively in wastewater-impacted source waters, due to their higher content of pharmaceuticals and other anthropogenic precursors with aromaticity,[31,86] the non-specific nature of the SUVA measurement renders it poorly suited to serve as a predictor of NDMA formation.

Nitrogen content has also been proposed as an important NDMA precursor and was evaluated here. Region 2 exhibited higher TDN concentrations in the distribution system (0.6 ± 0.2 to 0.85 ± 0.03 mg L^{-1}; Fig. 4a) than Region 1 (0.16 ± 0.02 to 0.20 ± 0.01 mg L^{-1}), indicating potentially higher amounts of nitrogen-containing organic precursors. Here, it is important to recognize that this difference is partially due to the presence of chloramines in Region 2. Nevertheless, no significant relationship between NDMA and TDN was observed in either region (Region 1: $\rho = 0.18$, $p = 0.4$; Region 2: $\rho = 0.10$, $p = 0.7$; Fig. 4b), which is consistent with some previous field studies relating NDMA occurrence to nitrogen content (*e.g.*, TDN or total Kjeldahl nitrogen (TKN)).[13,20,21] This finding may indicate that TDN, which contains both nitrogen-containing organic species (dissolved organic nitrogen, DON) and inorganic species (NO_3^-, NO_2^-, NH_3), is

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too general a measure to capture a more restrictive set of nitrosamine precursors in these systems (DON was not calculated for this study). Some studies have focused on the relationships between NDMA formation potential (FP) and DON specifically, observing that DON-enriched isolates (i.e., low DOC/DON ratios) corresponded to elevated NDMA FP.[83,85] However, others have observed no discernible relationship between NDMA FP and bulk DON.[33,37] While the DON in these systems may contain NDMA precursors, such precursors are likely only a small contribution to this bulk measurement;[2,33] consequently, DON measurements may be poorly suited for comparing overall precursor content between different sources. Additionally, low-level DON measurements can be obscured by the presence of inorganic-N species.[33,87] Distinct relationships between these individual inorganic-N species and NDMA occurrence have also been observed;[12,22,23] nitrite can contribute to NDMA formation via nitrosation,[5] and chlorination of naturally ammonia-containing waters can lead to the formation of chloramines, though these effects are typically only observed at high concentrations of these species.[2,55] More detailed measurements (e.g., relative amounts of organic and inorganic species) may elucidate the combined influence of these compounds on NDMA formation in a particular system.

In addition to these water quality parameters, linear distances between the treatment plant and sampling locations were evaluated as a potential proxy for water age in each region (distance in this context refers to the geographic distance traveled between a sample point and the DWTP, rather in-pipe length traveled, as detailed in Text S4 and Fig. S7). Samples collected in Region 1 were geographically distributed across longer distances (1.4 to 11.3 km) than those in Region 2 (6.4 to 9.4 km), where samples were more tightly clustered around a central distribution location (Fig. 1). Water distribution points that are farther away from a treatment plant may correspond to areas of higher water age (i.e., longer residence time), due the longer time expected for water to travel through the distribution system to these locations,[81] and may reflect the association between longer residence times and elevated NDMA occurrence.[6,7,12,17,63] However, while this association may be applicable in systems where water generally follows a predictable flow path (e.g., a dead-end system), the assumption is less likely to apply in systems where interconnected pipes allow for continuous circulation (e.g., a grid iron system). A positive relationship between NDMA and distance was seen in Region 1 ($\rho = 0.67$, $p < 0.001$; Fig. 4b), consistent with previous studies.[13,63] This finding suggests that linear distance could indeed be an appropriate proxy for water age in systems such as Region 1, where users are more geographically dispersed. In contrast, Region 2 did not display a significant relationship with distance ($\rho = -0.092$, $p = 0.7$), which may be a consequence of the small, interconnected distribution region. While these results indicate that the use of linear distance as an indication of potential water age may not reflect distribution system complexity, the value of evaluating distance is that it is essentially a "free" parameter, i.e., it requires no analytical capabilities or equipment beyond the ability to determine GPS locations. Utilities with limited resources may be able to use these relationships (e.g., in conjunction with chlorine residual measurements) to assess whether distribution network extremities could represent areas of higher water age where elevated concentrations of NDMA may be present.

The influence of other water quality parameters (pH, temperature, specific conductance) was also interrogated. Region 2 exhibited higher pH and specific conductance than Region 1, and a broader range of temperatures was observed in Region 2 (Fig. 4a), in part due to seasonal differences. A positive correlation between NDMA and pH was seen in Region 1 ($\rho = 0.51$, $p = 0.01$; Fig. 4b), although no such correlation was observed in Region 2 ($\rho = 0.23$, $p = 0.3$). This positive correlation in Region 1 is consistent with previous work which illustrated that NDMA formation from chloramination of dimethylamine was maximized between pH 6 and 8 (ref. 24) and increased with increasing pH within a similar range (pH 6–9),[11,56] though it is unclear if this effect applies with chlorination. This effect has been seen with some other NDMA precursors as well,[88] though these reactions would reasonably be impacted by the speciation of both monochloramine and amine precursors.[36,89] The lack of correlation observed in Region 2 may have been influenced by these speciation dynamics; alternatively, the narrower pH range in this system may have simply precluded observation of these impacts.

A positive correlation was observed between temperature and NDMA occurrence in Region 2 ($\rho = 0.62$, $p = 0.005$), consistent with some prior studies.[2,88] However, Region 1 displayed no significant relationship between NDMA and temperature ($\rho = -0.0023$, $p = 0.99$). Other studies have observed a reduction in NDMA formation at high temperatures due to increased auto-decomposition of monochloramine at high temperatures;[88,90] the lack of relationship seen in Region 1 may be influenced by competition between these positive and negative effects. No significant relationship between specific conductance and NDMA occurrence was present in either region (Region 1: $\rho = 0.21$, $p = 0.4$; Region 2: $\rho = 0.38$, $p = 0.09$). Conductivity is a general measure of water quality and can sometimes be used as an indicator of freshwater pollution by wastewater discharges,[91,92] but is not a strong predictor of organic precursor content and its effect on NDMA formation is not established. Specific conductance has not been linked to NDMA formation in previous studies.[12]

Co-occurrence of DMF with NDMA

Since DMF was identified as an NDMA interferent in samples where it co-occurred, DMF was quantified in sample extracts and its relationship with NDMA was investigated. Recovery-adjusted concentrations of DMF in waters ranged from 0.64 ± 0.07 μg L^{-1} to 11.8 ± 0.2 μg L^{-1} in post-flush samples from Region 1 (MDL = 0.2 μg L^{-1}; 100% detection rate), with no detections in Region 2 (Fig. 4a) (note that recovery adjustment

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is necessary since the SPE method was not optimized for DMF, but this adjustment may introduce uncertainty; see Fig. S9 and Text S6 for validation and discussion of this approach). As with NDMA, pre-flush samples in Region 1 had higher DMF concentrations than their corresponding post-flush samples (Wilcoxon rank-sum test; $p = 0.009$). In Region 2, DMF was detected only in some pre-flush extracts ($n = 2$ locations), suggesting the DMF may have been formed due to household-level stagnation as well. Additionally, finished water at DWTP1 contained a lower DMF concentration (0.64 ± 0.07 μg L^{-1}) than samples within the distribution system (1.70 ± 0.003 μg L^{-1} to 11.8 ± 0.2 μg L^{-1}), and there was a significant positive correlation between DMF and NDMA in post-flush water samples in Region 1 (Fig. 4b; $\rho = 0.90$; $p < 0.001$). These results indicate that DMF in Region 1 tended to increase with residence time, suggesting that DMF co-occurred with NDMA as a DBP in Region 1. Limited data are available regarding the occurrence of DMF as a water contaminant,[93–95] but previous mechanistic research has observed the formation of DMF alongside NDMA from the reaction between monochloramine and DMA.[24,29] It is unclear why this relationship was only observed in the chlorinated system in the current study (Region 1) and was not observed in the chloraminated system (Region 2). Other studies have noted that DMF can also serve as a precursor to NDMA under certain chloramination conditions,[35,96] which may further influence these relationships (or lack thereof). That is, DMF may be both formed and consumed within the treatment system. Additional investigation in chlorinated systems would be necessary to determine if the co-occurrence of DMF and NDMA is widespread, *i.e.*, whether DMF could be used as a proxy for NDMA occurrence in certain systems. Whether or not such a proxy exists, the identification of DMF as a potentially overlooked interferent for NDMA in drinking water should be considered in future NDMA studies using LC-MS.[51]

Predictive model of NDMA occurrence in Regions 1 & 2

To investigate whether any of the observed correlations could be leveraged to identify areas of elevated NDMA occurrence, a predictive equation for NDMA occurrence in the distribution system and finished water was derived based on certain water quality parameters at each location, similar to those utilized for other DBPs.[81,97] The independent variables included in model fitting were DOC, TDN, SUVA, chlorine residual (free or total), distance, pH, temperature, specific conductance, and TTHMs; DMF was excluded as it is not routinely monitored. Original measurement units were retained for all parameters. Stepwise regression was performed using MATLAB's "stepwiselm" function with an entry p-value of 0.05 and was limited to an intercept and linear term for each predictor. NDMA concentration was related to four significant variables: free or total chlorine, temperature, specific conductance, and distance (eqn (1); further details regarding model sensitivity in Table S15, Fig. S10 and Text S7).

$$\text{NDMA [ng L}^{-1}] = 0.0068 - 0.25 \text{ (Free or total Cl}_2 \text{ [ppm])}$$
$$+ 0.0084 \text{ (Temp [°C])}$$
$$+ 0.0018 \text{ (Sp. Cond. [μS cm}^{-1}])$$
$$+ 0.015 \text{ (Distance [km])} \quad (1)$$

This model was effective for predicting NDMA concentration in the distribution systems of these two regions (the R^2 value of the model was 0.92 and the mean absolute error (MAE) was 0.059 ng L^{-1}; see Fig. 5 and Table S16). NDMA varied inversely with chlorine residual (free or total) across both regions, consistent with observed Spearman correlations. There was a positive correlation with temperature in this model, though this relationship was only seen in the Spearman correlation for Region 2. This could suggest that temperature is not necessarily a driving variable on its own but may become significant when considering interrelated effects. The positive relationship with specific conductance in this model was not observed in either region independently, and specific conductance is not known to have a bearing on NDMA occurrence. Nevertheless, conductivity may be indirectly related to overall water quality *via* incidental correlation with a true precursor. Alternatively, this result could be a numerical artifact arising from confounding differences between the two regions. As such, we caution against overinterpretation of the physical significance of these model results, due to the limited sample set and narrow parameter ranges observed in this study. Nonetheless, a similar framework could be applied within other distribution networks to predict system-specific trends in NDMA occurrence using similar parameters. Furthermore, if additional nitrosamines were detected in greater frequency, comparable models could be developed. Laboratory approaches to develop such models could also provide a route to understanding the mechanisms of formation for those larger nitrosamines (in the absence of field detection of those structures).
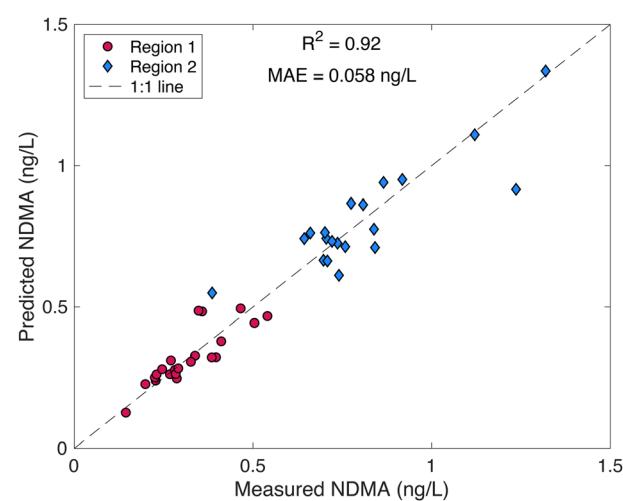
Fig. 5 Predicted *versus* measured NDMA levels in two municipal water systems. Predicted values were determined using water quality criteria and eqn (1); measured values were determined experimentally. A 1 : 1 line (dashed) is shown for comparison.

Notably, none of the terms expected to be representative of organic NDMA precursor content (*i.e.*, DOC, SUVA, TDN) emerged as quantitatively significant predictors, indicating that these parameters could not capture the precursor variability in this dataset. This finding may be due to the narrow parameter ranges observed in this study, suggesting that these bulk measurements were not sufficiently granular to capture the true chemical changes arising from NDMA formation dynamics. While the utility of a rapid screening proxy for nitrosamine formation is clear, more detailed measures may be necessary (*e.g.*, key amine species or the FP test developed by Mitch *et al.*[90] to act as a surrogate for total precursor content) to inform nitrosamine prediction.

Previous efforts to apply similar frameworks to nitrosamine occurrence and FP exist[21,37,86,98,99] (Table S17 and Text S8). Some derive coefficients for a pre-defined set of variables, such as DOC; with this approach, Chen and Valentine[98] incorporated source-specific coefficients to a kinetic model of NDMA formation, while Chen and Westerhoff[37] noted an inability to predict NDMA formation potential for different types of sources (*i.e.*, potable and wastewater sources) with a universal model. Other studies have begun with a larger set of variables and used algorithmic techniques (*e.g.*, stepwise regression, hybrid genetic algorithm) to identify a reduced set of predictor variables for nitrosamine concentration; Leavey-Roback *et al.*[86] found influent UV254 to be one of 8 significant predictors, while Cai *et al.*[21] found chemical oxygen demand in finished water as one of 5 predictors, and Moradi *et al.*[99] found monochloramine residual as one of 3 predictors. While these models employ some common variables (UV254, DOC), there is heterogeneity in their base set of model inputs (*e.g.*, inclusion of polydiallyldimethylammonium chloride dose (a flocculant associated with NDMA FP[86]), bromide concentration, or turbidity measurement), challenging direct intercomparison.

Further investigation of the relationships between NDMA and standard water quality parameters would facilitate future monitoring efforts and provide a better understanding of the interactions driving NDMA formation. While specific NDMA formation mechanisms have been the subject of extensive study[11,24,28,30,55] and large-scale monitoring efforts have revealed valuable insights into NDMA occurrence trends (*e.g.*, UCMR2), our understanding of NDMA formation in real-world drinking water systems remains challenging due to the complex nature of these systems. Our results showed a significant negative relationship between NDMA and chlorine residual in both systems, highlighting the importance of this parameter for anticipating changes in NDMA concentration over time in the distribution system. There is still uncertainty among previous studies regarding whether bulk organic parameters (*e.g.*, DOC, TDN, SUVA) are sufficiently representative of NDMA precursor content,[12,13,21,33,36–38] and the lack of consistent relationships across the two regions studied here suggests that these relationships may be site-specific. However, system-specific relationships with routinely collected water quality measurements can be valuable for assessing temporal variations deriving from changes in precursor content within a particular source water and can provide valuable information about changes in NDMA formation throughout a particular treatment system. Specifically, residence time post-disinfection (*i.e.*, water age in a distribution system) emerged as a highly relevant variable in both systems studied here. The higher NDMA concentrations associated with more depleted chlorine residuals (compared to initial dose) may reflect increases in NDMA formation with higher water age, and the elevated concentrations in pre-flush samples appear to reflect further increases in residence time due to household stagnation. Ultimately, NDMA and other nitrosamines will still need to be monitored directly for accurate knowledge of exposure due to site-specific variations, but simple screening tools can facilitate prioritization of critical monitoring.

Conclusions

Using a robust analytical method capable of measuring NDMA concentrations as low as 0.15 ng L^{-1}, we observed widespread occurrence of NDMA at low levels (ND – 1.32 ng L^{-1}), but detected few other nitrosamines, across one chlorinated and one chloraminated distribution system. Notably, these concentrations fell below the MRL of the methods used in UCMR2 (2 ng L^{-1}) and many other studies,[13,14,54] indicating that low-level nitrosamine occurrence may be obscured in historical surveys due to analytical limitations. Due to the potency of NDMA as a potential carcinogen, it is critical to collect occurrence data using methods capable of assessing concentrations below its negligible risk level of 0.7 ng L^{-1}, to gain a fuller picture of potential exposures at the tap. Additionally, we observed elevated concentrations of NDMA in many pre-flush samples, representative of what a homeowner would consume, compared to respective post-flush samples, which are more representative of a distribution system. This could suggest that standard monitoring practices, which require a period of tap flushing prior to sample collection, fail to capture true exposures for chemicals that are dynamically forming in distribution systems.

The occurrence of NDMA and other contaminants in a drinking water system can have serious consequences for communities, yet nitrosamine monitoring is often cost-prohibitive for utilities with limited resources. In general, small public water systems (serving populations less than 3300) exhibit higher rates of noncompliance with public standards than large systems, which is often attributed to a lack of technical and financial capacity.[100] Data collected during UCMR2 revealed that NDMA was detected with higher frequency and at higher concentrations in smaller systems; however, only a fraction of these systems was sampled (less than 1%), highlighting a need for further monitoring at small utilities.[7] Leveraging routinely collected water quality measurements to guide these NDMA monitoring efforts could help allocate resources efficiently to cover all populations, irrespective of distribution system size. The predictive framework presented here highlighted key water quality data that could be leveraged to estimate system-specific NDMA

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concentrations (*e.g.*, chlorine residual), though the broader applicability of this model is limited by the narrow parameter ranges and low concentrations observed in this study. As such, further monitoring would be needed to better understand trends in NDMA occurrence across different sites, which could be used to enhance this framework.

One barrier to effective regulation of NDMA as a drinking water contaminant is its relationship to other DBPs. In the USEPA's determination not to make regulatory determinations for the nitrosamines in Contaminant Candidate Lists 3 & 4, the agency notes that "DBPs need to be evaluated collectively, because the potential exists that the control of one DBP could affect the concentrations of other DBPs or the necessary treatment".[49,101] Most notably, the use of chloramination as a secondary disinfectant strategy has become increasingly popular for reducing the prevalence of THM formation in treated drinking waters,[102] but chloramination is linked to higher occurrence of NDMA, here and in previous studies. NDMA concentrations were highest in the chloraminated system in this study (Region 2), while TTHMs concentrations were highest in the chlorinated system (Region 1). In dealing with this challenge, it may be important to determine drivers of overall toxicity by considering both concentration and toxicity of each compound[103] and tailor DBP control strategies minimize overall toxicity (*e.g.*, by optimizing a pre-oxidation step to deactivate nitrosamine precursors while minimizing formation of regulated DBPs[72]). These trade-offs complicate efforts to minimize the overall health impacts of DBPs[45,46,72] and will require robust, large-scale monitoring and holistic consideration of health risks and remediation strategies to overcome.

Author contributions

Kristen A. Riedinger: conceptualization, formal analysis, investigation, methodology, project administration, validation, visualization, writing – original draft, writing – review & editing. Nicolette A. Bugher: investigation, methodology, validation, writing – review and editing. Annabella S. Wardle: investigation. Kathleen M. Vandiver: investigation, writing – review and editing. Barathkumar Baskaran: methodology, writing – review and editing. Zion Michael: validation. Glen Andrew D. de Vera: methodology, resources, writing – review and editing. Desiree L. Plata: conceptualization, supervision, funding acquisition, resources, writing – review and editing.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

In addition to data included within the main text and supplementary information (SI), all data and metadata associated with the results discussed in this article can be found online at FAIRDOMHub: https://fairdomhub.org/studies/1403.

Supplementary information: this SI document includes: methodological details for sample collection and analysis of *N*-nitrosamines and other water quality parameters; discussions of interferences and quantification accuracy; all *N*-nitrosamine concentrations in post- and pre-flush samples; summaries of prior NDMA surveys and previous predictive frameworks. See DOI: https://doi.org/10.1039/d5ew00861a.

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