Identification of *N*-Nitrosodimethylamine Precursors to Improve Their Control

by

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ABSTRACT

N-nitrosodimethylamine (NDMA) is a probable human carcinogen and drinking water disinfection by-product. NDMA forms as the product of reactions between chloramines and precursor compounds in water. This dissertation aims to provide insight into the removal of NDMA precursors, their nature, and a method to aid in their identification. Watershed-derived precursors accounted for more of and greater variability to NDMA formation upon chloramination than polymer-derived precursors in environmental samples. Coagulation polymers are quaternary amines, which have low NDMA yield but high use rates. Watershed-derived precursors were removed up to 90% by sorption to activated carbon, but activated carbon exhibited much less (<10%) sorption of polymer-derived precursors. Combined with literature NDMA molar yields of model anthropogenic compounds, where anthropogenic chemicals in some cases have NDMA yields >90% and biological compounds always have yields <2%, trace, organic, amine containing, anthropogenic chemicals were implicated as the most likely source of NDMA precursors in the watershed. Although activated carbon removes these precursors well, identification of individual compounds may result in more cost effective mitigation strategies. Therefore, I developed a method to isolate NDMA precursors from other organic matter into methanol to facilitate their identification. Optimization of the method resulted in a median recovery of NDMA precursors of 82% from 10 surface waters and one wastewater. The method produces 1,000X concentrated NDMA precursors and, in collaboration with the University of Colorado Center for Environmental Mass Spectrometry, time of flight mass spectrometry (TOF-MS) was performed on multiple treated wastewater and raw drinking water isolates. During TOF-MS, tertiary amines can cleave to form a neutral loss and an R group ion that is dependent on the original structure and I wrote a software program to “trawl” exported TOF-MS spectra for the diagnostic neutral loss resulting from fragmentation of tertiary amines. Methadone was identified as one new NDMA precursor that occurs at concentrations that form physiologically relevant levels of NDMA in surface water and wastewater. The approach used here to identify NDMA precursors is adaptable to other unknown disinfection by-product precursors given that a functional group is known that can 1)control sorption and 2)produce a predictable diagnostic fragment.

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1 Introduction

After the discovery of a contaminated drinking water well by John Snow in Soho, London in 1854, physicians and scientists raced to determine better ways to treat drinking water. Initial methods using slow sand filtration were relatively effective, only being surpassed by the use of chemical disinfectants (oxidants), employed in the U.S. as a method to inactivate water-borne pathogens in drinking water since the early 1900s (USEPA, 2000). The use of disinfectants has effectively eradicated pathogenic infection from contaminated drinking water, but disinfection with free chlorine, the most commonly used disinfectant in the U.S. (USEPA, 2006a), has been associated with an increased risk of bladder cancer. Through targeted studies of water chemistry changes post-disinfection, drinking water disinfection by-products (DBPs) were discovered in the 1970s (Bellar *et al.*, 1974; Rook, 1974). The two most common groups of DBPs, with the highest mass fraction, trihalomethanes (THMs) and haloacetic acids (HAAs), were discovered first, and are known rodent and probable human carcinogens (Eschenbrenner, 1945; Eschenbrenner and Miller, 1946; Richardson and Postigo, 2012). However, it is notable that not all identified DBPs pose a human health risk (carcinogenicity, genotoxicity, cytotoxicity, etc.). As civil and environmental engineers, it is our duty to reduce the risk associated with exposure to DBPs of health concern.

In this effort, the U.S. Environmental Protection Agency (EPA) regulated THMs and HAAs in 1998 (USEPA, 1998). It was previously found that chloramination and/or activated carbon reduced the formation of THMs and HAAs (Lykins *et al.*, 1988; Norman *et al.*, 1980). Thus, EPA suggested chloramination as an alternative disinfectant to free chlorine to reduce formation of THMs and HAAs. In an effort to comply with

DBP regulation, there was a 37% increase in utilities practicing chloramination between 2007 and 2010 (Li, 2011). However, it was later discovered that chloramination can produce nitrosamines, which are hundreds of thousands of times more carcinogenic than the regulated THMs and HAAs (Peto *et al.*, 1991). Due to a lack of complete understanding of DBP formation mechanisms, many believe the EPA did not have enough evidence regarding health effects and mitigation before providing regulation, and that by regulating in haste, EPA may have caused an increase in health risk from exposure to nitrosamines instead of THMs and HAAs.

EPA has waited 20 years since the discovery of *N*-nitrosodimethylamine (NDMA) in drinking water (the most commonly occurring nitrosamine) (Graham *et al.*, 1995; USEPA, 2014) to determine if regulation of nitrosamines is warranted, and some of this hesitancy likely comes from the previous unintended consequences of regulation and the suggested non-selective treatment strategies (i.e. suggesting switch to chloramination caused formation of more toxic NDMA instead of THMs and HAAs). Ideally, EPA will have the knowledge required to regulate NDMA without causing formation of new DBPs or other unintended consequences. This requires a complete understanding of the formation mechanisms of NDMA from precursors and the identity of precursors themselves will help provide insight into more selective mitigation strategies (i.e. removal of precursors at the drinking water plant or source water protection). This dissertation aims to provide insight into the removal of NDMA precursors, their nature, and a method to aid in their identification.

1.1 Dissertation Organization

The overarching research question was, “**What are the likely organic chemicals responsible for NDMA formation in water and how can they be removed?”** This dissertation is organized into chapters guided by research questions.

Chapter 2 contains the relevant portion of a full literature review of nitrosamine research. I primarily wrote the portion of this published literature review that is included as Chapter 2 while the full text is contained in Appendix A. The body of the dissertation (Chapters 3, 4, 5, 6, and 7) is guided by the research questions below. Each question lead to conclusions that informed further research. The synthesis chapter summarizes the answers to the research questions and merges the conclusions from the individual chapters. The final chapter provides a point by point summary of the conclusions from this dissertation and provides recommendations for future research.

1.2 Research Questions

- Are wastewater NDMA precursors amenable to adsorption on activated carbon? (Chapters 3 and 4)
- Does activated carbon remove polymer-derived NDMA precursors? (Chapter 4)
- Are NDMA precursors removed on activated carbon better than UV_{254} absorbance and dissolved organic carbon? (Chapter 4)
- Is it possible to achieve recovery of concentrated, watershed-derived, NDMA precursors from a sorbent? (Chapter 5)
- Do NDMA precursors in concentrated whole water samples fragment during collisionally induced dissociation to one or more diagnostic ion(s)? (Chapters 6 and 7)

2 Background

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I was the primary author of the text included in this chapter which comprises approximately 20% of the full journal paper text. The full journal paper is included as Appendix A.

2.1 Introduction

As a low-cost control option for the Trihalomethane (THM) Rule (McGuire and Meadow, 1988), chloramines are increasingly used to control the formation of THMs, haloacetic acids (HAAs), and other halogenated disinfection by-products (DBPs) (Diehl *et al.*, 2000), and were selected as best available technology for consecutive systems in the Stage 2 DBP Rule (USEPA, 2006b). However, chloramination is associated with the formation of nitrosamines, which are emerging by-products of health and regulatory concern (Mitch *et al.*, 2003a). The U.S. Environmental Protection Agency's (USEPA's) Integrated Risk Information System database indicates for six nitrosamines that drinking water concentrations in the low ng/L level are associated with a 10^{-6} lifetime excess cancer risk. Accordingly, California's Department of Public Health (CDPH) set 10 ng/L notification levels for three nitrosamines (California Department of Public Health, 2013), and California's Office of Environmental Health Hazard Assessment (OEHHA) set a 3 ng/L public health goal for *N*-nitrosodimethylamine (NDMA) (OEHHA, 2006). The USEPA included 6 nitrosamines in the Unregulated Contaminant Monitoring Rule 2 (UCMR2) (USEPA, 2006a) and 5 on the Contaminant Candidate List 3 (CCL3) (USEPA, 2009). USEPA will make a preliminary regulatory determination for nitrosamines in 2015 and, if they intend to regulate, will propose in 2016. With the increasing reliance of utilities on chloramination, it is critical to identify options to control the formation of nitrosamines down to potentially low ng/L levels, while maintaining compliance with other DBP and microbial pathogen regulations.

2.2 Nitrosamine Formation During Chloramination.

Early mechanistic research suggested nitrosamine formation by a reaction between monochloramine and organic amine precursors (Choi and Valentine, 2002; Mitch and Sedlak, 2002). Subsequent mechanistic research indicated that monochloramine was not a significant precursor; nearly all nitrosamine formation could be explained via reactions involving the low concentrations of dichloramine (i.e., ~5%) that always coexist with monochloramine under typical chloramination conditions according to the equilibrium (Schreiber and Mitch, 2006a):

$2\ NH_2Cl + H^+ \leftrightarrow NHCl_2 + NH_4^+$

Briefly, the nucleophilic attack of unprotonated secondary amines on dichloramine forms a chlorinated unsymmetrical dialkylhydrazine intermediate (e.g., Cl-UDMH), which is then oxidized by dissolved oxygen to the corresponding nitrosamine. The reaction occurs slowly (i.e., days), indicating that nitrosamines should accumulate within chloraminated distribution systems (Mitch *et al.*, 2003a; Mitch *et al.*, 2003b). Additional studies with model precursors, described later, demonstrated that tertiary and quaternary amines also serve as nitrosamine precursors. Molar yields of NDMA from most model secondary and tertiary amines were ~2% (Mitch and Sedlak, 2004), and were an order of magnitude lower for quaternary amines (Kemper *et al.*, 2010). However, yields from chloramination of tertiary amines containing a β-aromatic ring (e.g., ranitidine) were up to ~90% (Shen and Andrews, 2011b). Formation increased with pH due to the increasing prevalence of the active unprotonated form of the amines. Application of chloramines to authentic source waters indicated that NDMA formation increases with temperature (Krasner *et al.*, 2012a). Because this pathway relates to the predominant association of nitrosamine formation with chloramine disinfection, this reaction pathway is likely the most important pathway for drinking water treatment.

2.3 Nitrosamine Precursors

This section describes the state of knowledge of the relative importance of different types of bulk and trace level organic precursors for nitrosamines potentially present or added to drinking waters (Table 2-1).

Development of FP and SDS tests. Most previous research on nitrosamine precursors has used formation potential (FP) tests. The FP test maximizes nitrosamine formation using much higher monochloramine doses than applied during drinking water treatment. The first NDMA FP test applied preformed monochloramine at a 140-mg/L dose for 10 days (Mitch *et al.*, 2003b). More recently, a “reactivity” based method was developed, in which chlorine was added at three times the total organic carbon (TOC) concentration of the sample (on a mass basis with Cl_2) and sufficient ammonia to (typically) reach a Cl_2/N mass ratio of 3:1 (Krasner *et al.*, 2004; Krasner *et al.*, 2007), where the ammonia was added first. Samples were held at pH 8 at 25°C for 3 days. This method has been used for treated wastewaters, reclaimed waters, watershed, and drinking water samples (Krasner *et al.*, 2009b; Krasner *et al.*, 2012b). However, previous work (Krasner *et al.*, 2012b) generated NDMA from drinking water sources using FP tests, even when no NDMA is reported from actual treatment, illustrating that FP tests are used to represent precursor loading rather than formation under typical conditions.

Optimization of treatment and disinfection, necessary for continued use of chloramination for DBP control, must be performed under realistic conditions. In recent work (Krasner *et al.*, 2012a; Shah *et al.*, 2012), realistic simulated distribution system

(SDS) and uniform formation condition (UFC) tests for nitrosamine and halogenated DBP formation were developed. The UFC test involves a chlorine dose sufficient to leave ~2.5 mg/L as Cl_2 residual after 3 minutes, ammonia addition to achieve a Cl_2/N weight ratio of 4.75:1, and a reaction in the dark for 3 days at pH 8 and 25°C, all intended to mimic a “standard” set of realistic chloramination conditions. Alternatively, SDS tests match actual site-specific plant operating conditions. Bench-scale SDS tests of treated water yielded NDMA, THM, and HAA levels that closely matched observed formation in the corresponding distribution systems (Krasner *et al.*, 2011), indicating that the SDS test is suitable for exploring treatment and control research.

Nitrosamine formation from chloramination of model precursors. Chloramination is the major cause of nitrosamine formation in North American drinking waters, and amines are expected to be the major source of precursors during chloramination. Amides, the other major category of organic nitrogen precursors, react orders of magnitude more slowly than amines with chloramines, due to the electron-withdrawing carbonyl groups adjacent to the nitrogen (Mitch and Sedlak, 2004; Walse and Mitch, 2008). Although nitrosamine formation from amides is low over short chloramine contact times, the slow release of secondary amines from certain amides by hydrolysis can form significant concentrations of nitrosamines over timescales of ~1 week (Mitch and Sedlak, 2004). Examples include the solvent dimethylformamide and the herbicides dimethyldithiocarbamate and diuron (Chen and Young, 2008; Mitch and Sedlak, 2004; Padhye *et al.*, 2013).

Although primary amines can be nitrosated, primary nitrosamines decay nearly instantaneously, releasing nitrogen gas and a carbocation. Thus primary nitrosamines have not been isolated (Ridd, 1961). Most mechanistic research has addressed secondary amines (Choi and Valentine, 2002; Mitch and Sedlak, 2002; Schreiber and Mitch, 2006a; Shah and Mitch, 2012), which can directly form stable secondary nitrosamines. While most research has focused on NDMA formation from dimethylamine (DMA), other secondary amines can form their corresponding nitrosamines upon chloramination (Schreiber and Mitch, 2006b).

Tertiary amines may also serve as significant precursors. Upon exposure to chlorine, tertiary amines decay nearly instantaneously and quantitatively to release an aldehyde and a secondary amine capable of forming a stable secondary nitrosamine upon subsequent chloramination (Mitch and Schreiber, 2008). There was no regioselectivity regarding which of the alkyl substituents on the tertiary amines were eliminated as the aldehyde. Similar reactions pertain to chloramination of tertiary amines, although the conversion of the tertiary amine to a secondary amine was slower due to the lower reactivity of chloramines compared to chlorine. The net result is that nitrosamine yields from most tertiary amines during chloramination are comparable to those from secondary amines (i.e., ~2%).

However, a subset of tertiary amines, where one of the alkyl substituents contained an aromatic group in the β-position to the nitrogen (e.g., a benzyl functional group), exhibit far higher yields of NDMA during chloramination (Le Roux *et al.*, 2011; Shen and Andrews, 2011a; Shen and Andrews, 2011b). Such functional groups are observed in certain pharmaceuticals. For example, ranitidine, the active component in the antacid Zantac®, formed NDMA at yields of 60-90% (Le Roux *et al.*, 2011; Shen and Andrews, 2011a; Shen and Andrews, 2011b). These higher yields suggest that these tertiary amines can form nitrosamines without proceeding through a secondary amine intermediate, although the specific pathway is unclear.

Although the positive charge on quaternary amines hinders reactions with chloramines, model quaternary amines formed NDMA at yields ~0.2%, likely via pathways involving degradation of quaternary amines to secondary amines initiated by radicals (Kemper *et al.*, 2010; Padhye *et al.*, 2010). As indicated below, quaternary amines are important functional groups in personal care products (e.g., shampoos), and materials used for drinking water treatment (e.g., cationic coagulation polymers and certain anion exchange resins).

NDMA formation from bulk organic matter. While bulk organic matter analytical parameters (TOC, UV_{254}) and other precursors (bromide) or operating conditions (chlorine dose, pH, temperature) can be used to predict the formation of regulated DBPs across a range of waters, no such relationships were found between dissolved organic nitrogen (DON), nitrite, ammonia or bromide and the formation of ng/L levels of NDMA (Chen and Westerhoff, 2010). Average DON levels in drinking waters are on the order of 0.2 mg N/L (200,000 ng N/L), which equates to dissolved organic carbon (DOC)/DON ratios of ~18/1 (Lee and Westerhoff, 2006). To produce 50 ng/L of NDMA requires only ~500 ng N/L of precursor amines, assuming 2% molar yield, or on the order of only 0.25% of the average DON in source waters. This perhaps explains why bulk measurements of DON in different water sources may not be good surrogates for NDMA precursors. However, within a watershed, DON may correlate with NDMA FP, if correlations exist between bulk DON and the subset of NDMA precursors.

Just as hydrophobic organic acids (i.e., humic substances) were shown to contribute the most towards THM formation, efforts to compare the reactivity of different bulk organic matter fractions towards NDMA formation have been forged. NDMA formation from organic matter isolates in the presence of monochloramine requires one nitrogen atom in organic matter to react with inorganic nitrogen in chloramines, based upon $^{15}N\text{-}NH_2Cl$ experiments (Mitch *et al.*, 2009). Generally, the hydrophilic fractions tended to form more NDMA than hydrophobic fractions, and base fractions tend to form more NDMA than acidic fractions when normalized to a carbon basis (Chen and Valentine, 2007). NDMA yields (ng NDMA FP/mg DOC) ranged from 22 to 78 in one study (Chen and Valentine, 2007), but after accounting for the contribution of each fraction to the total DOC of the river water, the low reactivity of the hydrophobic acid fraction still accounted for nearly 70% of the NDMA FP . However, Dotson *et al*. (2009) found that hydrophobic acids had no reactivity to form NDMA. Additional studies with isolates from multiple surface waters and wastewaters, confirmed a trend for isolates with greater nitrogen enrichment (base and colloid fractions) having higher NDMA yields (Lee *et al.*, 2007b)). The base fractions were the most reactive, with yields of up to 6 ng/mg DOC (Dotson *et al.*, 2009). The reactivity of wastewater effluents was substantially higher than that of algal-impacted waters. Despite representing <3% of the DOC in bulk waters, the base fraction accounted for ~60% of the NDMA in a wastewater effluent.

In another study, the vast majority of DON in bulk wastewater effluent organic matter and the NDMA FP were hydrophilic in nature (Pehlivanoglu-Mantas and Sedlak, 2008). Low molecular weight compounds, capable of passing through a 1000 Da ultrafilter, contained >60% of the NDMA precursors in wastewater effluents (Pehlivanoglu-Mantas and Sedlak, 2008). In separate research, NDMA formation from different size fractions of organic matter indicated that colloidal material produced NDMA – perhaps from sorbed trace organic chemicals – otherwise, <2,500 Da material yielded NDMA (Krauss *et al.*, 2010).

Origin of NDMA precursors in source waters. Treated wastewater effluent organic matter (EfOM) generally contains higher levels of NDMA FP than drinking water NOM, including eutrophic water supplies (Bond *et al.*, 2011; Krasner *et al.*, 2008; Krasner *et al.*, 2009a; Nawrocki and Andrzejewski, 2011; Russell *et al.*, 2012). In many cases, the fraction of wastewater effluent in drinking water sources, based upon the levels of wastewater indicators, such as boron, the anticonvulsant primidone or the artificial sweetener sucralose, correlated well with NDMA FP in drinking water sources (Krasner *et al.*, 2008). EfOM from a biological WWTP includes soluble microbial products (SMPs) (Barker and Stuckey, 1999), where laboratory-generated SMPs from activated sludge were found to contribute to the formation of NDMA (Krasner *et al.*, 2008). However, organic matter isolates from SMPs had lower NDMA FP yields than bulk wastewater EfOM (Dotson *et al.*, 2009). The particular association of NDMA formation and municipal wastewater effluents suggests that anthropogenic chemicals may be important.

One study of Chinese source waters and drinking waters examined the occurrence of nine nitrosamines and their corresponding secondary amines (Wang *et al.*, 2011c). Secondary amine concentrations ranged from 0.1 to 4 μg/L in these waters, which were likely impaired by industrial effluents. Although secondary amines can be important precursors in certain waters heavily impacted by specific industrial effluents, in most natural waters (Gerecke and Sedlak, 2003) or municipal wastewaters (Mitch and Sedlak, 2004), dimethylamine concentrations were not sufficient to explain NDMA formation.

Trimethylamine concentrations in wastewater effluents also were insufficient to explain NDMA formation (Mitch and Schreiber, 2008). However, tertiary amines are common functional groups in anthropogenic chemicals and, as noted above, most form nitrosamines at yields comparable to secondary amines. A subset of β-aryl tertiary amines formed NDMA at significantly higher yields, such as pharmaceuticals like ranitidine. Such pharmaceuticals are microconstituents of wastewater-impacted waters, but may explain a significant fraction of NDMA formation if they form NDMA at high yields upon chloramination. However, in a survey of wastewater-impacted surface waters, ranitidine was only detected with a frequency of 1.2% and the maximum concentration was at the 10 ng/L detection limit (Kolpin *et al.*, 2002). A decomposition by-product of ranitidine was also shown to have a high yield to form NDMA (Le Roux *et al.*, 2012b), but it is unclear whether such by-products occur in significant concentrations in source waters.

Alternatively, although NDMA yields from quaternary amines in FP assays were ~0.2% (Kemper *et al.*, 2010), quaternary amines are macroconstituents of monomers and polymers in an array of consumer products (e.g., shampoos). However, their concentrations in wastewater-impacted waters are unknown, due to the difficulty of quantifying polymer concentrations.

Contribution of water treatment materials towards NDMA formation.

Cationic polymers. Many cationic treatment polymers (e.g., polyamines, polyDADMAC) used as coagulant or dewatering aids in drinking water treatment can degrade and release NDMA precursors (Bolto, 2005; Kohut and Andrews, 2003; Najm and Trussell, 2001; Wilczak *et al.*, 2003). In one study, the age of polymer feed stocks was not shown to affect NDMA FP (Kohut and Andrews, 2003). Chlorination of backwash water from filters fed with polyDADMAC-coagulated water formed elevated levels of NDMA (Wilczak *et al.*, 2003). There has been considerable research into the residuals and removal of polyelectrolytes used in water treatment (Bolto and Gregory, 2007). Unfortunately, techniques to monitor residuals after coagulation have detection limits on the order of μg/L, and these are likely inadequate to monitor for ng/L levels of NDMA FP. Nonetheless, FP tests can provide sufficient information on polymer impacts (Krasner *et al.*, 2012b).

Polyamines produced more NDMA than polyDADMAC, and the highest levels of NDMA were found around pH 8 during chloramination (Park *et al.*, 2009). For polyamines, the tertiary amines terminating polymer chains were mostly responsible for NDMA formation, while degradation of the quaternary amine ring in polyDADMAC, which lacks tertiary amines, accounted for the NDMA formation (Park *et al.*, 2009). Accordingly, for polyamines, lower molecular weight polymers produced more NDMA than higher molecular weight forms, and NDMA formation was unaffected by the molecular weights of polyDADMAC polymers (Park *et al.*, 2009). During ozonation, degradation of the quaternary ammonium ring of polyDADMAC by hydroxyl radicals produced dimethylamine, which can form NDMA during subsequent chloramination (Padhye *et al.*, 2011a). Used as an alternative polymer, polyacrylamide resulted in substantially less NDMA FP than polyDADMAC (Labernik *et al.*, 2010), in accordance with its lack of dimethylamine functional groups.

Anion-exchange resins. Anion exchange units use strong (quaternary amine) or weak (tertiary amine) base polymeric resins. Fresh trimethylamine- and tributylamine-based type 1 and dimethylethanolamine-based type 2 anion exchange resins released NDMA and their corresponding nitrosamines (e.g., *N*-nitrosodibutylamine from tributylamine-based resins), likely due to shedding of manufacturing impurities (Kemper *et al.*, 2009). The extent of such shedding was highly variable among commercially available resins (Singer and Flower, 2012). The resins can also degrade over time releasing organic precursors that might contribute to formation of their corresponding nitrosamines within distribution systems when chloramines are applied downstream (Nawrocki and Andrzejewski, 2011). Higher levels of nitrosamine precursors were observed after regeneration cycles, and particularly after periods of flow interruption, where the resins were bathed in stagnant water (Singer and Flower, 2012). In full-scale anion exchange treatment systems, shedding of precursors declined after multiple regeneration cycles (Krasner *et al.*, 2012a; Singer and Flower, 2012). Exposure of resins to chlorinated tap water produced NDMA in the effluents (Kimoto *et al.*, 1980; Najm and Trussell, 2001). When magnetic ion exchange resin (MIEX) was used to treat 3 wastewater effluents, NDMA FP increased from 156-287 to 266-344 ng/L, whereas the increase for 3 drinking waters was from 10-12 to 14-18 ng/L (Gan and Karanfil, 2012). A similar increase was not observed in deionized water treated with MIEX. The mechanism for greater formation is not well understood, but it was found that increasing wastewater content increased NDMA FP after MIEX treatment. Because cation exchange resins do not use amine-functional groups they did not release NDMA or NDMA precursors (Kemper *et al.*, 2009).

Distribution system synthetic materials. Recent field and bench-scale studies show that certain rubber seals and gaskets in potable water systems can be a source of NDMA in chloraminated water systems (Morran *et al.*, 2011a; Teefy *et al.*, 2011). The vulcanization process of rubber production is known to release NDMA (Incavo and Schafer, 2006; Spiegelhalder and Preussmann, 1982)). While PVC pipe materials were relatively unreactive in forming NDMA in chlorinated or chloraminated water, rubber components (pipe rubber ring joint lubricant [in the form of water-soluble gel]; natural rubber seal rings, ethylene propylene diene terpolymers and styrene-butadiene rubber) leached NDMA in chlorine-free water and formed NDMA after chloramination (Morran *et al.*, 2011a). Periods of stagnation resulted in significant increases in NDMA levels. There was no apparent relationship between NDMA release and exposed surface area or newer versus older exposed materials. NDMA levels resulting from sealing ring leaching, on the order of 10 to 25 ng/L, would undermine any NDMA-reduction processes at the water treatment plant (Morran *et al.*, 2011a). In another study, elevated NDMA levels were observed in a potable water distribution storage tank that was equipped with temporary gaskets (ethylene propylene diene monomer M class rubber; NSF/ANSI 61 certified for drinking water use) (Teefy *et al.*, 2011), and the gaskets were determined to be the source of NDMA and other nitrosamines (N-nitrosodibutylamine [NDBA] and N-nitrospiperidine [NPIP]).

Table 2-1 Importance of different precursors for nitrosamine formation in drinking waters

Precursor	**Importance**
Amine-containing coagulation polymers	High
Effluent-impacted source waters	High
Pharmaceuticals and personal care products	Moderate/High
Distribution system materials	Moderate
Anion exchange resins	Moderate
Soluble microbial products	Limited
Agricultural chemicals	Limited
Bulk DON	Low
Algae	Low

2.4 Removal of Nitrosamines and their Precursors

Nitrosamine removal can occur by sorption to activated carbon or UV photolysis within drinking water plants. However, due to the slow kinetics of nitrosamine formation during chloramination, nitrosamine formation continues within chloraminated distribution systems. Because nitrosamines can continue to form in distribution systems unless the precursors have been removed or transformed, the discussion will focus on removal of nitrosamine precursors (Table 2-2).

Coagulation and polymer optimization. Coagulation using four different German waters at multiple ferric chloride dosages concluded that <10% removal occurred of NDMA, N-nitrosodiethylamine (NDEA) or N-nitrosopyrrolidine (NPYR) FP (Sacher *et al.*, 2008). Alum coagulation (40 or 80 mg/L) of a wastewater-dominated river showed <10% removal of NDMA FP (Krasner *et al.*, 2008). Likewise, lime softening had no significant impact on NDMA FP (Mitch *et al.*, 2009). It has been shown that the majority of NDMA precursors are <1 kDa and that this fraction of NOM is poorly removed by coagulation (Xu *et al.*, 2011).

Coagulation, due to the frequent inclusion of amine-based cationic polymers, typically increases NDMA FP (Bond *et al.*, 2011). One study involving 3 treatment plants (typically 2 sampling events each) found that NDMA FP increased by 43 to 82% at plants using polyDADMAC and was not changed (±18%) at the plants that did not use a cationic polymer (Krasner *et al.*, 2012b). High polymer doses can leave residual polymer in the effluent (Novak and Montgomery, 1975; Novak and Langford, 1977). One bench-scale study found polyDADMAC residual in all samples in which it was used as a coagulant alone, at concentrations of at least 100 µg/L. When polyDADMAC and alum were used concurrently, detection of polyDADMAC after filtration was reduced, indicating a need for polymer dose optimization (Becker *et al.*, 2004). For example, the dosage of coagulant could be raised to compensate for a reduction in polyDADMAC dosage in order to maintain good turbidity removal and filter run lengths (Labernik *et al.*, 2010).

Physical adsorption of nitrosamine precursors. Because they are fairly hydrophilic (e.g., K_{OW} = 0.27 for NDMA) (ATSDR, 1989; Mitch *et al.*, 2003b), nitrosamines sorb poorly to activated carbon. Furthermore, chloramines are typically added after activated carbon treatment, so nitrosamines will normally not be present in drinking waters treated by activated carbon. Because adsorption of nitrosamines after formation is not feasible, sorption can only be applied for the removal of nitrosamine precursors. Although research regarding sorption of precursors is in its infancy, one study has shown 50% NDMA FP reduction in 3 of 4 surface waters exposed to powdered activated carbon (PAC; Calgon F300) at a dose of just 5 mg/L (Sacher *et al.*, 2008). A PAC dose of 20 mg/L produced reductions of 90% or greater. However, the water was in contact with PAC for 7 d in both cases to assure that adsorption equilibrium was established, whereas in conventional treatment water is only in contact with PAC for hours.

NDMA FP was reduced in a municipal wastewater effluent by both PAC and granular activated carbon (GAC) (Hanigan *et al.*, 2012). PAC reduced NDMA FP after a 4 hour contact time by 37 and 59% at doses of 3 and 8 mg/L, respectively. Using GAC at a 10 min simulated empty bed contact time to treat a mixture of 90% surface water and 10% wastewater, NDMA FP breakthrough was less than 20% after 10,000 bed volumes. For both GAC and PAC treatments, removal of NDMA FP exceeded removal of DOC and UV, surrogate measures for traditional DBP precursors, including THMs. Similarly, pilot- and full-scale studies using GAC demonstrated 60-80% reduction in NDMA FP in surface waters (Hanigan *et al.*, 2012). Farré *et al.* (2011) found that NDMA FP was reduced from 250 to 50 ng/L using pilot-scale biologically active carbon (BAC) columns at a wastewater reuse facility. Biologically active sand filtration removed precursors poorly, suggesting the importance of adsorption onto the BAC.

For specific trace organic compounds which may produce NDMA upon chloramination, sorption affinity can be inferred from octanol-water partitioning coefficients, but this is increasingly difficult for higher molecular weight compounds with acid or base functional groups (Redding *et al.*, 2009). Low molecular weight amine precursors sorb poorly to GAC. For example, the Freundlich parameters for dimethylamine were K_f = 0.92 mg/g and 1/n = 0.84 (Hwang *et al.*, 1994). In a GAC pilot-plant study, it was shown that several pharmaceutical precursors of NDMA sorbed well to BAC (Farré *et al.*, 2011). Even the most poorly absorbed compound, roxithromycin, was reduced ~98% across BAC. However, in another study some pharmaceuticals that would sorb readily to activated carbon from deionized water were poorly removed from surface waters (e.g., <1% removal of carbinoxamine after 24 h), presumably due to competition for sorption sites from other organic constituents (Hanigan *et al.*, 2012).

Nitrosamine precursor removal by riverbank filtration. Riverbank filtration has been shown in Europe to remove nitrosamine precursors via biodegradation (Sacher *et al.*, 2008). Recently, riverbank filtration was shown to be effective at a site in the U.S. (Krasner *et al.*, 2012d). Travel time varied from ~21 to 90 days. The riverbank filtration-treated water was diluted somewhat (~30%) by local groundwater. Based upon this dilution factor, the true removal of TOC was ~30%, and the removal of NDMA FP was 64%. Thus, NDMA precursors appeared to be better removed than the bulk NOM.

Pre-oxidation of nitrosamine precursors. Previous research has demonstrated that pre-oxidation of waters with chlorine, ozone, chlorine dioxide, permanganate, ferrate, hydrogen peroxide, and even sunlight are capable of reducing NDMA formation during subsequent chloramination by deactivating NDMA precursors (Charrois and Hrudey, 2007; Chen and Young, 2008; Lee *et al.*, 2007a; Lee *et al.*, 2008). To evaluate precursor deactivation under drinking water-relevant conditions, recent research evaluated the reduction in NDMA formation in authentic waters associated with combinations of pre-oxidants (chlorine, ozone, chlorine dioxide, and low or medium pressure UV) applied at exposures relevant to 3-log removal of *Giardia* at 5°C with post-chloramination conducted under conditions relevant to drinking water distribution (Shah *et al.*, 2012). Ozone was the most effective of the four pre-oxidants, generally achieving 50% reduction in NDMA formation for exposures $\leq$0.4 mg•min/L, roughly 20% of the exposure range relevant to *Giardia* control. Chlorine achieved similar results at exposures ~70 mg•min/L, nearly half that relevant to *Giardia* control. Chlorine dioxide and UV treatment were relatively ineffective over exposures relevant to disinfection. However, reductions in NDMA precursors of ~30% were observed for UV fluence relevant to advanced oxidation (~1000 mJ/cm^2). In some waters, chlorine promoted NDMA formation at low exposures, but formation declined again at higher exposures. In other waters, chlorine dioxide promoted NDMA across the range of exposures.

Maximum precursor deactivation by free chlorine is anticipated at pH ~8.5–9, where there is maximum co-occurrence of the active oxidant (HOCl, pK_a = 7.5) and the reactive deprotonated amine precursors (pK_a ~10-11) (Lee and von Gunten, 2010). Krasner and colleagues (2008) evaluated the impact of pH and temperature on NDMA formation on various drinking waters, where there was a 3-min free chlorine contact time before ammonia addition. In many waters, they observed at pH 8 or 9 that there was more NDMA formation at 5°C than at 25°C. To clarify these trends, these researchers varied the pre-chlorination and post-chloramination temperatures. The results indicated that nitrosamine formation increased with temperature during post-chloramination. However, precursor deactivation increased with temperature during pre-chlorination. In some waters, the reduction in precursor deactivation at 5°C enabled higher nitrosamine formation overall than at 25°C, despite the slower formation during post-chlorination. At pH 7, such a temperature effect was not observed, most likely due to poor precursor deactivation over this short chlorination time resulting from the low prevalence of deprotonated amines.

Unfortunately, increasing pre-oxidant exposures for control of NDMA formation promotes the formation of regulated and unregulated DBPs associated with each pre-oxidant, including THMs, HAAs, and chloral hydrate for chlorine; bromate, chloropicrin, and chloral hydrate for ozone; chlorite for chlorine dioxide; and chloropicrin and chloral hydrate for medium pressure UV treatment (Shah *et al.*, 2012). For the application of each pre-oxidant at ~60-100% of the exposures relevant to *Giardia* control to different waters, the median concentrations of regulated by-products did not exceed relevant maximum contaminant levels (MCLs), but these values were exceeded in some waters. Because ozone was able to deactivate precursors effectively at low exposures relevant to disinfection, its use for NDMA control may minimize these risk tradeoffs associated with the formation of other by-products. For example, bromate was never detected at >3 μg/L when 8 waters were pre-ozonated at exposures that reduced NDMA formation by 50% after post-chloramination. While similar studies have not yet been conducted for other pre-oxidants, the results of previous research suggest that permanganate, ferrate, hydrogen peroxide, and sunlight would be less effective for NDMA precursor deactivation than ozone and chlorine (Chen and Young, 2008; Lee *et al.*, 2008).

Modification of method of chloramine application. Based upon the dichloramine pathway for nitrosamine formation during chloramination, the addition of chlorine prior to ammonia was suggested to reduce nitrosamine formation during chloramination by preventing the occurrence of high chlorine to ammonia molar ratios at the point of chlorine injection, and thereby minimizing dichloramine formation (Schreiber and Mitch, 2005). This technique was successfully pilot-tested at a municipal wastewater recycling plant (Mitch *et al.*, 2005). It was also pilot tested at a drinking water plant (Krasner *et al.*, 2008). The order of addition of chlorine and ammonia at pilot scale often had no impact. However, when there was an effect, chlorine added first resulted in less NDMA formation.

Destruction of nitrosamines by UV treatment. UV treatment is the most widely practiced method for destroying nitrosamines at reuse facilities (Mitch *et al.*, 2003b). Because a UV fluence of ~1,000 mJ/cm^2 is required for a log order reduction in NDMA (Sharpless and Linden, 2003), UV treatment for nitrosamine destruction is more expensive than for disinfection. While effective for destruction of nitrosamines, UV treatment at fluence near 1,000 mJ/cm^2 is only partially effective at destruction of nitrosamine precursors (see above). Because chloramines are usually applied after UV treatment at drinking water treatment plants, there would generally be no nitrosamines present to destroy and, moreover, there would be formation of nitrosamines in the chloraminated distribution system. Nonetheless, UV treatment to destroy nitrosamines was designed for a drinking water treatment plant on an effluent-dominated river, where there were nitrosamines in the river water (Swaim *et al.*, 2006).

Table 2-2 Importance of drinking water unit processes to control NDMA formation

Treatment	**Features**	**Importance**
Polymer Optimization	• Reduction in polyDADMAC dosage can reduce, but not eliminate NDMA formation.	High
Precursor Pre-Oxidation	• Involves risk tradeoffs because increasing pre-oxidant exposure promotes the formation of DBPs associated with each pre-oxidant. • Ozone most effective, followed by chlorine • UV treatment only partially effective at advanced oxidation process fluence • Chlorine dioxide relatively ineffective	High
Alternative Polymer	• Nearly all cationic polymers currently in use will contribute to nitrosamine formation because they are amine-based. Epi-DMA polymers are more potent precursors than polyDADMAC. Polyacrylamide has much less precursors than polyDADMAC.	High
Activated Carbon	• Activated carbon is more efficient at removing NDMA precursors than TOC in limited studies. • The ability to remove precursors for other nitrosamines is limited to one study in China.	High
Riverbank Filtration	• Limited evidence shows that riverbank filtration can remove NDMA precursors.	Moderate
Modify Chloramination Protocol	• Minimizes dichloramine, the active inorganic chloramine for promoting nitrosamine formation • Involves a hydraulic mixing phenomenon. Needs more pilot- or full-scale testing to characterize importance.	Moderate
Biofiltration	• Biofiltration may remove NDMA precursors, but can also increase NDMA formation by transforming some precursors into more potent forms.	Low or Moderate
UV Treatment	• Full-scale applications ongoing for hazardous waste treatment and wastewater recycling applications • Destroys nitrosamines, but only modest destruction in nitrosamine precursors (see pre-oxidation). Nitrosamine formation would continue from remaining precursors within chloraminated distribution system.	Low
Anion Exchange	• Anion exchange resins can increase nitrosamines. • The ability of anion exchange resins to remove nitrosamine precursors is unclear.	Low
Coagulation and Softening	• Neither process significantly removes NDMA precursors.	Low

2.5 Summary and Conclusions

Mechanistic studies and results from occurrence studies suggest that the most important mechanism for nitrosamine formation during disinfection is the chloramination of amine precursors. Mechanistic studies have indicated that yields of NDMA from chloramination of most secondary and tertiary amines are ~2%, but can be >80% for certain tertiary amines with β-aryl functional groups. Wastewater-impaired source waters exhibit NDMA precursors, suggesting the importance of anthropogenic constituents. Specific precursors have not been characterized in wastewater-impaired waters, but could include either tertiary amine-based microconstituents forming NDMA at high yield, or quaternary amine-based macroconstituents of consumer products forming NDMA at low yields. Quaternary amines also serve as the predominant functional groups in common drinking water cationic coagulation polymers and anion exchange resins, that have proven to be important nitrosamine precursors.

The effectiveness of UV treatment for nitrosamine destruction has been demonstrated for wastewater recycling operations (Table 2-2). However, UV treatment is substantially less effective at destroying nitrosamine precursors, especially at fluence levels used for disinfection. UV is unlikely to be useful at nitrosamine control at drinking water treatment plants, because NDMA formation happens slowly within chloraminated distribution systems. However, it may be effective if significant nitrosamine concentrations occur in source waters.

Avoiding chloramination may solve a NDMA problem. However, there are reasons for employing chloramines, including reducing halogenated DBP formation. Where utilities practice chloramination for secondary disinfection, two promising approaches may reduce nitrosamine exposure. First, nitrosamine precursors can be deactivated upstream of chloramination by strong pre-oxidants. Over oxidant ranges applied typically for disinfection, the order of effectiveness of oxidants for NDMA precursor destruction was ozone > chlorine >> chlorine dioxide ≈ UV. However, each oxidant forms DBPs. Accordingly, reduction in the formation of nitrosamines must be balanced against increased formation of halogenated DBPs. Second, nitrosamine precursors can be physically removed before chloramination. Recent research suggests that PAC or GAC may be more effective at removing NDMA precursors than at removing the bulk NOM. However, this has not been observed in all cases, so more research is needed in this area.

NDMA formation has been associated with the occurrence of amines in wastewater-impacted source waters and the use of amine-based cationic coagulation polymers and anion exchange resins. An alternative strategy for chloraminating utilities is to avoid precursors. Utilities could blend source waters to minimize wastewater impacts. Utilities could optimize the cationic polymer dose to minimize applied doses. Unfortunately, nearly all cationic polymers and anion exchange resins currently available are amine-based. However, polyacrylamide has less NDMA precursors than polyDADMAC. Over the longer term, development or use of non-amine-based treatment polymers is desirable.

Any modifications to water treatment plant operations could influence the efficiency of plant operations, affect the formation of other DBPs, or alter pathogen control. PolyDADMAC and certain anion exchange resins are important sources of nitrosamines and/or nitrosamine precursors. However, polyDADMAC is widely employed for sedimentation, sludge dewatering, filtered water turbidity control, and filter run time lengthening. Similarly, anion exchange resins are widely employed for control of nitrate and arsenic. If pre-oxidation is required to transform nitrosamine precursors prior to chloramine addition, then the formation of regulated (e.g., bromate from ozonation, THMs/HAAs from chlorination, chlorite from chlorine dioxide), and non-regulated (e.g., halonitromethanes from ozone or medium pressure UV treatment) halogenated DBPs will increase. Use of PAC or GAC could be used to reduce precursors for nitrosamines, but will increase the cost of water treatment.

Conclusions. The discovery of halogenated byproducts of chlorine disinfection in the 1970s forced regulators and utilities to seek to balance the acute risks associated with pathogen exposure against the chronic risks associated with lifetime exposures to potentially carcinogenic chemical byproducts. Use of chloramination for secondary disinfection has increased in the United States, Canada, UK, Australia, and China to minimize the formation of regulated halogenated byproducts associated with chlorination, yet chloramination has been found to promote the formation of other potentially carcinogenic byproducts, including nitrosamines. One approach to this problem, favored in northern Europe, is to reduce or minimize disinfectant application and byproduct precursors using activated carbon or other technologies to remove dissolved organic matter and produce biostable water. This approach has not been targeted in the United States and other countries due to concerns over cost. It is likely that disinfection in the United States and elsewhere will seek to minimize the overall risks of exposure to pathogens, and byproducts from primary (e.g., chlorine and ozone) and secondary (i.e., chloramination) disinfectants.

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3 Contribution and Removal of Watershed and Cationic Polymer *N*-Nitrosodimethylamine Precursors

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3.1 Abstract

N-nitrosodimethylamine (NDMA) is a disinfection by-product formed when chloramines react with watershed- or water treatment polymer-derived precursors. We examined the sorption potential of both precursor groups to powdered and granular activated carbon (PAC and GAC). Activated carbon reduced the formation potential (FP) of NDMA by 30 to 80% when only watershed precursors were present. Polydiallyldimethylammonium chloride (polyDADMAC) precursors were not removed well by activated carbon. Seven samples of polyDADMAC from across the U.S. produced 47 ± 3 ng NDMA FP/mg active polymer after coagulation and settling, which is about one third of the NDMA FP formed in DI water. Polyamine (340 ng/mg) formed NDMA when diluted in DI water with chloramines but the precursors were effectively removed by activated carbon. PolyDADMAC use always increased NDMA FP of the settled water, regardless of dose, suggesting that the optimum dose should be based on turbidity removal with consideration for balancing NDMA formation.

3.2 Introduction

Disinfection with aqueous chlorine produces regulated trihalomethanes (THMs) and haloacetic acids (HAAs) when bulk natural organic matter (NOM) is present in the source water. Alternative disinfectants such as chloramines reduce the formation of chlorinated disinfection by-products (DBPs) (Guay *et al.*, 2005), and therefore, between 2007 and 2010, the number of U.S. water utilities using chloramines rose from 944 to 1,298 (37% increase) (Li, 2011). Unfortunately, chloramination can produce *N*-nitrosodimethylamine (NDMA) through reactions with organic nitrogen sources (Mitch *et al.*, 2003a; Richardson *et al.*, 2007). Compared to decades of research on mitigation of

THM and HAA formation, less is known about NDMA mitigation strategies. Strategies to limit NDMA formation involve physical removal or oxidation of organic precursors (Krasner *et al.*, 2013). Here, we focus on physical removal strategies and evaluate them using the two major classes of precursors that appear to exist: (1) watershed precursors, and (2) in-plant sources such as cationic polymers.

NDMA is a drinking water DBP with a carcinogenic risk level of 10^{-6} at lifetime exposure levels of 0.7 ng/L (USEPA, 2002). The Environmental Protection Agency (EPA) is currently considering regulating NDMA in the United States as indicated by its inclusion in Unregulated Contaminant Monitoring Rule 2 (UCMR2). Canada and two U.S. states (CA, MA) have already begun regulating NDMA in the form of notification or guidance at levels of 10-40 ng/L (California Department of Public Health, 2013; Health Canada, 2011; Massachusetts Department of Energy and Environmental Affairs, 2004). EPA is expected to make a regulatory determination in 2014, and therefore finding strategies to mitigate NDMA formation during drinking water treatment is important.

NDMA precursors are thought to be associated with anthropogenic sources containing reactive organic nitrogen groups such as secondary and tertiary amines (Krasner *et al.,* 2013). Among several other sources (agricultural chemicals, rubbers used in distribution system gaskets), cationic polymer use and trace organic compounds (pharmaceuticals, personal care products) in wastewater (WW) impacted surface waters are thought to be the primary factors affecting NDMA formation in drinking waters (Kohut and Andrews, 2003; Krasner *et al.*, 2013; Park *et al.*, 2009; Selbes *et al.*, 2013; Shen and Andrews, 2011a; Shen and Andrews, 2011b; Teefy *et al.*, 2011; Wilczak *et al.*, 2003). The most important NDMA mitigation strategies are thought to be precursor pre-oxidation, alternative polymers, activated carbon (AC), and optimization of polymer use (Krasner *et al.*, 2013). We showed that AC is an effective mitigation strategy for NDMA precursors of WW origin (Hanigan *et al.*, 2012). Powdered AC (PAC) and granular AC (GAC) removed NDMA precursors better than dissolved organic carbon (DOC) or organic matter absorbing light at 254 nm (UV_{254}), which are good indicators of THM and HAA precursors. Other research has also demonstrated removal of WW NDMA precursors with AC (Farré *et al.*, 2011; Sacher *et al.*, 2008). To date, the authors are not aware of any research that examines removal of polymer-derived precursors by AC and the impacts on NDMA formation. Furthermore, it is unknown whether the removal of watershed precursors by AC could potentially be offset by polymer use in terms of NDMA formation.

The objective of this study was to understand the contribution of watershed and polymer-derived precursors to NDMA formation and the ability to control that contribution using PAC and GAC. To represent the conceptual differences in reactivity and treatability of watershed and polymer NDMA precursors, Equation 1 has been developed.

$$NDMA\ FP_{total} = \left(1 - \Sigma_1^i \eta_{WS}\right) NDMA\ FP_{WS} + \left(1 - \Sigma_1^i \eta_{pDMC}\right) NDMA\ FP_{pDMC} + \left(1 - \Sigma_1^i \eta_{pAMN}\right) NDMA\ FP_{pAMN}$$

(Equation 1)

η is the dose dependent percent removal of precursors by activated carbon, oxidation, or other processes for different classes of NDMA FP precursors, including watershed precursors (subscript WS), polydiallyldimethylammonium chloride (polyDADMAC) precursors (pDMC), or polyamine-derived precursors (pAMN). It was our goal to determine estimates of the parameters in Equation 1.

We also aimed to investigate factors controlling the sorption of precursors such as PAC contact time, initial precursor concentration, and point of PAC addition in the treatment train. We used bench-scale experiments to validate pilot-scale observations about decreases in NDMA FP due to sorption, and increases in FP from polymer addition.

3.3 Materials and Methods

Sampling sources and experiments. ***Bench scale.*** Treated secondary WW effluent and surface water (SW) were taken from local sources (Phoenix, AZ) and transported directly to a laboratory where they were stored at 4°C until use (<2 weeks). WW was sampled from an activated sludge treatment plant (secondary effluent), and SW was sampled from the Central Arizona Project (CAP) canal system that receives Colorado River water. All samples were stored and transported in either amber borosilicate bottles or high density polyethylene containers. Typical water quality parameters are given in Table 3-1.

Table 3-1 Typical raw water quality parameters for selected source waters. NM = not measured

Source Water	DOC (mgC/L)	SUVA (L/mg-m)	TDN (mgN/L)	NDMA FP (ng/L)	Ammonia (mgN/L)	pH	Turbidity (NTU)
WW (sec. eff)	5.3-5.5	1.9	3.4	250-1000	<0.2 mg/L	~7.7	NM
SW – CAP	4.0	1.8	0.02	13	<0.2 mg/L	~8.1	2-10
10% WW + 90% SW	4.2	1.8	1.2	105	<0.2 mg/L	NM	NM
Ohio River Water	3-4	NM	1.3	9-19	<0.2 mg/L	7.6-7.8	22-41

Samples used Calgon WPH, which was selected based on previous results showing stronger adsorption of watershed-derived precursors than a lignite PAC (Hanigan *et al.*, 2012) and was obtained from Calgon Carbon Corp. (Pittsburg, PA). Hydrated aluminum sulfate was obtained onsite from a local water treatment plant. The polyDADMAC used in most of the testing was obtained onsite as a 20% active polymer solution (Polydyne Clarifloc C-4410, Polydyne, Riceboro, GA). In one experiment, multiple polyDADMAC samples were compared, and each of these was individually obtained from other treatment plants (Polydyne Clarifloc C-308P, C-378, C-338, C-4410, C-358, and Sterling Water Tech SW-104). Polyamine was obtained onsite from a full-scale treatment plant as a mix of 20% polymer, 80% aluminum chlorohydrate (CalChem CC2220, Modesto, CA). Bench-scale filtration was completed using precombusted (500°C for 5 hr) 0.6-µm GF/F filters (Whatman, Maidstone, UK).

Experiments were conducted using a six-paddle gang stirrer (Phipps and Bird PB-900) with 2-L rectangular vessels. For experiments with a coagulant and polymer, the coagulant was added to a 1.5-L SW (25°C) sample approximately 30 sec before the polymer. PAC was hydrated in reagent water for >24 hr before use at a concentration of 10 g/L. The polymer and the coagulant were added into the most turbulent zone located beneath the water surface and directly above the paddle. Samples were rapidly mixed (100 rpm) for 2 min followed by flocculation for 20 min (30 rpm) and settling for 1 hr (0 rpm). In some cases, the supernatant was decanted (750 mL), PAC was added to the supernatant, and the sample was mixed for 1 hr at 100 rpm. The samples were then filtered.

For experiments without coagulants, PAC was added directly to samples and mixed at 100 rpm. Unless specified, the PAC contact time was 1 hr. Samples were filtered after PAC contact. In blended samples, WW and SW were mixed before addition of PAC to simulate source waters of varying WW impact.

A bench scale GAC column was packed with Norit GAC 820. The column was 2.5 cm in diameter, was loaded at a rate of 176 m/d, and had a length of 12 cm. The column had a short empty bed contact time (1 min), but the experiment was not conducted to investigate sorption, but rather a potential interaction between the GAC surface and polyDADMAC.

Pilot scale. A pilot plant was operated in December 2012, treating water from the Ohio River in Louisville, Kentucky. Two treatment trains were operated in parallel to compare treatment scenarios. The treatment trains included presedimentation, coagulation/flocculation, sedimentation, and filtration (Figure 3-1). Filters contained either anthracite or GAC. The GAC (Calgon F820) was installed in January 2007 with about half being replaced in July 2010, and was effectively DOC saturated (<17% removal). The anthracite (100 cm anthracite, 25 cm sand, 176 m/d) and GAC (EBCT = 8.3 min, 100 cm GAC, 25 cm sand, 176 m/d) filters were backwashed approximately every 48 hr of runtime. In some experimental scenarios, PAC (Norit 20BF, Norit Americas, Inc., Marshall, TX, selected for on-site availability) was added ahead of the presedimentation basins (hydraulic retention time (HRT) was from 30 min to 60 min based on experimental scenario) or in the coagulation basin with the polyDADMAC. The pilot plant used Polydyne C-308P polyDADMAC polymer. Pilot testing was completed over 2 weeks, during which changes occurred in influent turbidity (range: 22 - 42 NTU). After changes to the operation of the pilot-plant were made, steady state was achieved before samples were taken (approximately three residence times (2.5 hr) passed between samples taken). Two experimental scenarios were conducted during each 24 hour period, with samples from the previous afternoon/evening setup taken in the morning, the operational conditions changed, samples taken again in the afternoon, and operational conditions changed again for sampling the following morning. Samples were grab samples taken nearly simultaneously (did not follow a plug of water), as the plant was assumed to be at equilibrium with only slow changes in influent FP. The pilot plant was operated using the same coagulant (ferric chloride) dose as the parallel full-scale plant, where jar tests were conducted to determine optimal turbidity removal and polyDADMAC and PAC doses could be varied. Pilot-scale experiments were conducted using water at ambient temperature (9.4 < °C < 10.6), and samples were collected in duplicate and stored in an onsite refrigerator until they were transported overnight to the laboratory refrigerator in coolers containing ice packs.

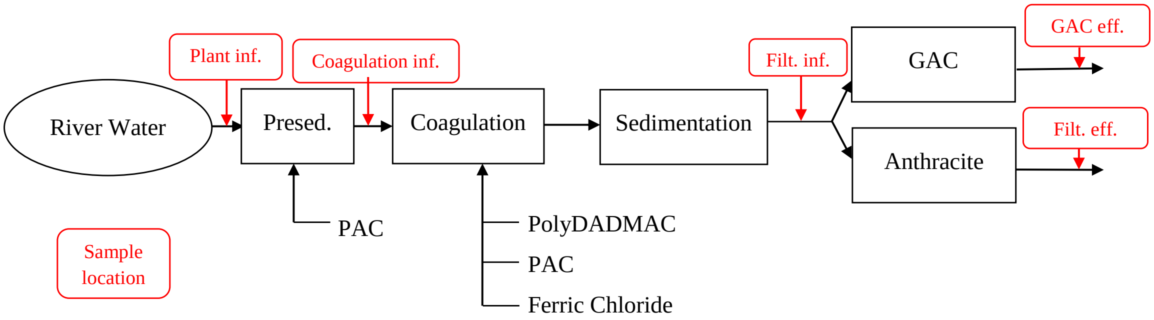

Figure 3-1 Schematic of one of the two pilot plant treatment trains

Full Scale. Three full-scale treatment plants with GAC were sampled, two of which were designed for TOC (THM precursor, extended EBCT) removal. Two were treating surface water from the central U.S. (EBCT = 3.8 or 21 min, Clarion A410P, General Chemical, Parsippany, New Jersey, and Polydyne Clarifloc C4410, respectively) and the other was treating local surface water (EBCT = 20 min, Polydyne Clarifloc C358) (all three used Calgon F400). No chlorine was added upstream of the GAC for the two plants with high EBCT, whereas chloramines were added upstream of the GAC for the plant with low EBCT. NDMA FP was measured across the GAC contactor and no chlorine was added upstream. The GAC contactors used for TOC removal had varying times of loading since regeneration (300 to 19,000 bed volumes). In one sample event, the plant with the low EBCT had GAC that had been in service for 2 months (one filter sampled) or 15 months (the other filter sampled). However, both filters were spent in terms of TOC removal (15% removal).

Reagents. All reagent water was >18.2 MΩ-cm (Megohm-cm) (NanoPURE™). Sodium hypochlorite (5.65–6%) was purchased from Fisher Chemical (Fairlawn, NJ). Sodium tetraborate, boric acid, and ascorbic acid were also purchased from Fisher Chemical. Ammonium chloride was obtained from Sigma Aldrich (St. Louis, MO). Table 3-2 gives typical virgin carbon characteristics for activated carbon used in this study (not all carbon used was virgin).

Table 3-2 Activated carbon characteristics

Activated Carbon	**Experiment**	**Type**	**Iodine Number (mg/g)**	**pH_{zpc} (Ref)**
Calgon F400	Three full scale plants	GAC	1000	8.5 (Dastgheib *et al.*, 2004)
Calgon F820	Pilot Scale	GAC	900	6.1 (Huang *et al.*, 2004)
Norit GAC820	Bench Scale	GAC	970	10 (This work)
Norit 20BF	Pilot Scale	PAC	800	Not available
Calgon WPH	Bench Scale	PAC	800	5.9 (Siddiqui *et al.*, 1994)

*Characteristics are for virgin activated carbon and thus do not likely represent used carbons

**All carbons had a base material of bituminous coal

Chloramination. For NDMA FP experiments, DOC and ammonia were first measured in the samples. Ammonia was negligible in all samples (<0.2 mg nitrogen/L). Samples were chloraminated using a preformed monochloramine (NH_2Cl) solution. Bench-scale samples were chloraminated at 3 × mg carbon/L (mg-C/L) = mg/L of NH_2Cl as Cl_2, and pilot-scale samples were mixed with 18 mg/L NH_2Cl as Cl_2. To prepare the monochloramine solution, NaOCl was diluted with borate buffer (pH 8) and DI water (final concentration 1.7-2.2 gCl_2/L). The NaOCl solution was added slowly to a pH 8 borate buffered NH_4Cl solution. The final monochloramine stock solution contained 200 mM borate and had a $N:Cl_2$ molar ratio of 1.2. The monochloramine concentration was measured after a reaction period of 1 hr at 25°C using an indophenol reagent (MonochlorF, Hach Company, Loveland, CO) to produce a colorimetric response that was measured using a Hach DR 5000 spectrophotometer.

Samples were buffered at pH 8 using 2 mM borate and dosed with monochloramine. Samples were chloraminated and allowed to react in the dark for 72 hr at 25°C, after which 5 mM ascorbic acid was added to quench any remaining monochloramine.

Analytical methods. NDMA was quantified in a process similar to EPA Method 521 (Munch and Bassett, 2004) employing addition of an isotopically labeled internal standard, solid-phase extraction onto AC cartridges, and quantification using GC/MS in positive chemical ionization mode with ammonia as the reagent gas. A complete description of the GC/MS conditions and NDMA analytical methods are available in Hanigan et al. (2012).

DOC and total dissolved nitrogen (TDN) were measured using a Shimadzu Total Organic Carbon (TOC)-V_{CSH} (Shimadzu Corporation, Kyoto, Japan) with attached Shimadzu TNM by applying standard method 5310 B (American Public Health Association *et al.*, 2005) . UV absorbance was measured using both a Hach DR5000 (Hach Company, Loveland, Colorado) and a Shimadzu Multispec-1501. pH_{zpc} was measured similar to Dastgheib et al. (2004) where 200 mg GAC is added to 40 mL of pre-boiled 0.1M NaCl solutions having different pH values and agitated for 48 hr. The solution at which pH does not change over 48 hr is considered the pH_{zpc}.

Statistical analysis. Statistical analysis was conducted using the analysis of variance and Tukey's honestly significant difference (Tukey's HSD) functions inside the R environment (R Development Core Team, 2012). Initial rejection of the null hypothesis resulted in pairwise difference of means analysis. For post hoc analysis, the confidence level was set at 0.95.

3.4 Results

Removal of watershed precursors by PAC. Multiple operating scenarios (22 discrete scenarios, 88 samples) at the pilot plant were intended to test the hypothesis that although watershed precursors are removed well by PAC, polyDADMAC-derived precursors are not. Raw water NDMA FP varied between 9 and 21 ng/L during pilot testing. When PAC was added to the presedimentation basins without cationic polymer, 3 to 20 mg/L of PAC reduced the NDMA FP by 4 to 17 ng/L (reduction = 57% ± 14%), respectively, when compared to raw water. Increasing PAC dose lead to greater NDMA FP reduction. PAC removed more NDMA FP (46% to 82%) than DOC (removal = 10% ± 7%) or UV_{254} (removal = 7% ± 5%) This is similar to our previous bench-scale findings in which between 37% and 91% of precursors of WW origin were amenable to removal by PAC (3 to 75 mg/L of Calgon WPH or Norit HydrodarcoB) (Hanigan *et al.*, 2012). These experiments confirm that PAC effectively removes "watershed" precursors at the pilot-scale.

NDMA FP was not linearly reduced as a function of PAC dose or contact time, as reduction varied daily based upon influent water quality. For example, 7 mg/L PAC reduced the NDMA FP between 43% and 72% across 5 days of sampling with the greatest reduction occurring at the shortest contact time (influent NDMA FP = 17 ng/L in both cases), and 20 mg/L PAC reduced the NDMA FP between 52% and 82% across 4 days of sampling (influent NDMA FP = 14 and 21 ng/L, respectively). Thus, some NDMA precursors may be more amenable to removal by PAC than others, and influent precursor sources and background organic matter varied with time in the source water. During the pilot-plant study, the river flow varied from 3,600 to 8,430 m^3/s and, presumably, the wastewater impact was lower when river flow was higher. Influent turbidity and pH varied from 22 to 42 NTU and from 7.6 to 7.8, respectively, during the pilot testing.

Varying the contact time in the pilot-scale presedimentation basin between 30 and 60 min, at PAC doses of 7 and 20 mg/L, produced similar NDMA FP reductions. Further investigation of the effects of PAC contact time was completed at bench scale using 90% SW and 10% WW (Figure 3-2). Contact time with PAC varied over typical HRTs for PAC treatment (15 to 120 min) and PAC dose ranged from 3 to 20 mg/L. All PAC doses decreased NDMA FP relative to the control sample, but little to no change in removal of precursors occurred after 15 min contact time. Reduction by PAC in absolute NDMA FP at the pilot plant (4 to 17 ng/L NDMA FP) was less than that at bench scale (28 to 45 ng/L NDMA FP). However, the source water was different, the initial precursor loading was higher at bench-scale (SW mixed with WW), and NDMA FP percent removals were similar (standard deviation of percent removal always less than 6% at PAC doses of 3, 6, 9, and 20 mg/L during contact times of 0.25, 0.5, 1, 2 hr). Results from the pilot plant and from bench-scale experiments demonstrate that precursor adsorption is rapid enough to be achievable in water treatment plants under reasonable conditions.

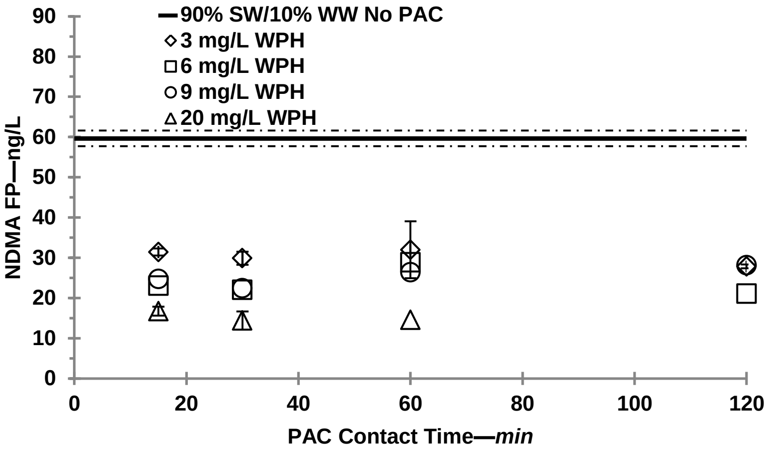

Figure 3-2 AC reduction of NDMA formation at multiple contact times
Note: PAC was contacted at 100 rpm in a gang stirrer. Blended source water (90% SW, 10% WW) was intended to simulate a wastewater-impacted DWTP influent. Error bars show individual samples (duplicate samples) with markers displaying the average.

To further investigate competitive sorption of NDMA precursors with NOM, blended water was produced by mixing WW and SW with the intent to vary both DOC and NDMA precursor loading. Blends between 10% WW (90% SW) and 100% WW resulted in initial DOC concentrations between 3.9 and 5.3 mg C/L, respectively. Initial UV_{254} varied from 5.1 to 10 m^{-1}. A single PAC dose (3 mg/L) was applied to all SW/WW blends. DOC removal was 5% with low WW content and generally decreased as the percentage of WW in the blend increased. UV_{254} removal exhibited a similar generally decreasing trend (from 14% to 9% with increasing WW content). NDMA FP of the blended waters increased with higher percent WW; 10% WW/90% SW had 52 ng/L compared to 132 ng/L and 162 ng/L for 50% WW/50% SW and 100% WW, respectively. Removal of NDMA precursors with 3 mg/L PAC varied from 15 to 40 ng/L with increasing WW content (Figure 3-3). When normalized to the NDMA FP of the associated control sample (the NDMA FP after PAC treatment was normalized to the

NDMA FP of the control sample for a specific WW/SW blend), NDMA FP removal was 17% to 34% at this relatively low PAC dose of 3 mg/L. Percent precursor removal was independent of initial NDMA FP or percent WW, as would be expected for trace organics removal in the presence of competing NOM (Knappe *et al.*, 1998; Westerhoff *et al.*, 2005). That is, the same percent precursor removal is observed independent of a higher (more WW) or lower (less WW) NDMA FP precursor level (Figure 3-3).

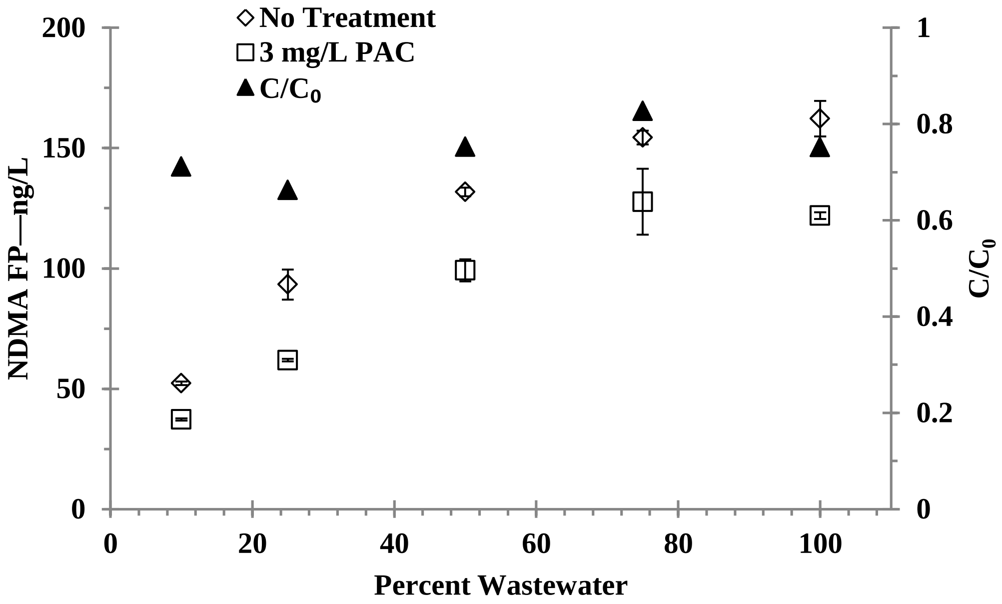

Figure 3-3 PAC adsorption of precursors at varying initial precursor loadings
Note: Precursor loading was adjusted by blending different amounts of SW and WW at ambient pH. PAC contact time = 2 hr. Triangles represent the fraction of NDMA FP remaining (C/C_0) after PAC treatment (right axis). Error bars show individual samples (duplicate samples) with markers displaying the average.

Removal of watershed precursors by GAC. Pilot tests were conducted to assess the removal of watershed and polymer-derived precursors by GAC versus an anthracite filter in filter adsorbers that had been operated for years (since 2007). DOC removal across the GAC filter was only 0.4 mg C/L (17%), indicating that the filter was nearly exhausted for DOC removal, whereas the anthracite removed only ~4% of DOC. Note, in this test, the settled water had somewhat more NDMA FP than the raw water (26 vs. 19 ng/L), the cause of which is unknown and could be precursor released from the pilot plant itself (rubbers, piping, etc.). When no polymer was used upstream during coagulation/settling, GAC reduced NDMA FP from 26 to 18 ng/L, while no change was seen across the anthracite filter. Even very close to complete DOC breakthrough, GAC contactors removed some of the precursors (31% in this case with an EBCT of 8.3 min), however, it is not clear how much of the precursors were watershed-derived. Previously, when using a similar GAC with an EBCT of 10 min, at 83% DOC breakthrough NDMA FP reduction was still ~85% (Hanigan *et al.*, 2012). Influent precursor loading was higher in the previous study (116 ng/L vs. 26 ng/L NDMA FP). Note, this pilot plant was set up to use GAC for biodegradation, not adsorption, whereas the cited previous study used virgin GAC at bench scale. Moreover, only one set of tests was available to evaluate GAC with no PAC or polymer.

Contribution of polymers to NDMA FP in the presence of watershed precursors. Nine polymers at varying doses were tested in different source waters to determine the contribution of polymer addition to NDMA FP in addition to watershed precursors. As part of an ongoing project, the polymers were acquired during routine sampling by several utilities from across the U.S. from on-site dosing tanks. At the pilot plant, three polymer doses were used to simulate low-, typical-, and overdosed polymer conditions (0.1, 0.4, and 1 mg/L polyDADMAC [dose of the active ingredient/polymer]). Prior to polymer addition, raw water at the pilot plant contained 9 to 19 ng/L NDMA FP. Addition of polyDADMAC solution during coagulation increased the NDMA FP between 1 and 57 ng/L across the coagulation basin, dependent on polymer dose. Equivalent yield is 62 ng NDMA FP/mg polyDADMAC (active polymer) (three polyDADMAC concentrations, linear fit, $R^2 = 0.99$). If we assume the polymer as monomeric, we find that it has a somewhat low yield (0.01%) when compared to other known NDMA precursors (e.g. dimethylamine = 1.2-2.6% (Mitch and Sedlak, 2004; Selbes *et al.*, 2013)). The increase in NDMA FP across the coagulation basin at all polymer doses indicates that not all polymer-associated precursors are removed during the coagulation and settling process.

Separate bench-scale testing (jar tests using a SW source) employed a wide range of polymer doses up to very high, unrealistic doses (0.1 to 25 mg/L polyDADMAC [active polymer]) added simultaneously with alum. Although polymer doses greater than 2 mg active polymer/L typically are not practiced at full scale, they were intentionally employed here to confirm the contribution of polymer to settled water NDMA formation. The results indicated that in either Ohio River water or CAP water, 1 mg of polyDADMAC dosed resulted in about 50 ng NDMA FP (50 ng NDMA FP / mg polyDADMAC or 0.0085% molar yield) (10 polymer concentrations, linear fit, $R^2=0.98$). Notably, although the polymer dose was high for many of the bench-scale samples, the “yield” of NDMA from polymer addition remained similar to that which was seen at the pilot plant (62 ng NDMA FP / mg polyDADMAC). No evidence existed indicating that an optimum polymer dose exists regarding minimizing NDMA FP, as NDMA formation always increased directly with increasing dose (i.e., higher polymer doses always increased NDMA FP).

In separate bench-scale experiments using CAP water, the polyDADMAC dose was held constant (1.5 mg/L polyDADMAC [active polymer]), and seven different brands/models of polymer were used in jar tests with alum (Figure 3-4). The NDMA yield of the settled water after polymer addition was 47 ± 3 ng NDMA / mg polyDADMAC (0.008% molar yield). DOC, UV_{254}, and NDMA yield were similar across all polymer sources.

When the polyDADMAC samples were diluted in DI water and monochloramine applied, the mean NDMA FP was 129 (standard deviation=15) ng NDMA/mg polyDADMAC (0.02% molar yield) and displayed greater variability in yield than the yield after coagulation with surface waters (Figure 3-4). This indicates that approximately one third (average NDMA yield after settling / average polyDADMAC NDMA yield in DI) of the polyDADMAC NDMA precursors are not removed during the coagulation process in the presence of aluminum sulfate and natural water matrices. Lee and Westerhoff (2006) previously showed that more DON is removed during alum coagulation with polyDADMAC than is added (the polymer contains organic nitrogen) as long as a threshold (overdose) is not exceeded, and about 2/3 of the polyDADMAC-derived NDMA precursors were removed in this study. Overall, the pilot- and bench-scale coagulation experiments with multiple polymers and doses show that use of polyDADMAC always increases NDMA formation.

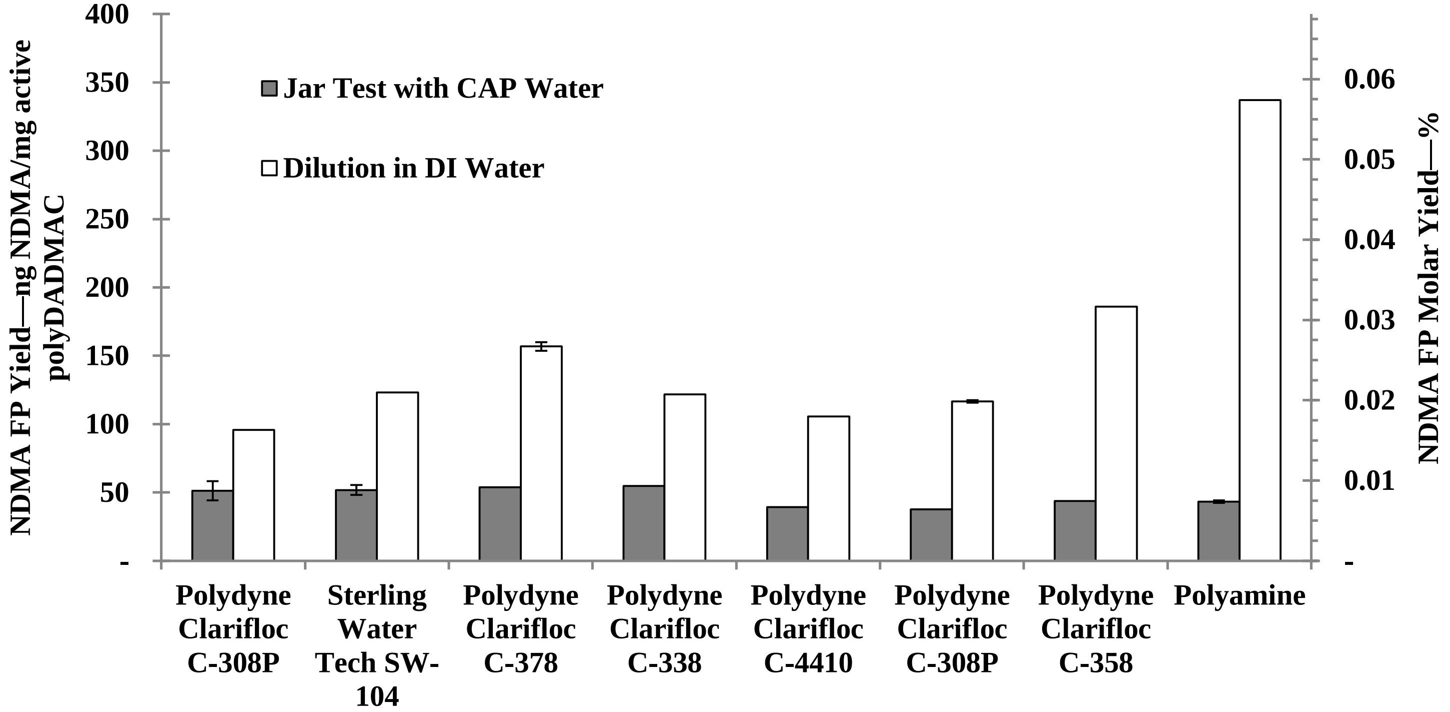

Figure 3-4 NDMA FP yields of selected commercially available polyDADMAC polymers (one polyamine)

Note: Clarifloc C-308P is shown twice as it was obtained from two separate treatment plants. The five error bars show 1 SD of triplicate samples. Molar yield assumes the polymer as monomeric, and does not apply to polyamine, which has a molecular weight of 102 g/mole monomer (molar yield of 0.006% and 0.046% for jar tested and diluted polyamine samples, respectively).

Removal of polymer-derived precursors with PAC. During an experiment at the pilot plant, one treatment train received PAC upstream of coagulation, while the other received PAC and polyDADMAC simultaneously in the coagulation basin to determine if PAC could remove polyDADMAC-derived precursors. The difference in NDMA FP across the entire treatment train between the train receiving PAC with coagulant and the train receiving PAC upstream was less than 4 ng/L, independent of PAC dose (ranging from 3 to 20 mg/L), indicating the point of PAC application does not strongly affect NDMA precursor removal, and that PAC does not remove polyDADMAC-derived precursors when used during coagulation (Table 3-3).

Table 3-3 Difference between pilot-plant treatment trains in which PAC was added upstream of polymer addition or at the same time as polymer addition. Data are averages of duplicate samples. Influent NDMA FP ranged from 12 to 15 ng/L NDMA FP

Polymer Dose (mg/L active polymer*)	**PAC Dose (mg/L)**	**Point of PAC Application Relative to Coagulation**	**Increase in NDMA FP across Treatment Train (ng/L)**
0.4	3	Upstream	29
0.4	3	Concurrent	25
0.4	20	Upstream	38
0.4	20	Concurrent	34

*Based upon bulk polymer containing 20% active polymer.

Jar tests using Ohio or Colorado River water were performed using metal salts and polyDADMAC (10 doses from low to extremely high [0.1 to 25 mg/L active ingredient]), and then the settled supernatant was removed and treated with PAC (3 to 20 mg/L). After some PAC additions, NDMA FP decreased, but in others, FP increased. The increase or decrease in NDMA FP was independent of water source, PAC dose, and polyDADMAC dose, but was typically less than the variability of the control samples. While there were some small changes in NDMA FP after polymer and PAC treatment, it was difficult to delineate between removal of small amounts of polyDADMAC-derived precursors and watershed-derived precursors (i.e., Equation 1), while polymer-derived precursors dominated this water based on NDMA FP after polymer addition (26 to 1600 ng/L) compared to raw water NDMA FP (9 to 15 ng/L).

To further investigate the removal of polyDADMAC-derived precursors at bench scale, experiments were conducted in which polyDADMAC was diluted with DI water (0.1, 1.5, and 2.5 mg/L polyDADMAC [active polymer]) and mixed with PAC (3 and 20 mg/L) for 1 hr. Where triplicate samples were conducted (0 and 20 mg/L PAC at 0.1 and 2.5 mg/L polyDADMAC), the NDMA FP of samples with PAC did not significantly differ from polymer-only samples at any polyDADMAC dose (Tukey's HSD, $p < 0.05$) (Figure 3-5). This work showed, at bench and pilot scale, that PAC did not adsorb polyDADMAC-associated precursors well.

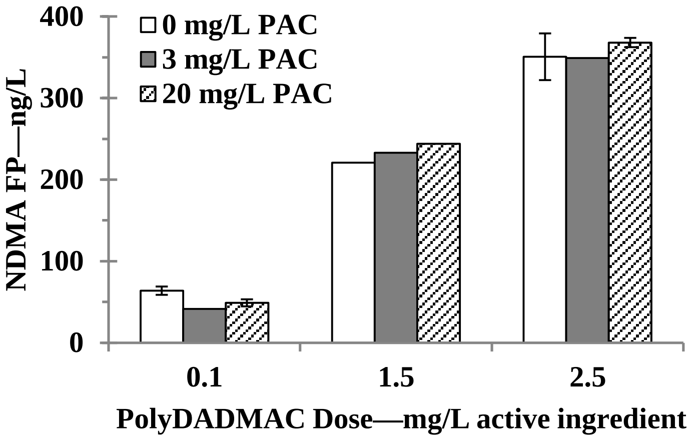

Figure 3-5 NDMA FP of polymer-associated precursors after exposure to PAC at bench scale. PAC was contacted for 1 hr in DI water at 100 rpm using a gang stirrer. Error bars show 1 SD of triplicate samples

Instead of polyDADMAC, polyamine was diluted in DI water (polyamine was sampled from a treatment plant, premixed with coagulant) and contacted with PAC, the polymer-associated precursors sorbed well. Without PAC, the NDMA FP of 1 mg/L polyamine (4 mg/L coagulant) was 340 ng/L (yield = 340 ng NDMA/mg polymer), higher than polyDADMAC and similar to the findings of Park et al. (2009) (Figure 3-4). Polyamine yielded 43 ng NDMA/mg polymer in jar tests with CAP water, indicating that much of the precursors were settleable, similar to polyDADMAC. However, adding PAC doses of 3 or 20 mg/L into DI water containing 1 mg/L active polyamine achieved 76% or 96% removal of NDMA FP, respectively (untreated NDMA FP = 340 ng/L), in stark contrast to polyDADMAC, which does not adsorb to PAC and is noteworthy due to the highly charged nature of both polymers. Polyamine-derived precursors also settled better than polyDADMAC-derived precursors. In jar tests with CAP water, 87% of precursors were removed during settling, compared to ~67% of polyDADMAC-derived precursors.

The sorption of polyamine should be further investigated with a polymer sample that is not premixed with coagulant to confirm these results.

In one test to investigate oxidative removal of polymer-derived precursors, polyDADMAC (1.5 mg/L active polymer) was diluted in DI water and contacted with free chlorine. After 24 hr, residual free chlorine was measured (<0.4 mg Cl_2/L) prior to conducting NDMA FP tests using preformed monochloramine. NDMA FP from the polymer was reduced from 180 ng/L to 110, 100, and 60 ng/L by 0.2, 0.5 and 1.0 mg Cl_2/L applied free chlorine. The lower chlorine doses likely dissipated in much less than the 24 hr hold time. Recently published data offers further evidence of the possibility that polyDADMAC-derived precursors may be pre-oxidized by long contact times and high levels of exposure (Krasner *et al.*, 2015; McCurry *et al.*, 2014; Shah *et al.*, 2012).

Moreover, as part of the pilot-plant testing, simulated distribution system (SDS) tests were conducted on the anthracite filter effluents, with a 20-min free chlorine contact time prior to ammonia addition (similar to that used at the full-scale plant). This resulted in NDMA formation of 3.6±0.7, 6.0±2.0, and 9.2±0.8 ng/L for the 0.1, 0.4, and 1 mg/L polymer doses (active ingredient), respectively. Note, the SDS NDMA formation with no polymer was 2.8±0.5 ng/L. For the tests with 0.4 and 1.0 mg/L of polymer (active ingredient), the SDS NDMA yields (formation above that in the tests with no polymer) were 8.2±4.7 and 6.4±0.7 ng/L, respectively. The yields were likely lower than the NDMA FP yields due to the destruction, transformation, or inactivation of precursors by pre-oxidation and lower NDMA formation under SDS conditions. Thus, free chlorine oxidation seems more effective at reducing NDMA FP from polyDADMAC than physical removal by activated carbon. The combination of watershed precursor removal from PAC and precursor loading from polyDADMAC use can be separated in the field if the addition of PAC and polymer occur in sequential unit processes, as was done at the pilot-scale plant.

Removal of polymer-derived precursors by GAC. Pilot tests without PAC but with polymer were conducted to assess removal of polymer-derived precursors by GAC. When the polyDADMAC dose was low (0.1 mg/L active polymer) or zero, the NDMA FP of the water increased from 16-19 ng/L in the raw water to 25-26 ng/L in the settled water (Figure 3-6), so the NDMA FP of the polymer-impacted sample was no different than the control sample. The NDMA FP of the GAC-filtered water with low polymer dose was 6 ng/L less than that of the anthracite-filtered water (22 versus 28 ng/L, all pilot plant samples taken in duplicate and averaged, replicates within ±0.3 ng/L of the averages). Thus, when the polymer dose was low, GAC was able to remove some precursors, likely those of watershed origin. The NDMA FP increased to 35 and 72 ng/L in the settled water for moderate and high polyDADMAC doses (0.4 and 1 mg/L polyDADMAC [active polymer]), which corresponded to increases of 9 and 46 ng/L, respectively, compared to the settled water with no polymer and increased further to 62 and 192 ng/L after GAC filtration. In contrast, for anthracite-filtered samples, the NDMA FP did not increase across the filter (Figure 3-6). Thus, at the pilot plant only, when polyDADMAC-derived precursors were present, GAC exacerbated the potential for NDMA formation, particularly at elevated polyDADMAC doses. This could not, however, be replicated at bench-scale, or at other full scale plants (see below).

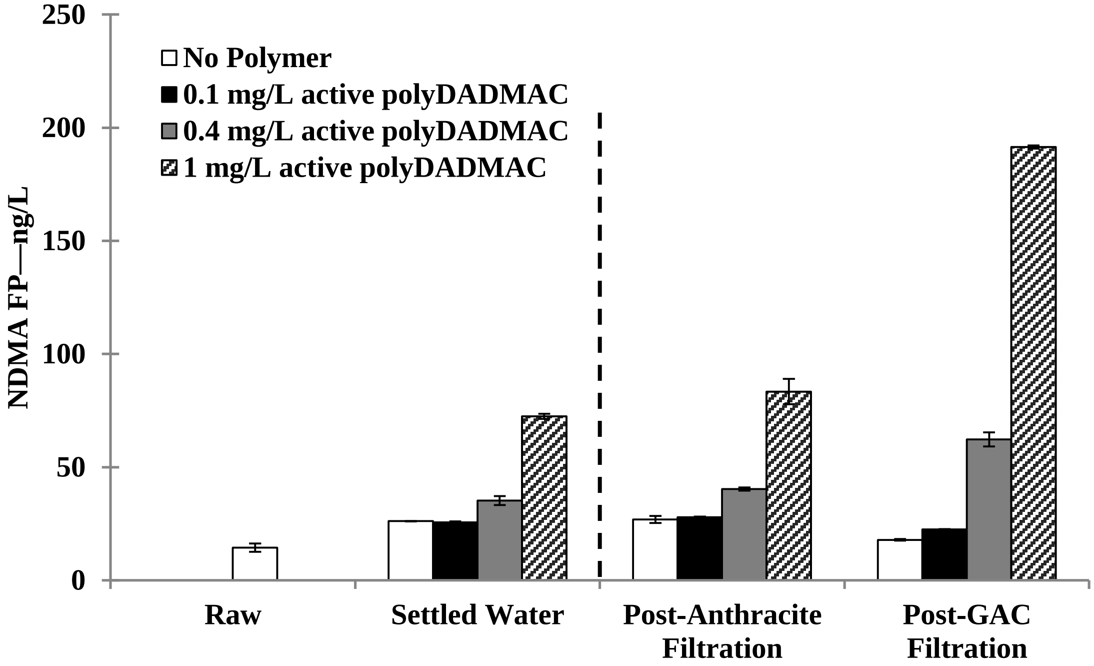

Figure 3-6 NDMA FP across multiple unit operations at the pilot plant. Raw water was coagulated with or without use of polyDADMAC, settled, and filtered with either anthracite or GAC
Note: The "raw" bar is an average of raw water NDMA FP during the four conditions tested (error bar shows 1 SD). Other data points are an average of duplicate samples with bars showing the individual samples. No PAC was used.

Three other full-scale treatment plants using GAC (two for TOC removal) and polyDADMAC as a coagulant aid were sampled twice to try to observe this phenomenon. At the two treatment plants operated for TOC removal (EBCT = 20 and 21 min, F400), polyDADMAC doses of between 0.15 and 0.26 mg/L of polyDADMAC (active polymer) were used at the treatment plants on the days of sampling. No increase was found in NDMA FP across GAC filters (300-19,000 bed volumes since replacement) at either treatment plant; in fact, NDMA FP decreased from 17 ng/L to 4 ng/L and from 14 ng/L to 5 ng/L although polyDADMAC doses were lower at these full-scale utilities than at the pilot plant and the conditions and usage of the GAC was different.

At the third full-scale plant (EBCT 3.8min, F400) the dose was 5 and 6 mg/L polyDADMAC (active ingredient). During one sampling event when the polymer dose was 6 mg/L, NDMA FP stayed the same or decreased across the GAC (from 152 ng/L in the settled water to 153 and 127 ng/L in the two absorber effluents, absorbers in use for 3 and 1 years, respectively). Note that the NDMA FP of the raw water was 57 to 73 ng/L, so the GAC influent was a mixture of watershed- and polymer-derived precursors. However, in the second sampling event, the polymer dose was 5 mg/L and NDMA FP increased from 155 ng/L in the settled water to 253 and 311 ng/L in the two absorber effluents. The absorbers were in service for 2 and 15 months, respectively, and in this sample event, the NDMA FP of the raw water was 61-76 ng/L. As noted previously, both filters were spent in terms of TOC removal (15% removal).

To further investigate this potentially important phenomenon, a bench scale GAC absorber was constructed using virgin GAC. DI water with 5 mg/L polyDADMAC (active polymer) was loaded for 11,000 bed volumes while NDMA and NDMA FP of the effluent were measured. No NDMA was formed in the column (effluent NDMA), and therefore any formation of NDMA at the pilot plant was unlikely to be through a “surface catalyzed” reaction pathway as described by Padhye et al. (2011b). With the exception of a single outlier sample that was not taken in replicate, NDMA FP in the effluent (effluent FP) also did not increase (number of samples = 12).

The situation where NDMA FP increased across the GAC filters receiving polyDADMAC treated water could not be replicated in the lab, and it is a conundrum. However, the samples from the pilot plant and full-scale plant were in duplicate and therefore we do not believe this to be erroneous data. It is possible that increasing NDMA

FP across GAC contactors could be specific to the plants used in this study (river flow and turbidity nearly doubled from 21 to 42 NTU during the 2 days of the pilot plant tests), or specific to GAC that has been in use for long period of time, with intermittent polymer use at the pilot plant. Although turbidity was higher in the influent of the GAC column during the second day of polymer testing at the pilot plant, when high polymer dose, anomalous testing was completed, both the anthracite and GAC filter effluent turbidity decreased from 4-9 NTU (filter influent) to 0.04 NTU (anthracite or GAC filter effluent). Clarification of the mechanism of increasing NDMA FP across GAC filters at high polyDADMAC doses requires additional work, presuming that this phenomenon can be replicated.

3.5 Discussion

Sorption of polymer-associated NDMA precursors. The dominant moiety in polyDADMAC is a positively charged amine group, which is responsible for bridging and settling negatively charged NOM during coagulation. Given that the polymer itself is positively charged at typical water treatment pH (pH 8 adjusted log K_{ow} [log D]<<0 and decreases with increasing polymerization (Chemicalize.org, 2013)), and that electrostatic interactions have greater energy than hydrophobic interactions (Crittenden *et al.*, 2012), we did not expect physisorption to dominate.

However, polyamine does sorb to activated carbon, unlike polyDADMAC, and therefore, another mechanism must be at hand. The inclusion of OH groups in the polyamine repeating chain structure may explain the affinity for sorption as polyDADMAC contains no O. Hydrogen bond acceptors exist as oxygenated groups (e.g. phenolic, protonated carboxyl, carbonyl) along the planar sheet edges in activated carbon, which exist in greater concentrations than simply negatively charged, deprotonated carboxyl groups required to attract the positively charged amine. However, inclusion of the OH group also increases the participation of hydrogen bonding with water. The N chain ends contained in polyamine but not in polyDADMAC have a lone electron pair that could be deprotonated at pH 8 (pKa ~ 8) further contributing to the electrophilic nature of the molecule and this also might explain the adsorption characteristics of polyamine (Chowdhury *et al.*, 2012; Mattson *et al.*, 1969).

Sorption of watershed precursors. For bulk NOM, matrix effects (competition) may play a role in sorption affinity. Larger molecules at high concentrations (mg/L levels), such as NOM, tend to block pores and thus make active sites within them unavailable for further sorption, whereas small molecules at trace concentrations (e.g., pharmaceuticals, anthropogenic chemicals) tend to be greatly outnumbered by active sites on the carbon surface. This is shown in Figure 3-3; as the concentration of WW is increased, the NDMA precursor concentration increases as well. However, the percentage of precursors removed remains nearly the same. This is similar to previous research that found that percent removal of trace organic molecules is independent of initial concentration (Knappe *et al.*, 1998) and with other work showing that as PAC dose increases, trace organic matter removal increases, independent of initial concentration of the trace organic matter (Li *et al.*, 2005).

The same observation as with PAC was observed in the pilot-scale results in which the GAC columns were expended for DOC and UV_{254} removal but still removed NDMA precursors. DOC and UV_{254} removals less than that of NDMA precursors was also observed in previous research using rapid small scale column tests (RSSCTs)

(Hanigan *et al.*, 2012). Previously >85% sorption of NDMA precursors was observed, whereas the pilot plant sorbed and/or biodegraded only ~30%. We attribute this to the exhaustion of the GAC, even for trace contaminants, as has been shown before on preloaded (exhausted) GAC (Knappe *et al.*, 1999).

Relative effects of activated carbon and polymer use on NDMA formation. To represent the conceptual differences in reactivity and treatability of watershed and polymer NDMA FP, Equation 1 was developed. For example, influent NDMA FP at the pilot plant ranged from 9 to 19 ng/L, and PAC (3 to 25 mg/L) in the presedimentation basin reduced NDMA FP by 4 to 17 ng/L. Given that 0.4 mg/L polyDADMAC (active polymer) has the potential to increase NDMA FP ~9 ng/L relative to alum coagulation alone, removal of watershed-derived precursors by PAC may result in no net effect on the NDMA FP in this scenario. Any dose of polyDADMAC at a concentration greater than ~0.4 mg/L (active polymer) could cause a net increase in NDMA FP at the pilot plant. It should be noted that many plants, including the full-scale plant associated with this pilot-plant, use PAC seasonally for taste and odor issues when river flow and turbidity are low, and because of the low turbidity, many times no polyDADMAC is used concurrently. Assuming that PAC can remove polyamine- and watershed-derived precursors simultaneously, and that PAC was fed into the coagulation basin, sorption of precursors by PAC could result in reduced settled water NDMA FP from both sources.

Estimated Freundlich parameters and yield ranges for the remaining variables are given in Table 3-4. The data from which Freundlich parameters are estimated are shown in Figure 3-7. The Freundlich 1/n for watershed precursors is greater than one, which is counter intuitive for strongly sorbed organic matter. We believe this is due to there being two groups of watershed precursors represented by a single 1/n; one group is strongly sorbed at low PAC concentrations and the other is not sorbed well, independent of dose. This is similar to our previous findings conducted with secondary wastewater effluent where ~5% of NDMA precursors were not removed even at PAC doses greater than 75 mg/L (Hanigan *et al.*, 2012). However, it should be noted that these parameters are not broadly applicable to all treatment scenarios, and site specific testing must be conducted.

Table 3-4 Equation 1 estimated parameters

Sorption Variables	**K (ng/mg)(L/ng)$^{1/n}$**	**1/n**	**R^2**
η_{WS}	0.035	2.400	0.98
η_{pDMC}	Not sorbed	Not sorbed	Not sorbed
η_{pAMN}	2.197	0.8129	0.94
Yield Variables	**Post Sedimentation Yield**	**Unit**	**R^2**
NDMA FP_{WS}	0 to 100	ng/L	
NDMA FP_{pDMC}	47-62	ng NDMA FP/mg active polyDADMAC	0.98 to 0.99
NDMA FP_{pAMN}	43	ng NDMA FP/mg active polyamine	1*

*Only two doses tested.

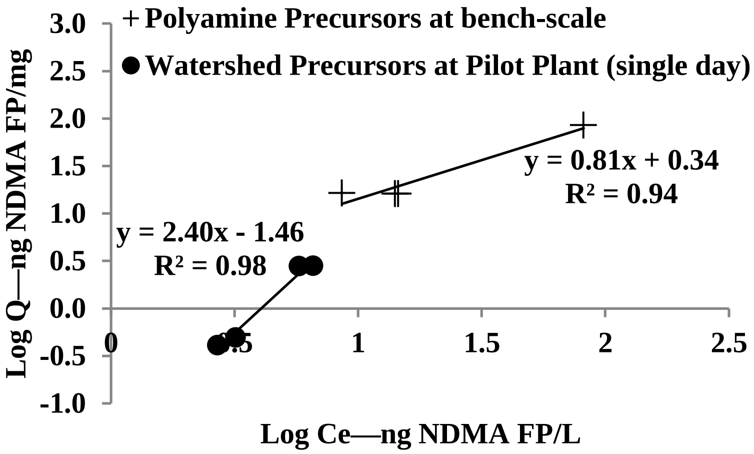

Figure 3-7 Freundlich isotherms for watershed- and polyamine- derived NDMA precursors. Watershed data shown is from a single day, due to temporal variability in precursor adsorption

This study showed that polyDADMAC-derived precursors are not sorbable by activated carbon, and therefore η_{pDMC} is set to zero. NDMA FP_{WS} is dependent on source water precursor loading, while NDMA FP_{pDMC} and NDMA FP_{pAMN} are functions of dose and yield.

Figure 3-8 is a graphical representation of Equation 1 that is based on results from this study. In Figure 3-8, we used influent and polyDADMAC-derived precursor loadings from the pilot plant, 15 ng/L NDMA FP and 62 ng/mg active polymer (based on high polymer dose where less polyDADMAC settled and likely a worst case scenario). Polyamine contribution was 43 ng/mg. PAC. Removal of watershed and polyamine-derived precursors follows the Freundlich functions in Table 3-4. Overall, Figure 3-8 demonstrates the complexity of understanding how to control NDMA precursors. In this modeled example, achieving a final NDMA FP of 10 ng/L or less could be achieved by: 1) not using polymer but using a low dose of PAC, 2) using 0.1 mg/L active polyDADMAC and 13 mg/L PAC, 3) using 0.1 mg/L active polyamine and 1 mg/L PAC, of 4) using 0.25 mg/L active polyamine and 2 mg/L PAC (these are theoretical data, that have not been confirmed directly). Alternatively, pre-chlorination could be explored.

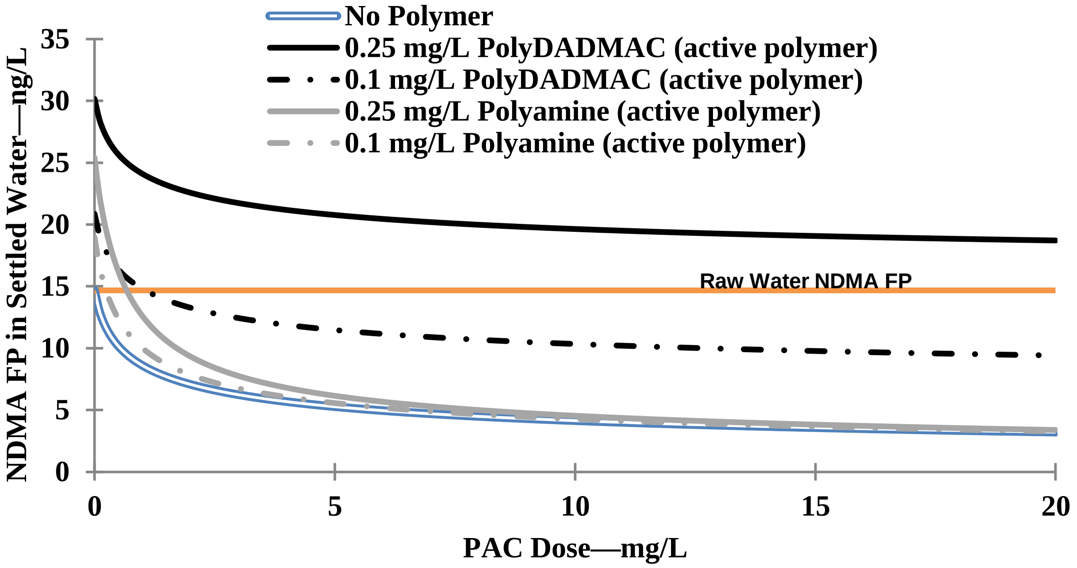

Figure 3-8 Conceptualization of NDMA precursor contribution and removal in the pilot plant

3.6 Conclusions

This study investigated the removal of polyDADMAC- and watershed-associated NDMA precursors by both PAC and GAC.

- Precursors were removed well by PAC (up to 82% removal at a dose of 20 mg/L PAC) and GAC, even on GAC columns that were expended for DOC removal (31%), although it is possible that some precursors removed by GAC were derived in the pilot plant itself (7 ng/L NDMA FP increase across sedimentation when no polymer used)

- Contact times longer than 15 minutes with PAC relevant within drinking water treatment did not impact removal of watershed-derived precursors to a great extent.
- PolyDADMAC reactivity in forming NDMA FP after simulated alum and polymer coagulation is 47 ng NDMA FP/mg active polyDADMAC, which was about one third the NDMA FP of the polymer diluted in DI water indicating that much of the polymer-derived precursors are removed during settling.
- PolyDADMAC-derived precursors were not removed to an appreciable extent by either PAC or GAC, but polyamine-derived precursors were removed well, up to 75% when mixed with PAC in DI water.
- At a pilot plant in the study, it was found that use of greater than 0.4 mg/L active polyDADMAC would cause a net increase in NDMA FP leaving the treatment plant, despite the use of PAC in a presedimentation basin to remove watershed precursors.

3.7 Acknowledgments

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4 Adsorption of *N*-Nitrosodimethylamine Precursors by Powdered and Granular Activated Carbon

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4.1 Abstract

Activated carbon (AC) has been shown to remove precursors of halogenated disinfection byproducts. Granular and powdered activated carbon (GAC, PAC) were investigated for their potential to adsorb *N*-nitrosodimethylamine (NDMA) precursors from blends of river water and effluent from a wastewater treatment plant (WWTP). At bench scale, waters were exposed to lignite or bituminous AC, either as PAC in bottle point experiments or as GAC in rapid small-scale column tests (RSSCTs). NDMA formation potential (FP) was used as a surrogate for precursor removal. NDMA FP was reduced by 37, 59, and 91% with 3, 8, and 75 mg/L of one PAC, respectively, with a 4-hr contact time. In RSSCTs and in full-scale GAC contactors, NDMA FP removal always exceeded that of the bulk dissolved organic carbon (DOC) and UV absorbance at 254 nm. For example, whereas DOC breakthrough exceeded 90% of its influent concentration after 10,000 bed volumes of operation in an RSSCT, NDMA FP was less than 40% of influent concentration after the same bed life of the GAC. At full or pilot scale, high NDMA FP reduction ranging from >60 to >90% was achieved across GAC contactors, dependent upon the GAC bed life and/or use of a pre-oxidant (chlorine or ozone). In all experiments, NDMA formation was not reduced to zero, which suggests that although some precursors are strongly sorbed, others are not. This is among the first studies to show that AC is capable of adsorbing NDMA precursors, but further research is needed to better understand NDMA precursor chemical properties (e.g., hydrophobicity, molecular size) and evaluate how best to incorporate this finding into full-scale designs and practice.

4.2 Introduction

N-Nitrosodimethylamine (NDMA) is an emerging contaminant of concern that has been listed by the Environmental Protection Agency (EPA) as a priority pollutant in drinking water with a cancer risk level of 10^{-6} based on a 0.7 ng/L lifetime exposure (USEPA, 2002). EPA included NDMA in the Unregulated Contaminant Monitoring Rule 2 (UCMR2) and is progressing on a timeline to make a regulatory determination of nitrosamines, including NDMA, by 2013. Canada has set a 40 ng/L guideline based on a 10^{-5} lifetime cancer risk (Health Canada, 2011), and several U.S. states have already set action or notification levels for NDMA. For example, the State of California has set a public health goal of 3 ng/L based on a lifetime cancer risk of 10^{-6} and a notification level of 10 ng/L (OEHHA, 2006).

Drinking water disinfection with chloramines is well known to reduce the formation of halogenated disinfection byproducts (DBPs) (e.g., trihalomethanes, haloacetic acids). Consequently, the number of drinking water treatment plants (WTPs) in the United States using chloramines as either a primary or a secondary disinfectant increased 37% (944 to 1,298) between 2007 and 2010 (Guay *et al.*, 2005; Li, 2011; Norman *et al.*, 1980). However, NDMA has recently been the subject of greater scrutiny, as it is preferentially formed by chloramines, carcinogenic, and genotoxic (IPSC, 2002; Mitch *et al.*, 2003a; Peto *et al.*, 1991; Richardson *et al.*, 2007). Therefore, there is a need to destroy (e.g., via pre-oxidation (Shah *et al.*, 2012)) or physically remove (e.g., via sorption) NDMA precursors while recognizing the potential to form other DBPs. As the EPA considers a regulatory determination for NDMA, it must consider the appropriateness (cost and technical feasibility, public health benefit) of drinking water treatment processes to control NDMA formation, and effective physical removal of NDMA precursors is currently not described in the literature.

NDMA can form in water during chloramination of either drinking water or wastewater (Jobb, 1994; Krasner *et al.*, 2009a; Krasner *et al.*, 2009b; Mitch and Sedlak, 2002; Sacher *et al.*, 2008). NDMA has been associated with the reaction between chloramines (primarily with trace levels of dichloramine present), and certain secondary, tertiary, and quaternary amines present in the water source (Choi and Valentine, 2002; Krasner *et al.*, 2009a; Krasner *et al.*, 2009b; Mitch *et al.*, 2005; Sacher *et al.*, 2008; Schreiber and Mitch, 2005). For example, cationic polymers, shampoos, pharmaceuticals, and ion exchange resins are all sources of amines capable of producing NDMA upon chloramination (Kemper *et al.*, 2010; Mitch and Sedlak, 2004; Park *et al.*, 2009; Sacher *et al.*, 2008; Shen and Andrews, 2011a; Shen and Andrews, 2011b; Wilczak *et al.*, 2003). Direct disinfection with chloramines is not requisite, as waters containing high concentrations of ammonia (wastewater treatment plant [WWTP] effluent) will form chloramines when disinfected with free chlorine. NDMA has also been shown to form during ozonation. Furthermore, several nitrosamines are byproducts of rubber decomposition or leaching in distribution systems (Morran *et al.*, 2011b; Teefy *et al.*, 2011). Therefore, unit processes capable of physically removing NDMA precursors should be capable of removing amine-containing organic moieties.

Wastewater effluent is known to contain nitrogenous precursors capable of forming NDMA (Mitch and Sedlak, 2004; Mitch *et al.*, 2005; Mitch and Schreiber, 2008; Schreiber and Mitch, 2006b; Sedlak *et al.*, 2005; Tezel *et al.*, 2011). Many drinking water sources are impacted by upstream WWTP discharges. Dotson et al. (2009) found no

NDMA formation in natural organic matter (NOM) isolates until the dissolved organic carbon (DOC)/dissolved organic nitrogen (DON) ratio became less than 20 mgC/mgN, except in a single outlier. The majority of the N-enriched organic matter (low DOC/DON) that formed NDMA occurred in certain N-rich fractions (e.g., hydrophilic bases) and especially in wastewater effluents. NDMA formation from WWTP isolates was substantially higher than that from algal-impacted waters. Several pharmaceuticals and personal care products (PPCPs) containing tertiary or quaternary amines have been shown to have nitrosamine formation potential (FP) when chloraminated (Kemper *et al.*, 2010; Shen and Andrews, 2011a; Shen and Andrews, 2011b). Although specific molar yields are low for most individual PPCPs, it is possible they are responsible for a large additive formation. Typical concentrations of PPCPs in drinking water influents are difficult to determine because of their low concentrations and because robust methods do not exist for all analytes of interest. However, at least one study has found ranitidine (a pharmaceutical with exceptionally high conversion to NDMA upon chloramination) occurrence in natural waterways, which gives some insight into the incidence of pharmaceuticals and their metabolites in the environment (Kolpin *et al.*, 2002). Therefore, physical removal of NDMA precursors should consider the effectiveness of removing both bulk DON materials with hydrophilic properties and trace-level organics such as pharmaceuticals.

Very little published data is available on successful removal of NDMA precursors from drinking waters. One study using very long contact times (7 days) with powder activated carbon (PAC) showed substantial removal of NDMA FP in drinking water matrices (Sacher *et al.*, 2008). However, the study did not show (for reference) how much dissolved organic matter (e.g., DOC) was removed. Another study showed good removal of NDMA FP across biologically active carbon (BAC) while treating a secondary wastewater effluent but noted that additional research was needed to separate sorption from biological degradation of the precursors (Farré *et al.*, 2011).

It is well documented that the formation of currently regulated DBPs (THMs, HAAs) are related to the levels of DOC and/or UV_{254} in water (Korshin *et al.*, 1997a; b; Sohn *et al.*, 2004; Westerhoff *et al.*, 2000). Thus, removal of DOC and UV_{254} by granular activated carbon predictably correlates with the removal of THM or HAA precursors (Chiu *et al.*, 2012). However, NDMA formation is not correlated to the bulk parameters of DOC or UV absorbance(Chen and Westerhoff, 2010). We hypothesized that the removal of NDMA precursors should not follow the trend in DOC or UV absorbance removal by activated carbon. First, PAC experiments with contact times more commonly used in water treatment (e.g., 4 hr) were conducted with a variety of water sources to demonstrate removal of precursors, including specific precursors previously known to form NDMA (pharmaceuticals) as well as those quantified by NDMA FP tests. Second, rapid small-scale column tests (RSSCTs) were conducted with GAC to evaluate the relative removal of bulk organic matter as quantified by DOC, UV absorbance, and NDMA FP. Finally, two drinking water facilities utilizing GAC were sampled to demonstrate removal of NDMA precursors. Our PAC and GAC results showed that NDMA precursors were removed much better than DOC or UV_{254}, and these results are to our knowledge the first to demonstrate this. Furthermore, these results are the first to call attention to the difference between NDMA precursor removal by AC and the removal of precursors (i.e., DOC, UV_{254}) for regulated DBPs (THMs, HAAs). Therefore, we believe this to be quite novel, with profound implications for drinking water and wastewater reuse systems, specifically on the design of PAC or GAC contactors if the goal is to control NDMA rather than THMs.

4.3 Materials and Methods

Water sources. Secondary wastewater effluent was used directly in some instances as it was known to contain NDMA precursors. In other cases, secondary wastewater effluent was used in combination (blended), with a surface water (SW) to represent potential drinking water sources impacted by wastewater.

Secondary effluent was collected from a WWTP (activated sludge treatment) in the Phoenix metropolitan area (AZ) and stored at Arizona State University (<4°C) until used. SW (Salt or Verde River water) was collected from the Salt River Project canal system (AZ), as described elsewhere (Baker *et al.*, 2006; Mash *et al.*, 2004). Typical water quality parameters are given in Table 3-1. Samples were filtered onsite (1 µM, CLR 1-10 Pall Corporation, Port Washington, NY). Two pilot systems used ozone and biofiltration. At Pilot Plant 1, a U.S. secondary treated wastewater was chloraminated before a reverse osmosis (RO) system, and the pilot system treated the RO concentrate in an attempt to maximize overall water recovery using a secondary membrane system. The RO concentrate was treated with ozone and BAC to mineralize and remove DOC in order to minimize fouling of the secondary membrane system. At Pilot Plant 2, ozone followed by BAC was used to treat water from the Yangtze Delta, China. Two full-scale GAC drinking water systems, Full-Scale Plants 1 and 2 (Empty bed contact time [EBCT] = 20 - 21 min), which employed coagulation/sedimentation upstream and no ozonation, were also evaluated for their potential to remove NDMA FP.

Separate batch adsorption experiments were conducted by spiking pharmaceuticals into >18.2 MΩ-cm water containing 1 mM $NaHCO_3$ (pH = 8.0). All glassware was detergent cleaned, acid washed (>24 hr submerged in 10% HCl), and heated to 500°C in a muffle furnace prior to use.

Table 4-1 Raw water quality parameters of selected water sources

Source Water	**DOC (mg/L)**	**UV254 (m^{-1})**	**TDN (mg/L-N)**	**NDMA FP (ng/L)**
Secondary WW Eff	5.5	10	3.4	1500
SW	4	7	0.02	13
SW blended with secondary effluent (WW):				
10% WW + 90% SW	3.9	7.5	0.64	116
50% WW + 90% SW	4.5	9.2	2.0	398
90% WW + 10% SW	5.2	11	3.3	552

Note: Samples for blends collected at different time of day on a different day than secondary effluent #1. Secondary effluent #1 was used for PAC bench scale experiments while blends were used for RSSCTs). pH of samples was between 7.5 and 8.2.

Reagents. All reagent water was >18.2 MΩ-cm and of laboratory grade. Sodium hypochlorite (5.65–6%) was purchased from Fisher Scientific (Fairlawn, NJ). Sodium borate, sodium hydroxide, and sodium sulfite were also purchased from Fisher Scientific. Ammonium chloride was obtained from Sigma Aldrich (St. Louis, MO). Dichloromethane (DCM) and methyl *tert*-butyl ether (MTBE) were purchased from EMD Chemical (Gibbstown, NJ). Deuterated NDMA (NDMA-d6) was purchased from Cambridge Isotopes (Andover, MA) and diluted to 100 µg/L before use. Anhydrous sodium sulfate cartridges (Bond Elut Jr.) were purchased from Agilent Technologies (Santa Clara, CA). Pharmaceuticals were purchased from Sigma Aldrich.

Hydrodarco B (HDB), Hydrodarco 3000 (HD3000), and GAC 820 were obtained from Norit Americas, Inc. (Marshall, TX). WPH was obtained from Calgon Carbon Corp. (Pittsburg, PA).

Adsorption of NDMA precursors. PAC studies with wastewater were conducted in triplicate in 1-L amber borosilicate bottles filled to 700 ml with sample. PAC experiments with pharmaceuticals were conducted in 250-mL amber borosilicate bottles. PAC slurries (WPH, HDB) were prepared in reagent water and allowed to hydrate for a minimum of 24 hr before use. A summary of carbon characteristics used for experiments is given in Table 4-3. Samples were agitated on a shaking table (~200 rpm). At prescribed times, samples were filtered to remove suspended PAC using glass-fiber filters that had been pre-combusted at 500°C (GF/F, Whatman, Maidstone, UK).

RSSCTs were conducted in accordance with previously established methods for the scaling of fixed-bed adsorber systems (ASTM, 2000; Crittenden *et al.*, 1987; Crittenden *et al.*, 1991). Proportional diffusivity was considered given the unknown composition of organic matter present in the wastewater and was used to determine the appropriate RSSCT parameters. A summary of the parameters used during the design is given in Table 4-4. HD3000 and GAC 820 were crushed manually with a mortar and pestle and wet sieved to obtain a mean particle diameter of 0.0049 cm (140 × 170 mesh). The RSSCTs were designed to adhere to constraints set by Crittenden et al. (1987) and Summers et al. (1995). Specifically, Reynolds number = 1.12 to limit dispersion effects, and Reynolds × Schmidt = 1000. Wall and channeling effects were mitigated by designing the column diameter to particle diameter ratio to be greater than 50. A simulated full-scale EBCT of 10 min was selected. Temperature was kept constant at 25

± 2°C. Piston pumps with stainless steel heads were used to distribute a single sample to the 4 columns, and the pH of the samples was not adjusted. Column effluent was collected in pre-combusted 1-L amber borosilicate bottles. Because of the relatively low flow rate from the columns (14.5 mL/min) compared with the large volume needed for analysis, samples were assumed to be taken at the midpoint of bottle filling.

NDMA FP. Chloramination was conducted using FP conditions in which an excess of monochloramine was allowed to react for 72 hr (or 7 d). In most tests, a monochloramine stock solution was prepared by adding sodium hypochlorite to a 1-M borate solution adjusted to pH 8. Free chlorine was measured three times by a Hach DR 5000 spectrophotometer, and ammonium chloride was added to produce a N:Cl molar ratio of 1.2. The solution was allowed to react in the dark for 1 hr. Ammonia (to confirm negligible background concentrations) and DOC were first quantified in the sample. Samples were buffered at pH 8 using 10-mM borate and dosed with the buffered monochloramine stock solution at three times the amount of DOC (3 × mg-C/L = mg/L of NH_2Cl as Cl_2) (bench scale PAC and RSSCT samples). In other tests, ammonia was added first and chlorine was added second to form an excess of chloramines *in situ* (Cl_2 = 3 × DOC and Cl_2/N weight ratio = 3:1 [full-scale samples] or 20 mg/L as Cl_2 [Pilot Plant 2]). The samples were allowed to react in the dark for 72 hr (or 7 d for Pilot Plant 2) at 25°C. The reaction was stopped using 0.1 g aqueous sodium sulfite or an excess of ascorbic acid. For each set of samples and related (bench, pilot or full scale) tests, all samples were evaluated using the same protocol.

Analytical methods. NDMA was extracted from samples following a protocol similar to EPA Method 521 (Munch and Bassett, 2004) or the standard method with

Ambersorb (American Public Health Association *et al.*, 2008). In method 521, solid phase extraction (SPE) AC cartridges (Supelclean Coconut Charcoal, Supleco, Belafonte, PA) were conditioned using DCM, MTBE, and finally deionized water (DI) water. NDMA-d6 was spiked into 500 mL of sample, and the samples were passed through the cartridges at 5 mL/min. The column was dried with ultra-high purity nitrogen. Adsorbed NDMA was eluted using 5 mL of DCM. The eluent was dried using a syringe cartridge containing anhydrous sodium sulfate. The sample was evaporated to 1 mL under ultra-high purity nitrogen.

The extracted samples in most cases were analyzed using a method similar to that of Charrois *et al.* (2004) with an Agilent 6890N/5973 inert gas chromatography/mass spectrometry (GC/MS) system operated in positive chemical ionization (CI) mode with ammonia as the reagent gas. The samples were eluted on an Agilent DB-1701P column after split-less injection (4 µL,15 psi initial, 45 sec pulse, followed by 10 psi) at 250°C using a reduced diameter solid-phase micro extraction (SPME) inlet liner (Sigma Aldrich). Helium was used as a carrier gas and was initially pulsed at 1.9 mL/min for 45 sec and then at 1.3 mL/min for the rest of the run. The temperature program was as follows: 40°C for 3 min, ramped to 80°C at 4°C/min, and finally ramped to 120°C at 20°C/min. The transfer line temperature was set to 200°C. The mass-selective detector was set to analyze for mass-to-charge ratios of 92 (NDMA + NH_4^+) and 98 (NDMA-d6 + NH_4^+). Quantification was performed against the NDMA-d6 internal standard. The Ambersorb standard method also utilized GC/MS-CI, whereas Pilot Plant 2 samples were analyzed using liquid chromatography (LC)/MS (Zhao *et al.*, 2006).

Pharmaceuticals were analyzed with a method similar to that of Yoon *et al.* (2003) using high-pressure LC (HPLC) (Alliance 2695 and Waters 2996 UV detector). In brief, a Waters 5 µm LiChrosorb® RP18 (4.6 mm × 10 mm) was used for reverse phase separation. A 200 µL sample loop was used for injections, and the solvent profile was isocratic, containing 10 mM H_3PO_4, and was 55% MeOH and 45% DI water at 1 mL/min.

DOC and total dissolved nitrogen (TDN) were measured using a Shimadzu Total Organic Carbon (TOC)-V_{CSH} by applying standard methods (American Public Health Association *et al.*, 2008). UV absorbance was measured using both a Hach DR5000 and a Shimadzu Multispec-1501.

4.4 Results and Discussion

PAC adsorption of NDMA FP from wastewater. Experiments previously conducted in our lab on two wastewaters with high (20–1000 mg/L) PAC dosages (WPM) (7-day contact time) suggested that NDMA precursor removal could occur (details summarized elsewhere (Krasner *et al.*, 2008)). In these waters, NDMA FP decreased from 371 ng/L in one wastewater (DOC = 9.7 mg-C/L) to 66 and 18 ng/L after 50 and 1000 mg/L PAC, respectively. In a second wastewater (DOC = 13.3 mg-C/L), PAC doses of 50 and 500 mg/L reduced NDMA FP from 1390 to 385 and 15 ng/L, respectively. A third sample of wastewater-derived soluble microbial products was also tested by growing bacteria on a nutrient broth in a simulated activated sludge system as described in detail elsewhere (Krasner *et al.*, 2008). PAC doses of 50 and 500 mg/L reduced NDMA FP from 78 to 25 ng/L and below the reporting level (2 ng/L), respectively. Independent of initial NDMA FP levels, 50 mg/L of PAC reduced NDMA

FP by 74 ± 7%, and >95% at PAC doses at or above 500 mg/L. These experiments suggested that AC could remove NDMA FP precursors, but these initial PAC dosages and contact times are unrealistic for WTPs.

A second set of experiments with a range of PAC doses of 15 to 210 mg/L and a contact time of 4 hr was conducted with a secondary treated wastewater (DOC = 6.6 mg-C/L) with a NDMA FP of 544 ng/L. Surprising to us, Figure 4-1 shows that even the lowest dosage of PAC removed 70% of the NDMA FP. Increasing dosages up to 75 mg/L continued to remove NDMA FP, achieving slightly more than 90% NDMA FP removal. PAC dosages higher than 75 mg/L achieved incrementally little additional NDMA FP removal. Thus, although NDMA precursors can be readily sorbed, even from a complex water matrix such as treated secondary effluent, a very small percentage (~5%) of NDMA FP exhibits a low affinity for PAC.

Experiments comparing two PAC types (lignite and bituminous based) at dosages reasonable for use in WTPs were performed with a secondary effluent (DOC = 5.6 mg-C/L) containing a NDMA FP of 1470 ng/L. Figure 4-2 shows the fraction of NDMA FP and UV absorbance at 254 nm (UV_{254}), where UV_{254} is a surrogate for strongly adsorbing organic matter. The two different carbon materials removed NDMA FP and UV_{254} differently, but both showed increasing removal as a function of PAC dose. The bituminous PAC had greater iodine #, surface area, and pore volume than the lignite, but lower molasses # (Table 4-3). In these experiments, the bituminous PAC removed nearly 40% of the NDMA FP with a low PAC dose of only 3 mg/L and higher removals of 59% and 91% with dosages of 8 and 75 mg/L, respectively. At a bituminous PAC dose of 3 mg/L, less than 15% of the UV_{254} was removed, compared with nearly 40% of the

NDMA FP. Bulk DOC removals were lower than UV_{254} removals (Figure 4-7). In all cases, NDMA FP removal was higher than UV_{254} or DOC removal, indicating a preferential removal of NDMA FP precursors in treated wastewater than the bulk NOM.

Although research regarding adsorption of NDMA precursors is limited, our findings support the limited other existing data suggesting that AC may have potential for NDMA FP reduction (Farré *et al.*, 2011; Krasner *et al.*, 2008; Sacher *et al.*, 2008). For example, one study showed ~50% reduction of NDMA FP in three of four SWs tested at a PAC dose of just 5 mg/L and 50–90% reduction at 20 mg/L (Sacher *et al.*, 2008). Other nitrosamines were found to form in quantities an order of magnitude lower than that of NDMA. Based on $R^2 \geq 0.9$ for Freundlich isotherms (NDMA FP versus residual NDMA FP) (Table 4-5), Sacher and colleagues (Sacher *et al.*, 2008) suggested that NDMA formation occurred from single solutes specific to their water source or from a specific group of solutes that adsorbed similarly (Sacher *et al.*, 2008). Isotherms for precursors for halogenated DBPs formed from bulk NOM do not typically correlate well due to the variability in precursors and their respective hydrophobicities. Because the objective was to generate isotherms in the latter study, the PAC contact time was long (7 d) and unrepresentative of full-scale treatment scenarios.

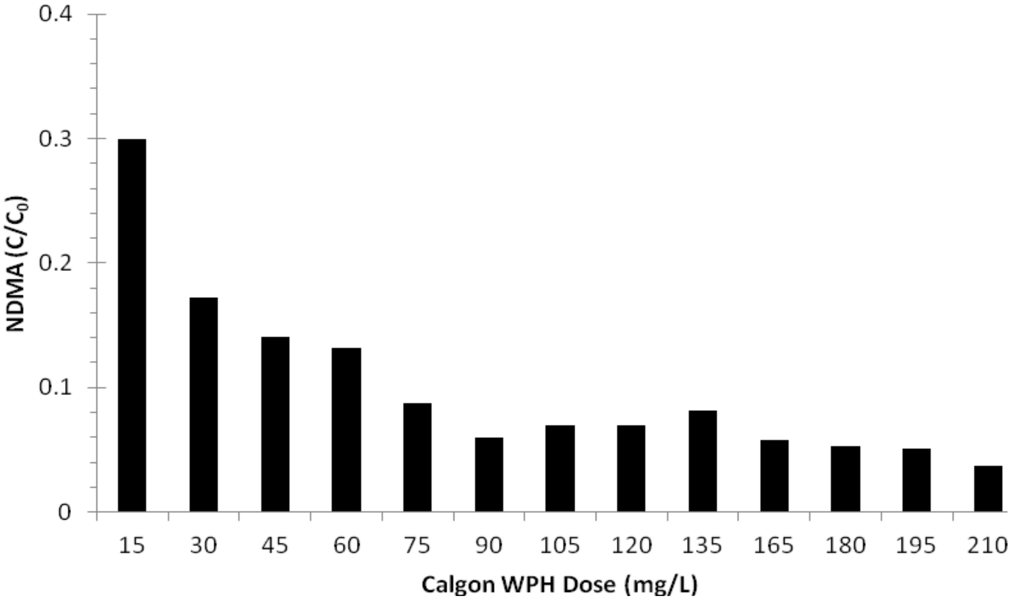


Figure 4-1 NDMA FP reduction with bituminous PAC in a secondary WWTP effluent; the control sample (C_0; no PAC) contained 544 ng/L of NDMA FP

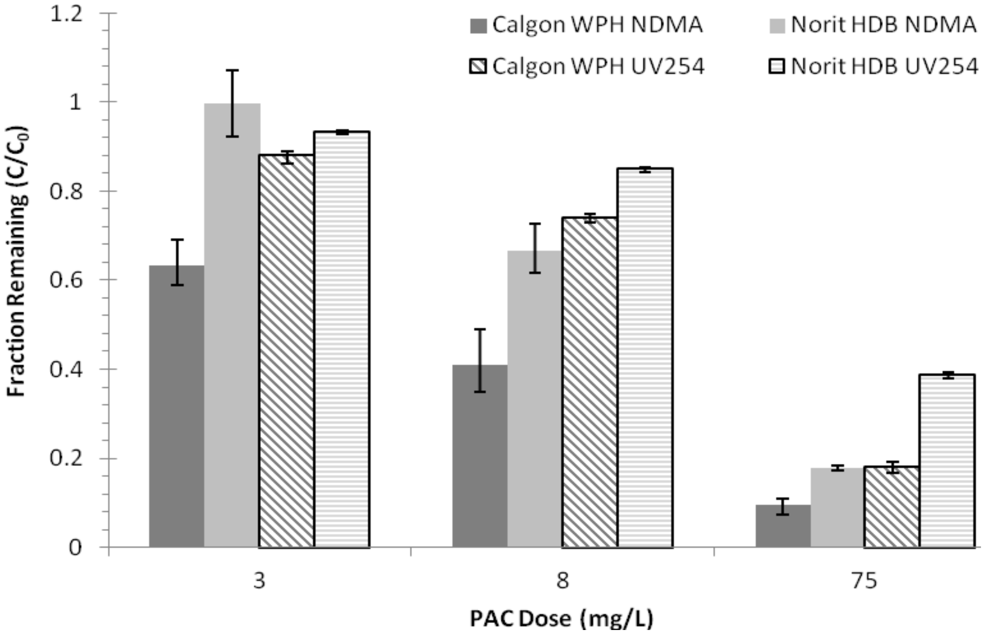
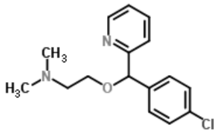
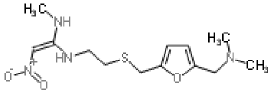
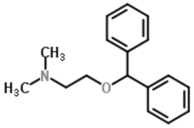
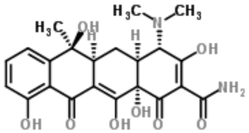
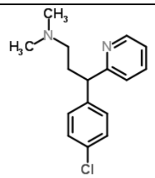


Figure 4-2 NDMA FP and UV_{254} absorbance reduction in a secondary wastewater effluent after treatment with bituminous (WPH)- and lignite (HDB)-based PACs. The control sample (no PAC) had a NDMA FP of 1470 ng/L and UV_{254} = 0.11 cm^{-1}

Sorption of NDMA-yielding pharmaceuticals by PAC. To further explore the removal of NDMA precursors, we selected five pharmaceuticals known to yield NDMA upon chloramination. Although, in general, these specific pharmaceuticals have not been detected in natural waterways (likely due to extremely low concentrations, a lack of inclusion in common monitoring programs, or their degradation products may be present), their combined conversion to NDMA or that of their degradation products or of other pharmaceuticals with amine moities could be potentially responsible for significant additive formation. Sorption experiments in pH buffered nanopure water (Figure 4-8) were fit by Freundlich isotherms. Relevant information on these pharmaceuticals and the isotherm parameters K_f and 1/n are presented in Table 4-1. In all cases, the 1/n values were less than unity, suggesting favorable sorption tendencies. For a final aqueous concentration equivalent to 10% of the initial dose, the order of removal from highest to lowest followed: carbinoxamine > ranitidine > diphenhydramine > tetracycline > chlorpheniramine. To understand the influence of competing sorbates, experiments with PAC were conducted in DI water (1 mM $NaHCO_3$) or a blend of SW and secondary effluent.

Figure 4-3 shows the fraction remaining of each pharmaceutical in the two water matrices after 24 hr along with controls (no AC). The presence of background organic matter in the blended waters had minimal effect on the sorption of ranitidine or tetracycline but decreased the removal of the other three pharmaceuticals. Carbinoxamine was not removed in the presence of other background organic matter (blended water). This suggests that the removal efficiency of some pharmaceuticals is strongly dependent on the presence of background, competing sorbates present in surface or treated wastewaters.

Table 4-2 Properties of selected NDMA-forming pharmaceuticals. Isotherm experiments conducted at pH 8 (Hilal *et al.*, 2005; Thompson and Davidow, 2009)

Pharmaceutical	**Common Name**	**Structure**	**Use**	**Molar mass (g/mol)**	**NDMA Molar Conversion (Shen and Andrews, 2010; 2011)**	**pKa (Thompson and Davidow, 2009)**	**Log K_{OW} (Hilal, 2005)**	**Log D (pH 8)**	**Experimental Freundlich K_f (µmol/mg AC)**	**Experimental Freundlich 1/n**
Carbinoxamine	Palgic		Allergy Relief	290.8	0.01-0.04	8.10	2.56	2.2	44.7	0.71
Ranitidine	Zantac		Antacid	314.1	0.75-0.98	2.7, 8.2	0.29	0.29, -0.12	4.3	0.21
Diphenhydramine	Benadryl		Allergy Relief	255.4	Unknown	9.00	3.11	2.1	31.6	0.80
Tetracycline	Sumycin		Antibiotic	444.4	0-0.04	3.3, 7.7, 9.5	-1.33	-1.3, -1.5, -2.8	7.2	0.56
Chlorpheniramine	Chlorphen-12		Allergy Relief	274.8	0.04-0.06	9.20	3.82	2.6	5.5	0.58

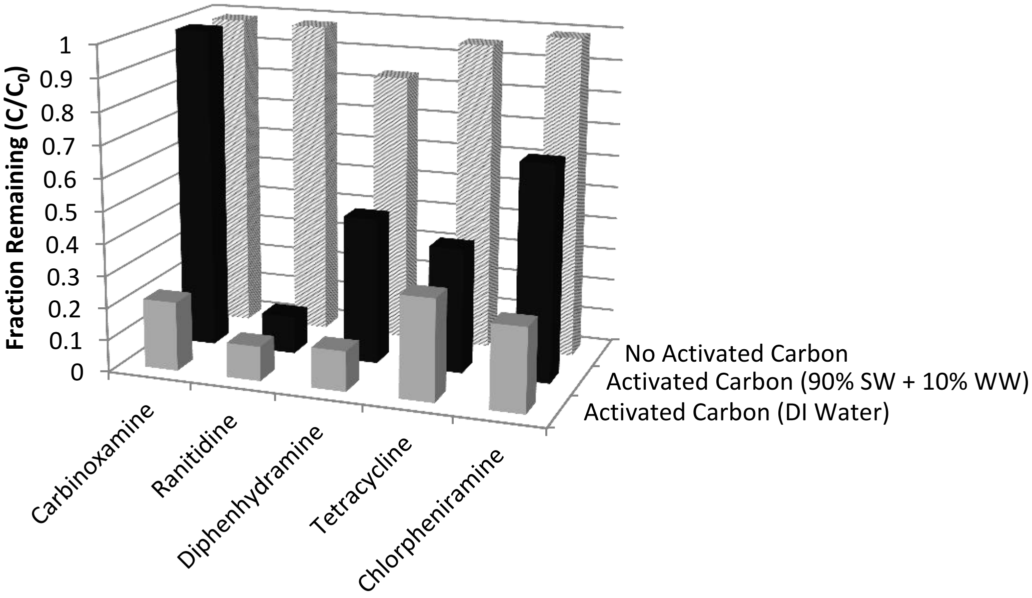


Figure 4-3 Fraction remaining of pharmaceuticals (C_0 = 150 µM) in DI water or blended surface and treated wastewaters after 24 hr contact time with PAC (WPH)
Note: PAC doses in DI water were selected to achieve roughly 75% removal and were 11, 25, 18, 28 and 54 mg/L for carbinoxamine, ranitidine, driphenhydramine, tretracycline and chlorophenirамine, respectively.

Removal of NDMA FP in RSSCTs. RSSCTs were conducted with three blends of SW and secondary effluent. For one blend, two different types of GAC (bituminous and lignite) were used. Table 4-1 summarizes the DOC, UV_{254}, TDN, and NDMA FP of the blended waters before they passed through the RSSCTs. TDN breakthrough occurred in less than 500 bed volumes in all experiments, indicating poor removal of DON, which is a bulk parameter, part of which contributes to NDMA formation (Chen and Westerhoff, 2010; Chiu *et al.*, 2012). Fifty percent breakthrough of UV_{254} and DOC occurred after approximately 3,500 and 4,000 bed volumes, respectively, and did not vary much among the blends of water or GAC types (Figure 4-4). In contrast, NDMA FP removal exceeded 50% in all cases, even after 10,000 bed volumes treated, providing insight into the longevity of GAC contactor life for NDMA precursor removal. Influent water with higher NDMA FP (90% WW + 10% SW blend) exhibited higher absolute levels of NDMA FP in the RSSCT effluent compared with the two other blended waters (Figure 4-5). In our batch and RSSCT experiments, the bituminous GAC (GAC 820) removed NDMA FP, DOC and UV_{254} slightly better than the lignite-based (HDB 3000) GAC did. The bituminous GAC had greater iodine # and surface area, but less pore volume and a lower molasses # than the lignite based GAC (Table 4-3). The results show continued removal of NDMA precursors even after nearly complete breakthrough (C/C_0 >85%) of DOC was achieved. The order of removal efficiency in the RSSCTs was NDMA precursors >> UV_{254} > DOC >> TDN. These are the first published NDMA precursor breakthrough curves using GAC.

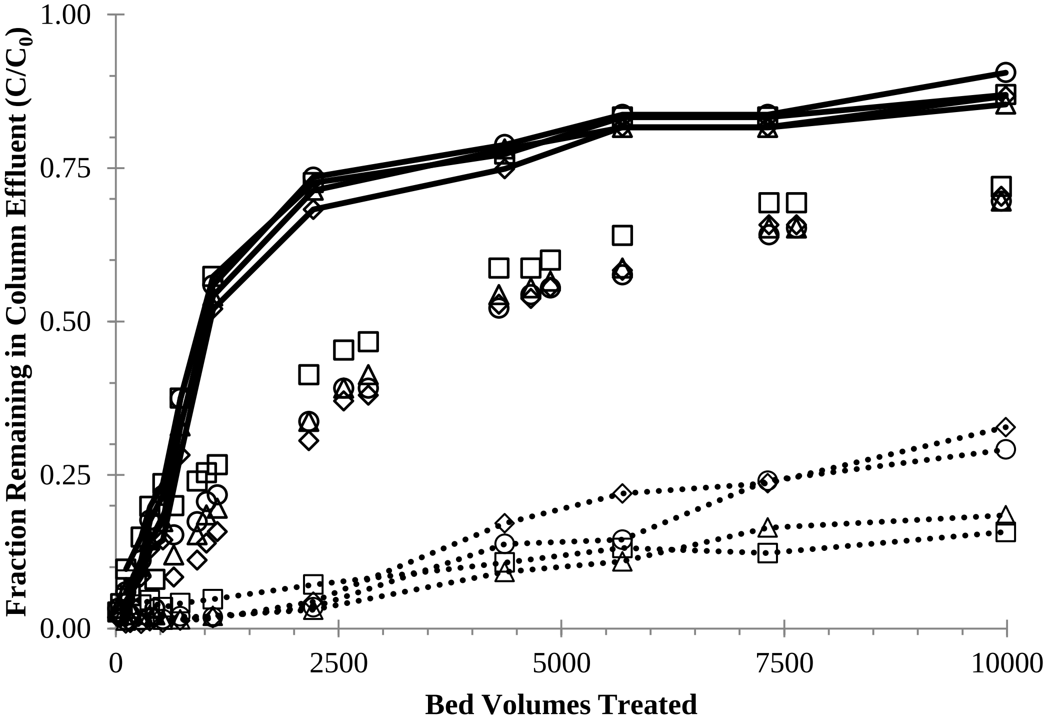


Figure 4-4 DOC and UV_{254} breakthrough in GAC packed beds using blended SW and secondary wastewater effluent

Note: Symbols and lines represent DOC breakthrough, whereas symbols alone represent UV_{254} breakthrough, and symbols with dashed lines represent NDMA FP precursor breakthrough with blends of SW and secondary effluent (WW) for GAC820 (◇ for 10% SW + 90% WW; △ for 50% SW + 50% WW; □ for 90% SW + 10% WW) or HD3000 (○ for 50% SW + 50% WW).

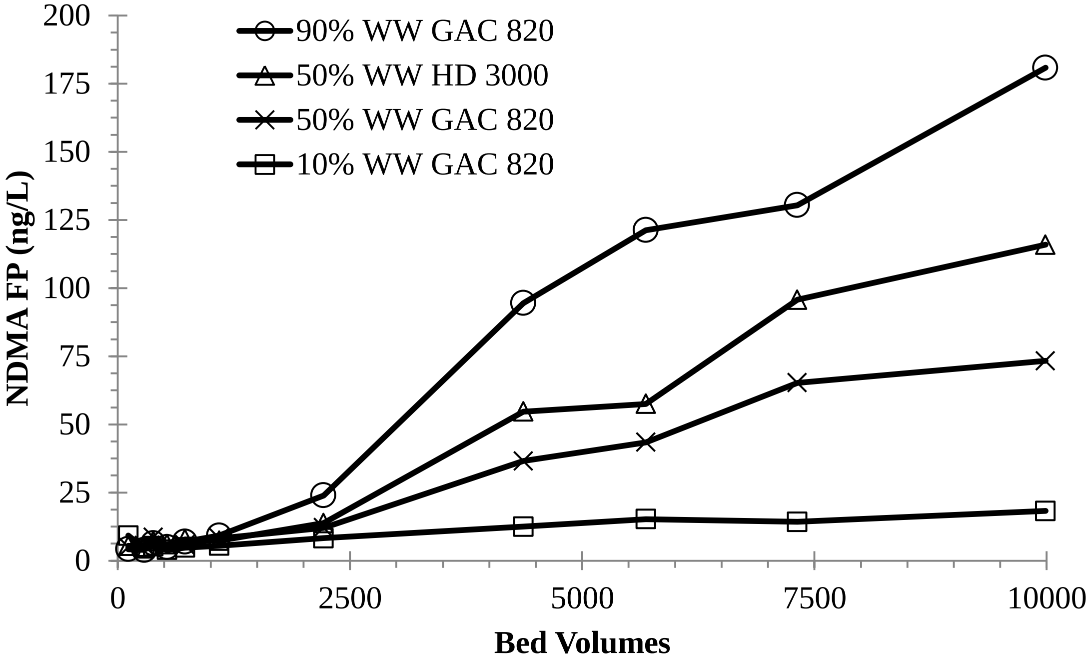


Figure 4-5 NDMA FP after GAC packed bed treatment with blends of SW and secondary effluent (WW). Control samples (no GAC) contained 116, 398, and 552 ng/L of NDMA FP in blends containing 10, 50, and 90% SW, respectively

NDMA FP removal in pilot-column studies and full-scale GAC applications. Preliminary evidence that NDMA FP can be removed at pilot and full scale was obtained. At Pilot Plant 1, the NDMA level was 315 ng/L in the RO concentrate (NDMA FP = 413 ng/L, which was the sum of the NDMA formed and the amount of precursors present [i.e., NDMA precursors = 98 ng/L]). This RO concentrate was then ozonated (NDMA = 265 ng/L; NDMA FP = 304 ng/L [i.e., NDMA precursors = 39 ng/L])—ozone destroyed a substantial portion of the NDMA precursors [11]—and treated using a BAC bed (EBCT = 15 min). After BAC treatment, the NDMA was only 3 ng/L and NDMA FP only 35 ng/L (NDMA precursors = 32 ng/L). DOC was reduced from 51 to 39 mg-C/L after BAC. Thus, BAC treatment removed almost all of the preformed NDMA, but a relatively low percentage (~20%) of bulk DOC or the NDMA FP precursors.

At Pilot Plant 2, BAC treatment consistently lowered NDMA FP over a period of 3 months of operation. NDMA FP after ozonation ranged from 16 to 66 ng/L (47 ± 19 ng/L), and BAC effluent always contained less than 11 ng/L (5 ± 4 ng/L); on any given sampling day, BAC achieved an average removal of 88 ± 6% (n = 7). DOC removal across the BAC was greater than 45% during the first month of operation but decreased to only 16% by the final sampling date. On this date, NDMA FP still decreased from 59 to 3.5 ng/L across the BAC (Wang *et al.*, 2012). Adsorption of bulk DOC was occurring during initial operations, where the ability to remove NDMA FP lasted longer than that of the DOC. This level of precursor removal by BAC in Pilot Plant 2 is comparable with pilot-plant data for a reclaimed wastewater that showed a 75% decrease in NDMA FP, from ~250 to ~50 ng/L, across BAC (Farré *et al.*, 2011). However, this was not the case for Pilot Plant 1, where it is possible that NDMA precursors were destroyed or altered by pre-ozonation (Shah *et al.*, 2012). In all three cases it is difficult to separate removal of NDMA formed or present at the pilot plants and removal of NDMA precursors by sorption onto AC and/or biodegradation. Nonetheless, in Pilot Plant 2, removal of NDMA FP could be compared to that of the bulk NOM over time, which likely involved an adsorptive process. It should be noted that extensive literature exists on NDMA sorption by virgin AC under relatively low flow rates; in fact, AC is used during the extraction of NDMA from water in the analytical method (Charrois *et al.*, 2004; Munch and Bassett, 2004; Ripollés *et al.*, 2011; Tomkins and Griest, 1996). Moreover, under the low level of precursors present in our waters, the findings suggest that NDMA formation via catalysis of amines on AC surfaces, which has been reported elsewhere (Padhye *et* *al.*, 2011b), is probably not important (note, in the full-scale GAC testing, NDMA was not detected at or above the minimum reporting level at either plant studied).

Full-Scale Plant 1 was sampled twice. The GAC influent DOC was ~2.7 mg-C/L, and achieved ~40% removal of DOC and ~60% removal of UV_{254} in a blended effluent from the GAC contactors. During one sampling campaign, NDMA FP decreased from 17 to 6.2 ng/L across the GAC system (64% adsorbed). During another sampling campaign, the utility also added free chlorine ahead of the GAC, and NDMA FP was reduced from 27 ng/L in the plant influent to 2 ng/L in the GAC effluent (93% overall reduction) owing to both oxidation [11] and sorption.

At Full-Scale Plant 2, samples were taken from several different GAC contactors that were regenerated individually and (EBCT = 21 min) supplied by a common feed water, which had not been pre-oxidized. Data for TOC, UV_{254}, and NDMA FP are presented in Figure 4-6 (influent normalized breakthrough curves are presented in Figure 4-9). GAC contactor influent water contained 1.6 mg-C/L of TOC, 2.9 m^{-1} of UV_{254}, and 14 ng/L of NDMA FP. GAC contactors had been operated for 33, 160, and 283 days after regeneration and these achieved 84, 74, and 54% reduction in NDMA FP, respectively. After varying periods of GAC packed bed contactor operation (i.e., days since last regeneration), the efficiency of TOC and UV_{254} removal decreased (Figure 4-6). After 160 days of operation, less than 30% of the TOC or UV_{254} was removed. NDMA FP removal exceeded 57%, even after the longest operating period, and was greater than TOC or UV_{254} removal for the two contactors that had the longest time since regeneration. The most recently regenerated contactor had only modestly greater TOC and UV_{254} reduction over NDMA FP. However, this could be an artifact of the fact that

NDMA FP was near the minimum reporting level in the latter contactor, where the accuracy of measurement is not as good. Nonetheless, this suggests that different types of NDMA FP precursors exist, one that is strongly sorbed to GAC and one that is not well sorbed by GAC.

We provided full-scale GAC results from two plants, one of which used pre-chlorination in one sample event but not in the other and at a second plant with no pre-oxidation. These full-scale results showed that NDMA precursors were better removed than bulk DOC and that even when there was DOC breakthrough, there was still good removal of NDMA precursors, as was shown in the RSSCTs. The pilot-scale results complement the bench-scale results as there are many plants in the U.S. that use ozone and GAC, perhaps more than use GAC alone. Moreover, Pilot Plant 2 was achieving good DOC removal for much of the testing, which allowed us to evaluate the ability of GAC to also remove NDMA precursors.

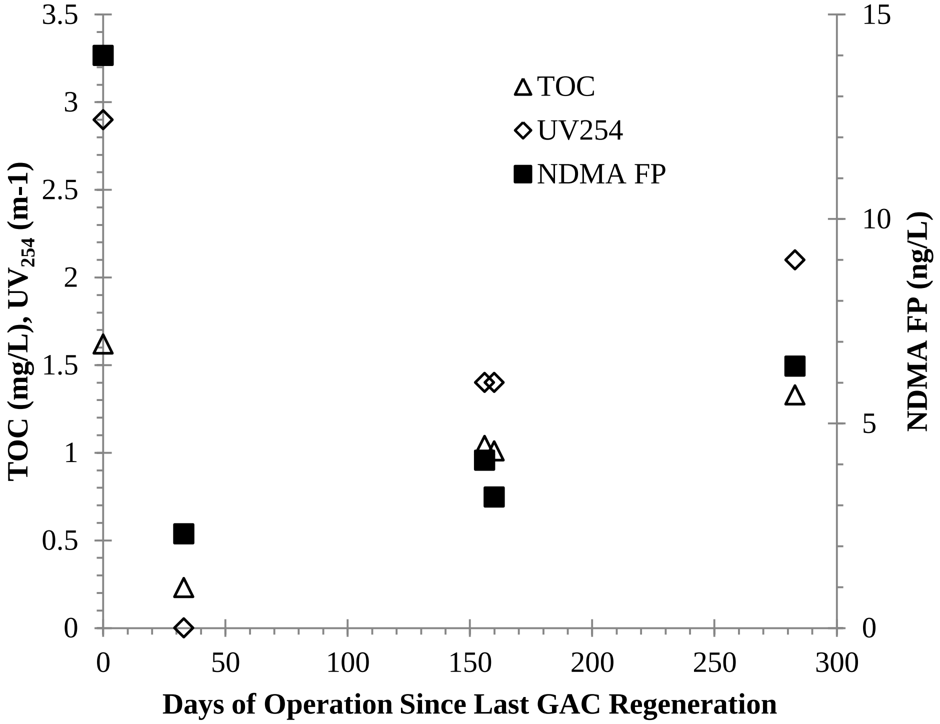


Figure 4-6 TOC, UV_{254}, and NDMA FP reduction across parallel GAC contactors being fed with a common coagulated/settled water at a full-scale WTP (data at time zero represent GAC influent results)

4.5 Acknowledgements

This research was supported by the Water Research Foundation (Project 4370) and managed by Djanette Khiari. The authors greatly appreciate the efforts by participating utilities to collect full-scale samples. Harsha Sharma conducted isotherms using pharmaceuticals as a visiting scholar at Arizona State University from Vellore Institute of Technology. Jun Wang and Chao-An Chiu provided laboratory help and instruction. NDMA testing at Metropolitan Water District was conducted by Eduardo Garcia and Tiffany Lee. The pilot test work in China was supported by the National Natural Science Foundation of China (Grant No. 51078208). Xiaobin Liao operated the

pilot test equipment, whereas Chengkun Wang and Jun Wang completed the majority of the analytical work.

4.6 Supporting Information

Table 4-3 Typical characteristics for PAC and GAC used. Particle sizes, iodine numbers, and molasses numbers were obtained from manufacturer literature

Activated Carbon	Particle Size	Iodine # (mg/g)	Molasses #	BET Surface Area (m^2/g)	Pore Volume (cm^3/g)
WPH	90% min less than 325 mesh	800	160	1087 (Shalaby *et al.*, 2009)	0.69 (Shalaby *et al.*, 2009)
HDB	90% min less than 325 mesh	550	500	546 (Jiang and Adams, 2006)	0.48 (Jiang and Adams, 2006)
HD3000	<10% outside of 8-30 mesh	650	450	676 (Cheng *et al.*, 2005)	0.711 (Cheng *et al.*, 2005)
GAC 820	8-20 mesh	970	220	908 (Chiu *et al.*, 2012)	0.5 (Chiu *et al.*, 2012)

Table 4-4 Summary of RSSCT design data for GAC fixed bed adsorber scaling

Design Parameters	Simulated Pilot Scale	RSSCT (PD)
Particle Radius (cm)	0.08025	140x170 mesh
Column Diameter (cm)	832	1.10
EBCT (min)	10.00	0.61
Re	29.28	1.12
Sc	893.7	893.7
Re*Sc	26,170.3	1,000.0
Flow Rate (mL/min)	13,290,480.0	14.5
Length of the Column (cm)	121.9	9.3

Table 4-5 Freundlich parameters for nitrosamine precursor adsorption onto F300 PAC (Sacher *et al.*)

Sample	1/n (F300)	K_f (F300)	R^2
NDMA FP			
River 1	0.77	1.5	0.95
River 2	1.29	0.067	0.99
River 3	2.25	0.00039	0.90
River 4	2.09	0.0015	0.95
NMOR FP			
River 4	4.11	0.038	0.94
NPYR FP			
River 4	1.05	0.15	0.94

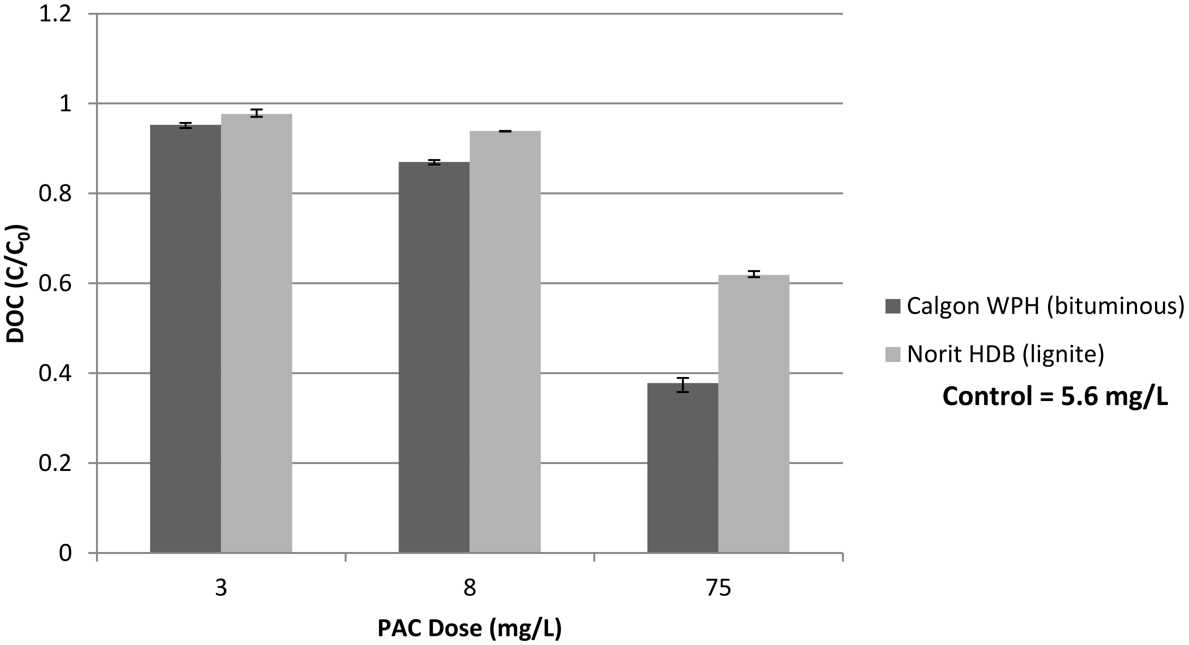


Figure 4-7 DOC removal in a secondary wastewater effluent by treatment with bituminous and lignite-based PAC

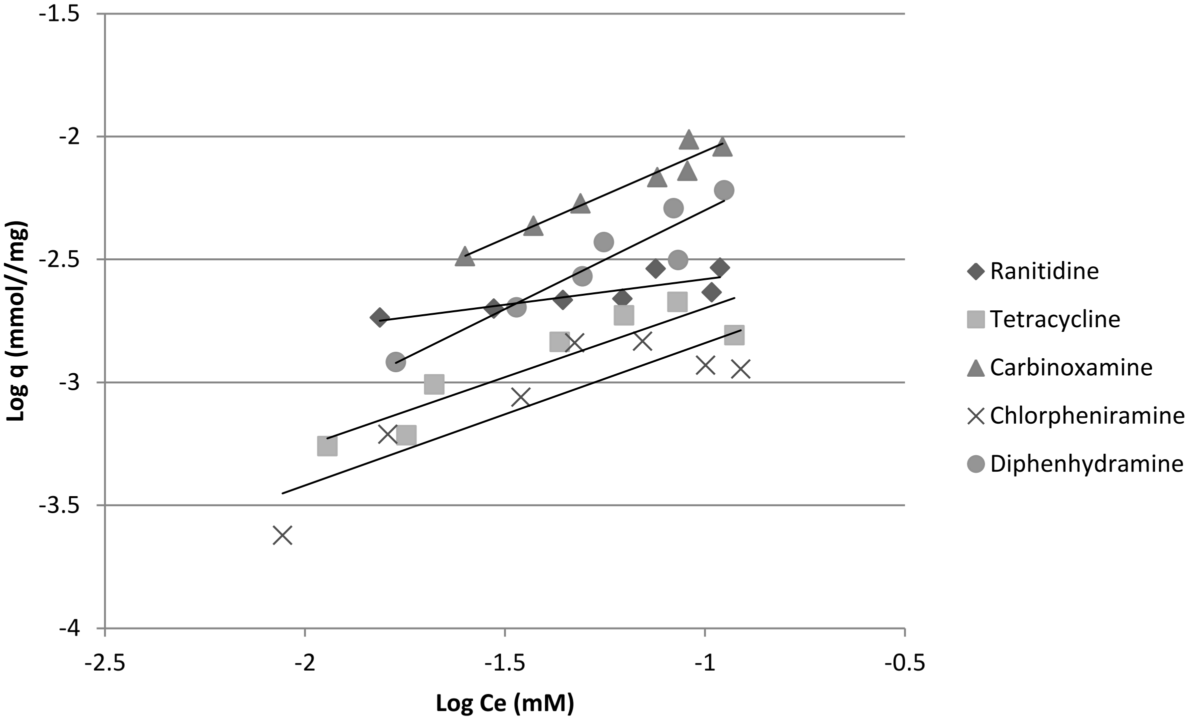


Figure 4-8 Adsorption isotherms of NDMA-forming pharmaceuticals in DI water onto Calgon WPH PAC. A bicarbonate buffer was used to adjust pH to 8

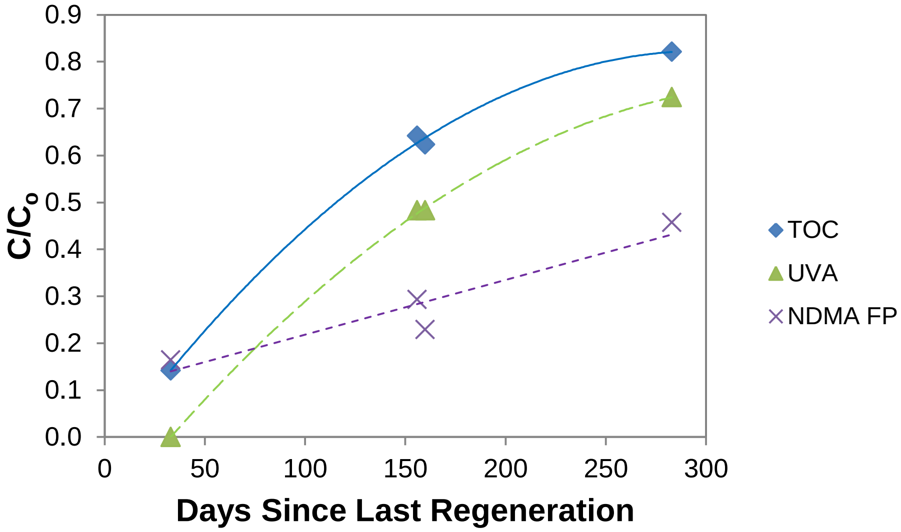


Figure 4-9 Influent-normalized breakthrough curves at a full-scale WTP across GAC contactors

5 Optimizing Isolation of Organic Bases from Water Helps to Identify *N*–nitrosodimethylamine Precursors

This chapter has been prepared for submission to Water Research.

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5.1 Abstract

Identification of *N*-nitrosodimethylamine (NDMA) precursors could lead to their control and improved understanding of NDMA formation during chloramination. This work aims to provide an isolation method for NDMA precursors with 1,000X concentration factor to facilitate mass spectrometry based identification. Multiple sorbates (C_{18}, cation exchange, activated carbon) and eluents (toluene, methanol, and dichloromethane) were investigated for their affinity and elution of NDMA precursors. In part because tertiary amines are potent NDMA precursors, the best approach found high recoveries of NDMA precursors using cation exchange resin loaded at pH 3, where bases and most acids are protonated, and eluted with 5% NH_4OH in methanol. Ammonia is subsequently removed using nitrogen gas. Neither the alkaline nor acidic conditions used in the sorption and recovery of NDMA precursors significantly impacted the reactivity of NDMA precursors. The method allows for rapid extraction of multiple sources of precursors by employing commercially available solid phase extraction cartridges. A median recovery of 82% for NDMA precursors was achieved from 11 surface waters and one wastewater at 1,000 fold concentrations into methanol. Activated carbon achieved high sorption but poor elution while C_{18} sorbed precursors poorly. This work provides the foundation for discovery of NDMA precursors that are responsible for NDMA formation in complex environmental samples, the significance of which has already been demonstrated by the discovery and quantification of the contribution of methadone to NDMA formation

5.2 Introduction

N-nitrosodimethylamine (NDMA) is a drinking water contaminant and chloramination disinfection by-product. The United States Environmental Protection Agency (USEPA) has classified NDMA as a probable human carcinogen and will determine whether it will regulate NDMA concentrations in drinking water in late 2015 based on its propensity to produce tumors in rats and mammalian cells (Peto *et al.*, 1991; USEPA, 2002; 2009). NDMA occurs within treatment plants and distribution systems and the pool of organic-nitrogen-NDMA-precursor material has been indicated to be highly influenced by effluent-impacted source waters, pharmaceuticals and personal care products, and amine-containing coagulation polymers (Krasner *et al.*, 2013). While amine-containing coagulation polymers originate inside the treatment plant and thus their contribution to NDMA formation can be minimized by reducing use (Hanigan *et al.*, 2015b), pharmaceuticals and personal care products are sourced primarily in wastewater effluents. Furthermore, the contribution of wastewater to drinking water treatment plant source water is increasing, and along with increasing use of chloramines (Li, 2011), indicates the potential for increasing NDMA formation in drinking water (Rice *et al.*, 2013; Rice and Westerhoff, 2015).

The current approach to understand NDMA precursors relies upon determination of NDMA yields in natural waters or mechanistic studies with model compounds (Kemper *et al.*, 2010; Mitch and Sedlak, 2002; Selbes *et al.*, 2013; Zhou *et al.*, 2014). Specific studies aimed at identification of NDMA precursors formed during chloramination have been focused on anthropogenic chemicals including a study showing the potential of 20 pharmaceuticals to form NDMA (Shen and Andrews, 2011b). Selbes et al. (2013) identified that tertiary amines with a single carbon between the N and an a benzyl-like structure are more reactive in forming NDMA. Tertiary amines generally have a higher NDMA molar yield than secondary and quaternary amines. However, to date there is inadequate occurrence data for these model NDMA precursors with high NDMA molar yield (e.g., ranitidine, dimethylbenzylamine) at occurrence levels plausible to account for any significant NDMA formation potential (FP), calling into question the relevance and contribution of currently studied organic precursors to NDMA FP of drinking water treatment plant source waters. Therefore, new strategies to isolate and identify trace-level tertiary amine NDMA precursors are needed.

We sought to select and optimize an isolation and concentration method for tertiary amine NDMA precursors from wastewaters and surface waters that would facilitate their subsequent identification by mass spectrometry. Assuming one mole of nitrogen in NDMA is derived in the precursor and one from monochloramine and that the precursors contain only one reactive N, a typical drinking water source water that produces 15 ng/L NDMA FP equates to a possible range of NDMA precursors concentration from 0.2 to 20.7 nM based on molar yields of precursors ranging from 1 to 100%. Thus, NDMA precursor identification by optical spectrometry is unlikely due to low precursors concentration and interferences from other organic molecules. Mass spectrometry identifications are also unlikely due to interferences and therefore pre-concentration and isolation is needed. Chen et al. (2014) previously described the potential for C_{18} and cation exchange solid phase extraction (SPE) cartridges to retain NDMA precursors. However, as was the case with our preliminary granular activated carbon (GAC) test, retention does not equate to recovery potential from the SPE using solvents. Therefore, we evaluated SPE cartridges containing materials from the Chen et al. study and a commercially available activated carbon and mixed mode hydrophobic cartridge known to retain pharmaceuticals. We evaluated various solvents for recovery of retained precursors. Mass balances on NDMA FP precursors loaded onto, passing through, and eluted off SPE cartridges were determined. We tested the final SPE and solvent and recovery technique on 12 waters.

5.3 Materials and Methods

Reagents. HPLC grade solvents were purchased from Fisher Chemical (methanol, toluene, Fair Lawn, NJ) and EMD Millipore (dichloromethane [DCM], Billerica, MA). Sulfuric acid (H_2SO_4) was also purchased from EMD Millipore. Reagent water used was either of HPLC grade (purchased from commercial sources) or was >18.2 MΩ-cm (NanoPURE™). Sodium hypochlorite, boric acid, and borax were purchased from Fisher Chemical. Sodium sulfate drying cartridges were from Agilent Technologies (Santa Clara, CA) and ammonium hydroxide (NH_4OH), d_9-methadone, and sodium hydroxide were from Sigma Aldrich (St. Louis, MO). An NDMA standard was purchased from Supelco (Bellefonte, PA) and the isotopically labeled d_6-NDMA standard from Cambridge Isotopes (Tewksbury, MA). Oasis MCX (500mg), HLB (500mg), and Sep-Pak C_{18} (1g) SPE cartridges were purchased from Waters (Milford, MA) while Discovery SCX (1g) was purchased from Sigma Aldrich (St. Louis, MO). Suwannee River natural organic matter (SRNOM) (1R101N) was purchased from the International Humic Substances Society (IHSS).

Sampling sources. Samples of the influents of 11 surface water, drinking water treatment plants were collected from different locations in the U.S. and Canada and shipped overnight in coolers with ice packs. One secondary wastewater effluent was collected from a local treatment plant before oxidant addition (secondary effluent). Sampling sources for this study had NDMA FP greater than 15 ng/L and were intentionally selected to determine if high NDMA precursor loadings could be isolated. The treatment plants had varying water quality as is shown in Table 5-1. Samples were filtered with pre-combusted Whatman GF/D (2.7 µm nominal pore size, GE Healthcare, Piscataway, NJ) immediately upon arrival to remove particles that may impede solid phase extraction. The samples were stored for a maximum of one week in a refrigerated (4°C) chamber.

NDMA precursor extraction and formation potential. Initial tests to maximize the recovery of NDMA precursors were conducted with a single matrix (wastewater secondary effluent) with high dissolved organic carbon (DOC) (>5 mgC/L) and total dissolved nitrogen (TDN) (>5 mgN/L). In one test, Norit GAC820 was packed into a 2.5 cm column (empty bed contact time = 10 min), and a sample was passed for 2,000 bed volumes. Recirculating methanol was pumped in reverse flow for 24 h to elute precursors from the column, and the methanol was evaporated to 1 mL. Prior tests found this to be adequate to have <5% precursor breakthrough (Hanigan *et al.*, 2012).

Most tests used an automated SPE system (Caliper Life Sciences Autotrace 280). SPE cartridges were rinsed with 10 mL of methanol, 10 mL of water, and 1 L of sample (neutral or pH 3). The loading rate was 5 mL/min. The columns were dried for 30 min with 15 psi nitrogen gas and subsequently eluted with 10 mL of a solvent (toluene, methanol, dichloromethane, or 5% NH_4OH in methanol). In one experiment, 500 ng/L d_9-methadone was spiked into the sample before extraction to quantify losses across the cartridge. The solvent was evaporated to 1 mL using a stream of nitrogen gas. Methadone is a confirmed high molar yield precursor of NDMA (Hanigan *et al.*, 2015a).

FP tests were conducted by adding preformed monochloramine. Preformed monochloramine was prepared by slowly adding via burette 250 mL of NaOCl solution to 250 mL solution of 10 mM borate buffered (pH 8) NH_4OH solution. The final $N:Cl_2$ ratio was 1.2, and the monochloramine concentration in the stock solution was ~2,000 $mgCl_2/L$ as measured by the indophenol colorimetric Monochlor F method (Hach Company, Loveland, CO).

500 mL samples were buffered with 10 mM borate buffer (pH 8) and an appropriate amount of chloramine solution was added. After a period of 72 hours in the dark at 25°C, the chloramines were quenched with 5 mM ascorbic acid and 200 ng/L of the deuterated NDMA standard was added immediately. Samples were stored for less than two weeks at 4°C in the dark before extraction.

NDMA precursor recovery was measured by reconstituting an appropriate volume of the isolate into 500 mL of Milli-Q water and chloraminating under FP conditions. To complete the mass balance recoveries on NDMA precursors, raw water samples were also chloraminated and recovery was calculated as the NDMA FP of the reconstituted sample divided by the raw water NDMA FP.

Analytical. NDMA itself was analyzed using solid phase extraction following EPA Method 521 (Munch and Bassett, 2004). Activated carbon cartridges were washed successively with DCM, methanol, and HPLC grade water before being loaded at a rate of 5 mL/min. The columns were dried using compressed nitrogen gas and eluted with 5 mL of DCM. The extract was evaporated to 1 mL using a gentle stream of nitrogen gas and transferred to a gas chromatograph vial via Pasteur pipette. NDMA was quantified by gas chromatograph mass spectrometry (GC/MS) (ammonia chemical ionization) using an isotopically labeled standard to quantify losses during solid phase extraction. The details of the GC/MS method can be found elsewhere (Hanigan *et al.*, 2012).

DOC and TDN were measured using a Shimadzu Total Organic Carbon TOC-VCSH (Shimadzu Corporation, Kyoto, Japan) with attached Shimadzu TNM by applying standard method 5310 B (American Public Health Association *et al.*, 2005).

The GC-MS analytical method for methadone can be found in the SI. Statistical analysis was conducted using the analysis of variance functions inside the R environment (R Development Core Team, 2012). The P value was set at 0.05.

Fluorescence was measured using a Horiba Aqualog (Kyoto, Japan). A 0.1 second integration time was used during measurement of emission from 200 to 625 nm and excitation from 240 to 400 nm. The CCD gain was set to medium. Inner filter effects and first and second order scattering were removed using the included Aqualog (v3.6.10) software. Ultraviolet absorbance was measured using a Shimadzu Multispec-1501 (Kyoto, Japan).

Table 5-1 Water quality characteristics and recovery of NDMA precursors in 1 L field samples, and potential sources of impacts to the water samples in this study. One SD given where triplicate samples were conducted. 12 ng/L was subtracted from the column effluent data shown for the purposes of the overall mass balance (isolate and effluent) due to precursor leeching from the columns.

Sample ID	NDMA FP (ng)	Column Effluent (ng)	Reconstituted NDMA FP (ng)	NDMA FP in Isolate (% of raw water)	NDMA FP in Effluent and Isolate (% of raw water)	Potential Source Water Impacts	DOC (mgC/L)	TDN (mgN/L)	SUVA (L/mg-m)	Conductivity (µS/cm)
SW 1	21 ±0.4	NM	20 ±0.8	95%	NA	WW	3.2	0.4	NM	NM
SW 1 (2nd sampling)	22 ±0.7	18 ±0.6	21 ±0.3	95%	123	WW	3.2	0.4	1.3	961
SW 2	36 ±1.8	25 ±0.8	29 ±1.2	81%	117	Ag, WW	5.3	0.4	2.3	196
SW 3	47 ±0.7	25 ±1.3	48 ±0.4	102%	130	WW, Ag, Indust	2.5	2.7	2.1	585
SW 4	97 ±4.6	44 ±1.8	57 ±3.3	59%	92	Ag, WW	6.0	2.7	5.1	435
SW 5	112 ±4.9	50 ±4.8	71 ±7.2	63%	97	WW, Ag, Indust	6.4	3.2	0.4	639
SW 6	546 ±3.0	79 ±0.6	599 ±9.9	110%	122	WW	6.9	4.3	2.4	843
SW7	122 ±9.2	33 ±5.1	50 ±8.1	41%	58	Ag, WW	4.5	4.8	3.0	648
SW8	40 ±2.1	27 ±4.6	67 ±69.5	168%	205	Bio, WW, Ag	4.4	0.5	1.6	410
SW9	111 ±2.6	29 ±7.9	49 ±1.7	44%	59	WW	4.7	4.6	3.7	609
SW10	40 ±1.5	25 ±5.1	28 ±5.1	70%	103	Ag	4.3	0.5	1.3	411
WW 1	602 ±27.5	43 ±5.1	497 ±25.8	83%	88	WW	5.2	5.4	2.1	1151
18.3 MΩ-cm	26	12 ±1.4	34	131%	NM	NA	<0.5	<0.1	NM	NM

**12 ng subtracted to account for precursors leached from MCX cartridges into column effluent samples. NM=Not measured. NA= not applicable

5.4 Results and Discussion

Precursor recovery using activated carbon. Our previous research indicated that NDMA precursors were adsorbed well by GAC, but we did not attempt to elute or recover the precursors (Hanigan *et al.*, 2012). To examine the potential of GAC to sorb and elute NDMA precursors, two columns were packed with Norit GAC820 and loaded with 2,000 bed volumes of secondary wastewater effluent. We chose 2,000 bed volumes because we had previously shown non-detectable breakthrough of NDMA precursors using a similar water source with the same number of loaded bed volumes. To elute precursors, methanol was recirculated through the packed column for 24 h to elute precursors. The recirculating methanol was concentrated under a stream of nitrogen gas to 15 mL. Half of the extract was reconstituted back to initial concentration into pH 8 buffered Milli-Q water. The reconstituted sample was chloraminated and compared to the raw water. The mass recovery of NDMA precursors was only 30 to 40%. GAC has hydrophobic sites that methanol should have desorbed. But, GAC also has other surface functionality which can bind polar organics and this is part of the reason why GAC must be thermally regenerated rather than just solvent washed.

Comparison of NDMA precursor recovery using multiple SPE cartridges. Using SPE cartridges, we investigated the effect on NDMA FP precursor recovery of multiple sorbate and eluent combinations (Figure 5-1). To protonate potential tertiary amine NDMA precursors, cation exchange resins and one experiment with HLB were loaded at pH 3 while others were loaded at neutral pH of the water sample. We used acidic pH to protonate amines (positively charged) and organic acid functional groups (neutral charge). Ideally the protonated amine controlled the polarity of potential precursors. The greatest recovery was obtained by loading the two cation exchangers (SCX and MCX) at pH 3 and eluting them with 5% NH_4OH in methanol and resulted in 45% to 69% of the NDMA precursors loaded recovered in the isolate. When the same cartridges were separately loaded at pH 3 and eluted using DCM or neutral methanol rather than alkaline methanol, recovery was low (<7%), indicating that most NDMA precursors are cation exchanged, not hydrophobically associated and that the precursors have basic moieties, probably tertiary amines, that control their attachment to the resin. The two hydrophobic sorbents (C_{18} and activated carbon) resulted in the lowest NDMA precursor recovery (2% to 19%)

Blank samples (Milli-Q) were loaded onto the SPE cartridges to determine if precursors could leach from the packing material into the extracts or into the effluent of the columns. NDMA FP of the reconstituted blanks was less than the detection limit (~3 ng/L) for all cartridges indicating low precursor leaching during elution but approximately 12 ng/L NDMA FP leached from the MCX column into the effluent.

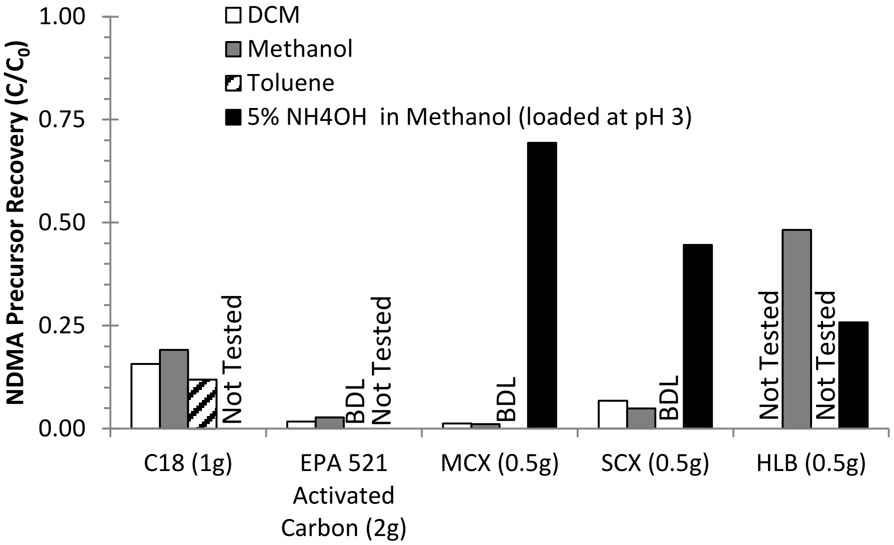


Figure 5-1 Secondary wastewater effluent NDMA precursor recovery after loading on SPE cartridges. Organic solvent eluates were reconstituted into Milli-Q water before FP tests were conducted. BDL indicates that the reconstituted sample had NDMA FP below the detection limit. The wastewater sample NDMA FP was 550 ng/L (C_0)

Optimization of precursor recovery. We proceeded to optimize recovery with the three most promising cartridges: MCX, SCX, and HLB. The SPE cartridges contain a small amount of sorbent (0.5 to 1 g, see methods), and therefore we wanted to ensure that poor recovery was not due to breakthrough of precursors. Figure 5-2 shows breakthrough of NDMA precursors into the effluent of MCX, SCX, and HLB cartridges after loading different volumes of a wastewater sample. Precursor breakthrough was lowest (<10% of influent NDMA FP in the effluent) using MCX, while a significant fraction of precursors broke through from HLB columns in the first effluent aliquot. It is possible that this is not “breakthrough” put poor initial precursor retention. Nonetheless, HLB was not able to sorb enough precursor mass to be a viable sorbent.

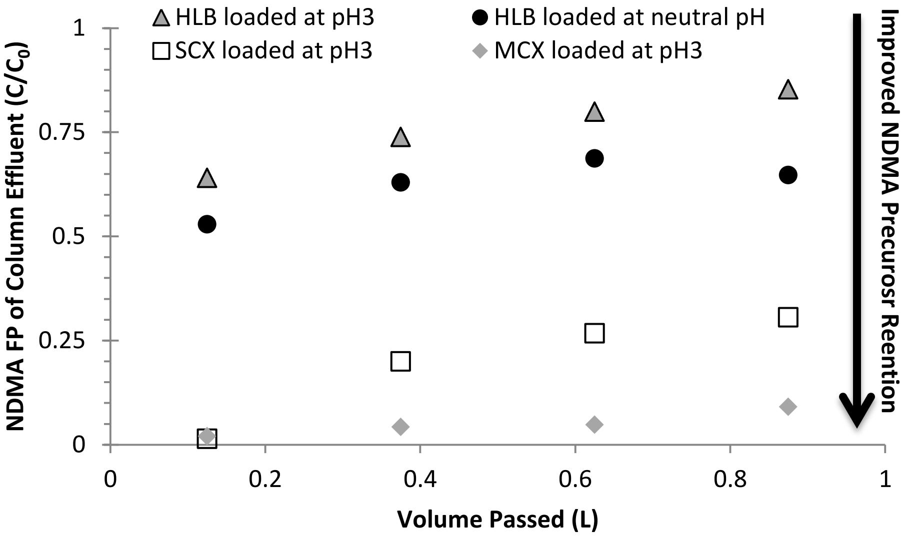


Figure 5-2 Breakthrough curves for multiple cartridges loading at varying influent pH. Data points shown are normalized NDMA FP of 250 mL composite samples. The loaded sample was wastewater secondary effluent with NDMA FP = 1210 ng/L (C_0)

To determine the maximum precursor mass that could be loaded to the best sorbent candidate (MCX), we loaded 2 L of secondary wastewater effluent and measured precursor breakthrough in the effluent (Figure 5-3). NDMA precursors began to break through the column after loading between 1.25 L and 2 L of wastewater. Breakthrough could be altered by the total dissolved solids of the sample, and the wastewater sample used in this test had a high conductance of 1.2 to 1.6 mS/cm. Therefore, we used a conservative estimate of the maximum loaded volume of 1 L when applying the method to isolate precursors from natural waters.

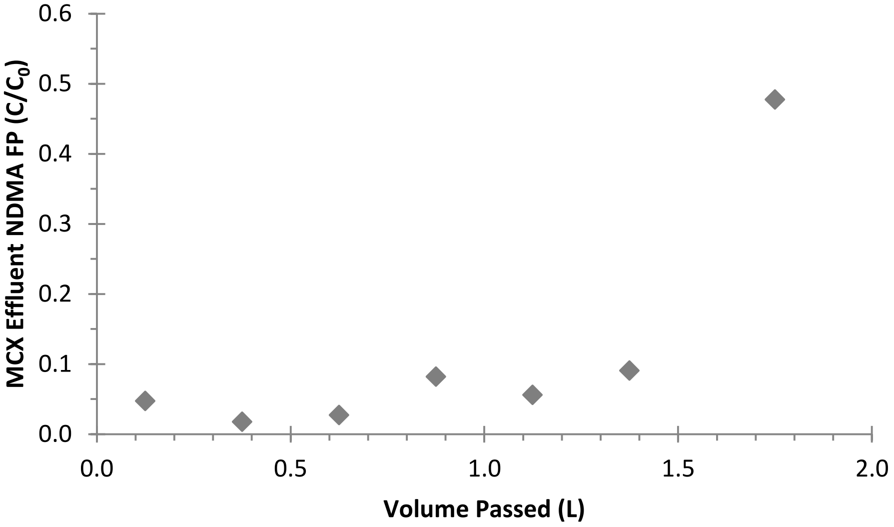


Figure 5-3 Breakthrough of NDMA precursors in the effluent of an MCX SPE cartridge loaded with pH 3 wastewater secondary effluent. The raw water (cartridge influent) contained 610 ng/L NDMA FP

Two other tests were conducted to ensure no transformation in NDMA precursors was caused by pH changes during loading and elution (acidic during loading and alkaline during elution). First, because acidification could hydrolyze precursors while loading the SPE cartridge, a wastewater sample was held at pH 3 for 3 h (approximate time to load the sample to the SPE cartridge) and then adjusted back to neutral pH using NaOH. There was no statistical difference between the NDMA FP of the pH adjusted sample and a sample that was held at room temperature without pH adjustment (Figure 5-5).

Because we are uncertain the composition of the isolated material, we attempted to determine if the reactivity towards NDMA of a complex mixture (Suwanee River natural organic matter (SRNOM)) would increase due to base hydrolysis of N containing NOM. Our concern was that ammonia from NH_4OH used to elute precursors could react with non-NDMA forming NOM to produce new NDMA precursors not present in the source water. Although other standards are available from the IHSS that are up to 2.5 times more nitrogen rich on a carbon normalized basis, we believed SRNOM is adequately representative of NOM that may be present in our samples. 5 mgC of SRNOM (approximate DOC concentrated from 1 L of a theoretical high DOC source water) was dissolved in both 5 mL methanol and 5 mL methanol containing 5% NH_4OH (simulating elution from the cation exchanger). Both samples were concentrated with nitrogen gas to 1 mL, confirmed to be neutral pH (due to ammonia volatilization), and 500 µL was reconstituted into 500 mL Milli-Q water. The NDMA FP was 14 and 17 ng/L for the samples without and with initial NH_4OH addition, respectively. The 3 ng/L difference was considered small and within the experimental and analytical error limits.

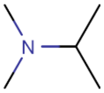
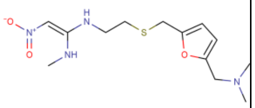
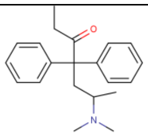
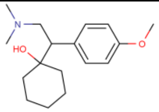
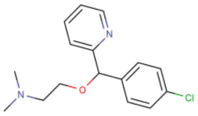
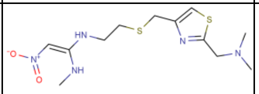
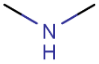
We also investigated literature of two known model amine precursors that have both high molar NDMA yield and the potential to occur in surface and wastewater. For example, the final step in synthesis of methadone is acid hydrolysis, and no evidence of further hydrolysis at either high or low pH was available in published literature. However, ranitidine is known to base hydrolyze at pH >9 (Haywood *et al.*, 1987). Ranitidine hydrolyzes completely in hours at the β-carbon of the nitrovinyl group, the opposite end of the molecule from the tertiary amine which has been previously shown to have little or no effect on reactivity in the formation of NDMA (Selbes *et al.*, 2013). Therefore, this literature and the two experiments above demonstrate that neither the alkaline nor acidic conditions used in the sorption and recovery of NDMA precursors significantly alter their reactivity.

Overall, the final optimized method for NDMA precursor isolation from water samples is as follows: 1) A single filtered sample is pH adjusted to 3 using sequential additions of ≤1M H_2SO_4. 2) 1 L of sample is pumped through MCX SPE cartridges (triplicate extractions) at 5 mL/min by an automated SPE system. The MCX cartridges were first rinsed with 10 mL methanol and 10 mL H_2O. After loading, the cartridges were dried for 30 min with 15 psi of compressed nitrogen gas. 3) Precursors are eluted from the SPE cartridges with 10 mL of 5% NH_4OH in methanol at a flow rate of 1.5 mL/min. 4) The resulting individual concentrates are blown down under a gentle stream of nitrogen gas to a final volume of 1 mL. The method isolates NDMA precursors from background matrices and provides a 1000X concentration factor.

Sorption mechanisms to mixed mode cation exchange resin. Table 5-2 shows properties of model NDMA forming compounds that are likely to control sorption. Most tertiary amines, including the model NDMA precursors shown in Table 5-2, have pK_a between 6 and 10. Thus, tertiary amines are protonated at acidic pH (positively charged) and deprotonated at alkaline pH (neutral). Therefore, we propose that the most likely mechanism controlling sorption to MCX resin at pH 3 and desorption at pH ~12 is protonation/deprotonation, and that most NDMA precursors are probably tertiary amines that have pKa in this range. Some secondary amines will also be sorbed and eluted using the optimized isolation method but they typically have molar yields that are orders of magnitude lower than tertiary amines.

Hydrophobicity may also control sorption, and Table 5-2 shows that some NDMA precursors may have hydrophobic groups. These groups probably control the sorption to C_{18}, HLB and activated carbon. MCX and SCX most likely outperformed these sorbents for several reasons; Activated carbon is difficult to elute due to multiple surface functionalities; while HLB and C_{18} elute well, hydrophobic forces (e.g., van der Waals) are weaker forces than polarity (e.g., electrostatic); MCX is a mixed mode resin, containing both hydrophobic groups and cation exchange sites. Therefore, MCX takes advantage of the potential for tertiary amine NDMA precursors to be ionized and their potential to contain hydrophobic moieties.

Table 5-2 Structures, pKa, and partitioning of selected model NDMA precursors. Some molar yields estimated from figures. Molar yields from multiple sources (Hanigan *et al.*, 2015a; Mitch *et al.*, 2009; Selbes *et al.*, 2013; Shen and Andrews, 2011b)

Chemical name	Structure	Teriary amine pKa (Chemicalize.org, 2013)	pH 8 Log D_{OW} (Chemicalize.org, 2013)	NDMA FP molar yield
Dimethylisopropylamine		10	-1.0	84%
Ranitidine		8	0.6	90%
Methadone		9.1	3.9	60%
Venlafaxine		8.9	1.8	<1%
Carbinoxamine		8.9	2.35	1%
Nizatidine		6.5	0.73	8%
Dimethylamine		10.5	-2.64	0.1%–1%

NDMA precursor recoveries from surface waters. The optimized isolation method was applied to 11 surface water samples with varying degrees of agricultural, wastewater, biological, and industrial impact and one secondary wastewater effluent. Source water characteristics, NDMA FP recoveries in the isolates, and overall NDMA FP recoveries are shown in Table 5-1. DOC, TDN, and NDMA FP ranged from 2.5 to 6.9 mgC/L, 0.4 to 4.8 mgN/L, and from 21 to 602 ng/L, respectively. The reconstituted NDMA FP precursor recoveries ranged from 41% to 168%, with a mean and median of 84% and 82%, respectively. The sample with the lowest recovery had the highest TDN of any surface water (4.8 mgN/L), although it is unclear how this may affect precursor retention and recovery. Other cations (Ca^{2+}, K^{+}, Na^{+}) that may overload the cartridge and interfere with organic base sorption were not measured.

The sample with highest recovery is likely affected by the greatest by experimental error associated with multiple measurements of low NDMA FP concentrations (40 ng/L in raw water) (see Table 5-1). No correlation was found regarding recovery of precursors in the isolates and DOC, TDN, conductivity, NDMA FP, or SUVA, of the raw water (Figure 5-6, Figure 5-7, Figure 5-8, Figure 5-9, and Figure 5-10, respectively) indicating that none of these characteristics individually controlled recovery of precursors.

To further determine breakthrough of NDMA precursors, the effluent of the cartridges was collected during the extractions of most samples. We conducted quantitative mass balances on UV_{254} and NDMA FP and qualitatively on total fluorescence. Mass balances on TOC could not be conducted because methanol was used to pre-clean the columns and interfered with analysis of the column effluents. The majority of the UV_{254} absorbing material was typically found in the effluent of the column, with little in the reconstituted samples. Total fluorescence was similar, with most of the raw water fluorescence being found in the effluent and little fluorescence typically in the reconstituted sample. In some cases, the effluent sample visually fluoresced to a greater extent than the influent (Figure 5-4). It is possible this is due to some fluorescent organic matter leaching into the effluent from the cartridge itself, or, more likely, a reduction in ionic quenchers of fluorescence in the effluent compared to the raw water. Therefore, it does not appear that there is a correlation between UV absorbance of fluorescence and NDMA FP. While we have previously shown a weak correlation between fluorescence and NDMA FP (Krasner *et al.*, 2015), it is more likely that fluorescence is an indicator of WW that contains NDMA precursors, rather than the precursors themselves being detected by fluorescence.

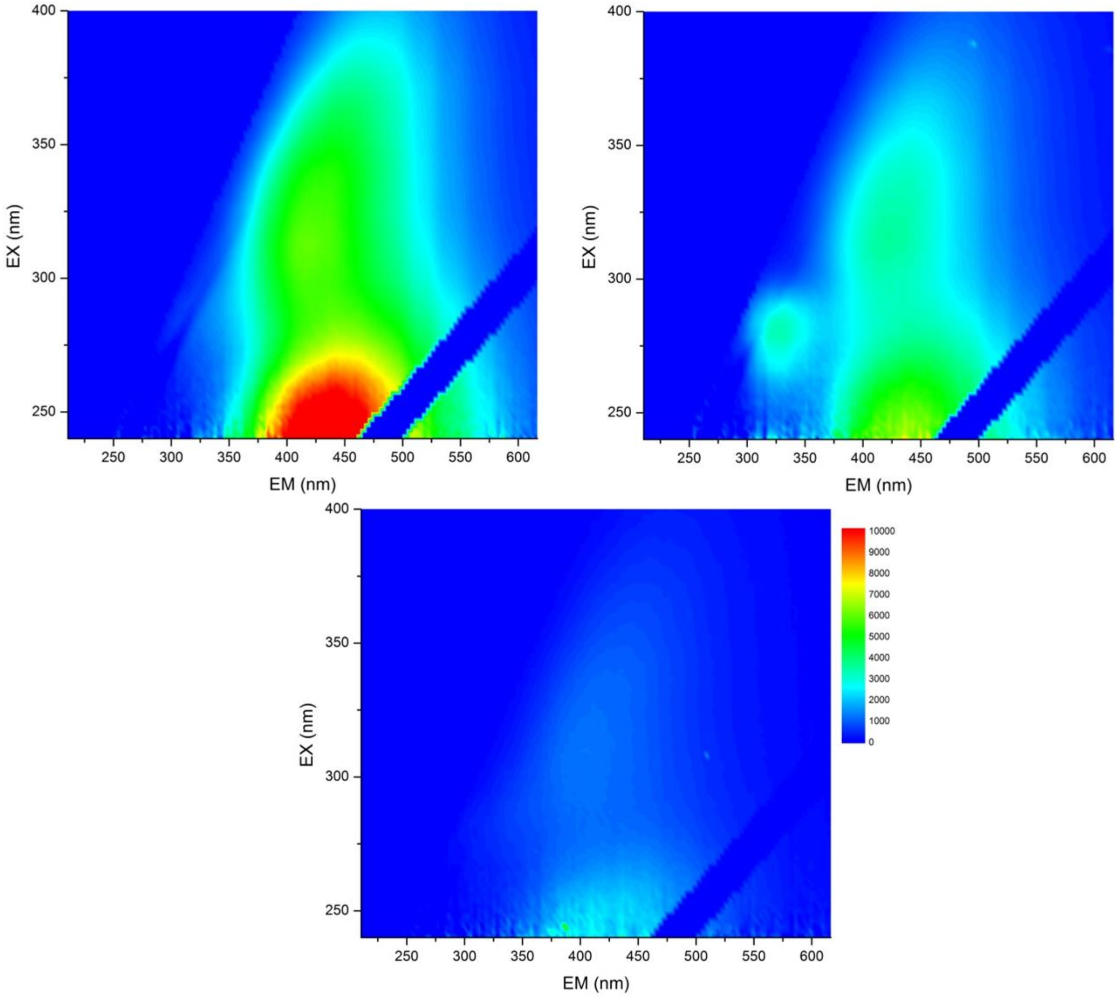


Figure 5-4 Excitation–emission matrices of a Canadian surface water. From top left: raw water, MCX column effluent, reconstituted sample from methanol isolate containing NDMA precursors. All are shown with the same scale

NDMA FP tests on the effluent of the columns were also conducted, and an overall mass balance on NDMA precursors was calculated. Total mass recovery ranged from 68% to 235% with a median of 124%. To determine the source of elevated overall mass recovery, a Milli-Q water sample was loaded onto a MCX cartridge in triplicate following the optimized protocol. Although the cartridges were rinsed with methanol and HPLC grade water prior to column loading, column effluents of Milli-Q loaded MCX columns contained 12 ±1 ng/L NDMA FP. Thus, some precursors leached from the cartridges into the collected effluents. When 12 ng/L was subtracted from all column effluent samples, the recalculated mass balances ranged from 58% to 205% with a median of 103% (Table 5-1). The highest and lowest recoveries again are associated with the two samples previously discussed to have the highest and lowest recoveries in the isolates, which impacts the overall mass balance.

We attempted to quantify the variability in the total method using a known NDMA precursor. A potent NDMA precursor, methadone, was discovered in isolates obtained using the method described herein followed by liquid chromatography coupled to quadrupole time of flight mass spectrometry (qTOF-MS). Following the discovery, we purchased an isotopically labeled standard to give some insight into the variability of the MCX cartridges for recovery of amines (Hanigan *et al.*, 2015a). The qTOF-MS method used to discover methadone will be the subject of a future publication and is outside the scope of this work. The isotopically labeled methadone was spiked into 6 L of wastewater, and the samples were extracted in sextuplet. When quantified in the extracts, methadone (unspiked) and labeled methadone (spiked) concentrates had coefficients of variation of 30% and 29%, indicating the variability in recovery of this model compound. Coefficients of variation in recovery NDMA FP from the surface waters and wastewater triplicate cartridge loadings also reflect this cartridge-associated variability; the mean coefficient of variation for all samples was 15%. One sample with higher variability had low NDMA FP, exacerbating experimental error. Excluding this sample, the mean coefficient of variation was 6.5%. Due to the variability in recovery efficiency, we recommend extraction of a sample with at least three cartridges (triplicate extractions in this work), resulting in eluates that can be analyzed separately to search for NDMA precursors, combined to create a composite sample, or combined and then further evaporated to create a concentrated composite. Finally, future work might evaluate the benefits of pre-cleaning the cartridges with alkaline methanol, followed by an acidic water rinse.

5.5 Conclusions

NDMA precursor discovery has been slow, with researchers proposing precursors and testing them individually for transformation to NDMA upon chloramination. Little knowledge of precursor occurrence is typically gathered, and, thus, the contribution to NDMA formation and their relevance as precursors is unknown. In this work, we provide the foundation for discovery of NDMA precursors that are responsible for NDMA formation in complex environmental samples. The method takes advantage of ionizable tertiary amines and concentrates most precursors 1,000 fold into an organic solvent. The resulting isolates are amenable to analysis using multiple mass spectrometry tools. In most samples, recovery was near 80% but in some cases recovery was either too low or too high to be considered successful. Nonetheless, in these samples the method was still successful at isolating some NDMA precursors which could be subsequently identified and confirmed to exist in the raw samples.

Using samples generated with the described method and further mass spectrometry techniques, our group has discovered methadone as an NDMA precursor and quantified its possible contribution to NDMA formation (Hanigan *et al.*, 2015a). This was the first discovery of an NDMA precursor of importance using this method and is an example of the contribution of this method to the field.

5.6 Acknowledgements

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5.7 Supporting Information

GC-MS analysis of methadone. The extract solution was analyzed using Gas Chromatography Mass Spectrometry on an Agilent 6890/5973 inert GC/MS system (Agilent, Santa Clara, CA). The system was equipped with an Agilent HP-5MS column (0.25mm x 30m×0.25µm, Agilent Santa Clara, CA). Helium was used as carrier gas at a constant flow rate of 1.2 mL/min. A generic temperature protocol (i.e., not optimized for methadone) was used in scan mode. In brief, 1 µL of sample was injected. The injector temperature was set at 300°C. The oven temperature started with a hold at 65°C for 10 minutes followed by an increase to 300°C and a final hold for 20 minutes at 300°C. The MS transfer line was set at 275°C, and the MSD was operated in electron impact mode and scanning from m/z 50 to 500 Da. Compound identification and quantification was performed using an authentic methadone standard.

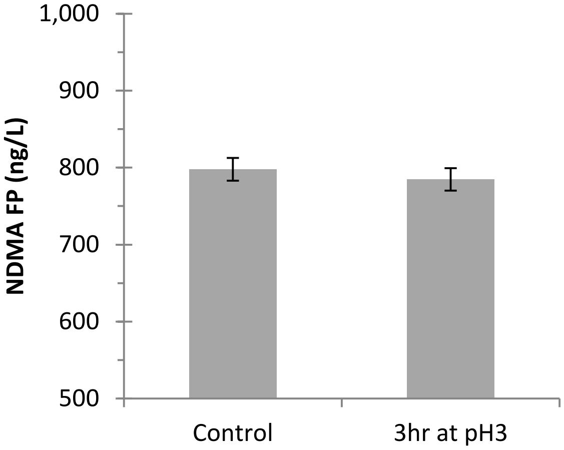

Figure 5-5 NDMA FP of wastewater secondary effluent held at pH 3 for the approximate time of SPE loading vs a neutral pH control sample

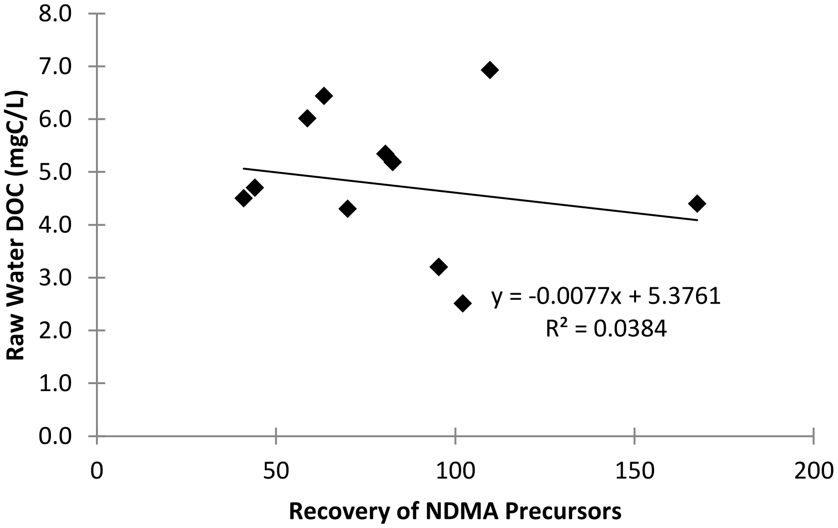

Figure 5-6 Recovery of NDMA precursors into methanol isolate and raw water DOC

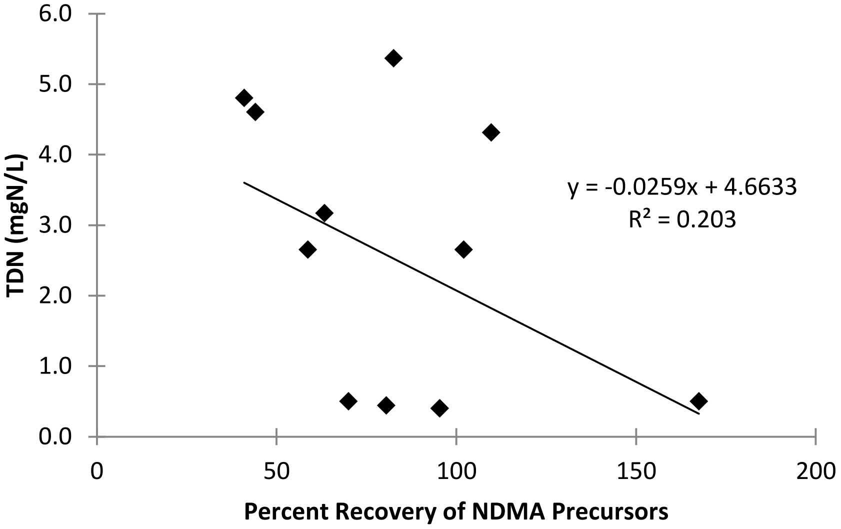

Figure 5-7 Recovery of NDMA precursors into methanol isolate and raw water TDN

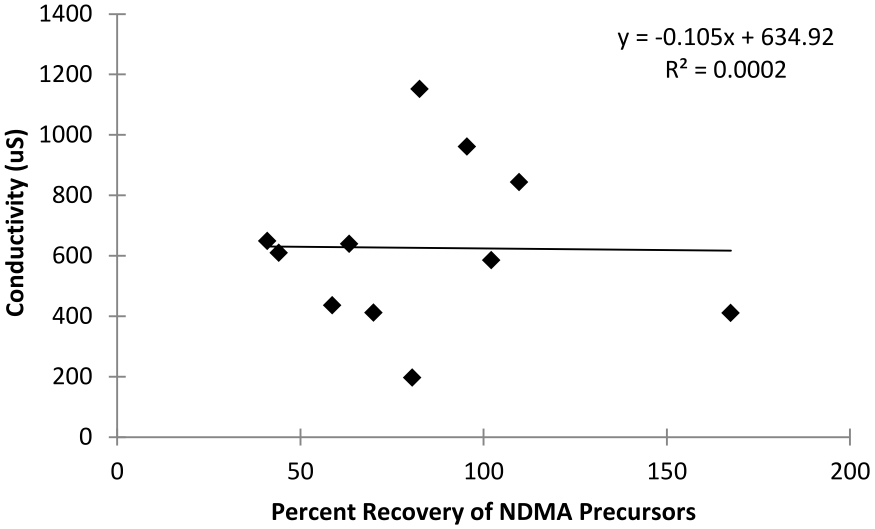

Figure 5-8 Recovery of NDMA precursors into methanol isolate and raw water conductivity

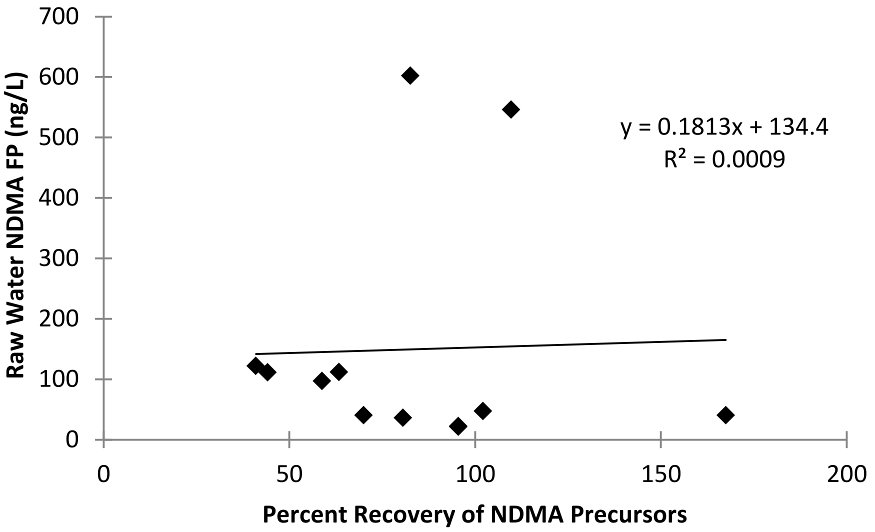

Figure 5-9 Recovery of NDMA precursors into methanol isolate and raw water NDMA FP

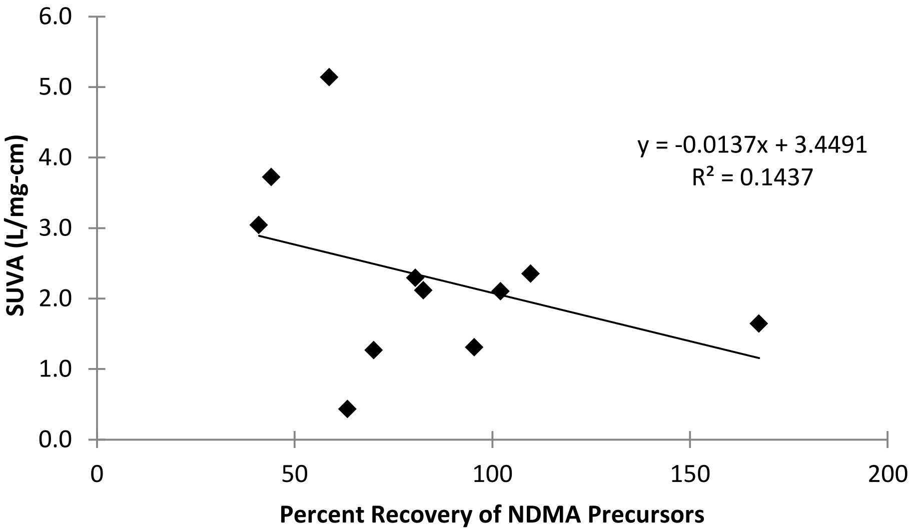

Figure 5-10 Recovery of NDMA precursors into methanol isolate and raw water SUVA

6 Hanigan Neutral Ion Fragment Trawler

This chapter has been prepared as part of a manuscript to be submitted by E. Michael Thurman and Imma Ferrer to the Journal of Chromatography A in 2015.

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6.1 Introduction

Time-of-flight mass spectrometry (TOF-MS) is a useful tool for characterizing complex environmental matrices. The greatest difference between TOF-MS and quadrupole MS is way in which mass to charge ratio is determined. Both may have multiple front-end separation configurations (gas/liquid chromatography), ion source configurations (electrospray, atmospheric chemical ionization, electron ionization, and chemical ionization), an additional collision cell and mass filter, or other changes to the system that are not specific to either TOF-MS or quadrupole MS. However, TOF-MS uses an ion modulator to pulse electrons to the detector, and the instrument records the time from modulator activation (pulse) to detection. Heavier (greater mass to charge ratio [m/z]) ions take more time to impact the detector, and, therefore, a full m/z range spectrum for each pulse can be calculated from the recorded pulse to impact times for multiple m/z ions simultaneously.

In contrast to TOF-MS, quadrupole MS relies upon a mass filter (quadrupole) in front of the detector. Therefore, an impact at the detector is assumed to be an ion of m/z equivalent to that at which the mass filter is set. The mass filter is typically capable of scanning individual m/z, resulting in full m/z spectrum collected over the time it takes the mass filter to scan the selected range. The time spent collecting a single m/z divided by the time taken to scan the full m/z range is referred to as the duty cycle.

The two greatest advantages of TOF-MS over quadrupole MS are improved duty cycle and higher mass accuracy. Quadrupole MS in scan mode results in a duty cycle of approximately 0.1%. While, intuitively, TOF-MS might seem to achieve 100% duty cycle because it collects all ions simultaneously, in reality the duty cycle is closer to 5%

to 30% (Chernushevich *et al.*, 2001). This is because the modulator is not activated continuously and must be pulsed in a manner that allows the slowest ion to reach the detector before a subsequent pulse. Nevertheless, TOF-MS results in significantly increased sensitivity over quadrupole MS and is therefore excellent at characterizing unknowns in complex environmental samples.

Additionally, TOF-MS typically results in <5ppm mass accuracy, approximately 10 times greater than quadrupole MS (Chernushevich *et al.*, 2001). Extending the flight path length in TOF-MS directly or through ion mirrors increases the accuracy by separating higher and lower mass ions to a greater extent. The accuracy in quadrupole MS is limited to the accuracy of the quadrupole mass filter, which cannot be as easily improved. This is due to the constraints of the mass filter electronics (radio-frequency field generator) and physical manufacturing of the quadrupole elements versus the nearly limitless length of the flight path in TOF-MS. The increased accuracy of TOF-MS allows for great enough discrimination to propose elemental compositions directly from mass measurements and is preferred for identifying molecules in complex matrices from proteins in serum to pharmaceuticals in the environment.

In order to definitively identify compounds, it is valuable to collide ions of a certain m/z with a gas to produce fragment ions. This is done with the help of additional quadrupoles (either quadrupole TOF-MS [QqTOF] or triple quadrupole MS [MS/MS]). The first additional quadrupole (Q1) is used as a mass filter, while the second serves as a collision cell (Q2) that can be filled with gas. In MS/MS, this results in three quadrupoles with the third acting again as the mass filter for the detector (Q3), similar to conventional quadrupole MS. In QqTOF, this results in two quadrupoles; the first (Q1) again acts as a mass filter, the second (Q2) is filled with collision gas, but in this case the third quadrupole is replaced with the TOF-MS.

Fragment ions (daughter ions) can help to confirm proposed structures when Q2 is filled with an inert gas and Q1 is set to discriminate for the parent ion. In some cases when using MS/MS, Q1 is set to scan while Q3 filters for only a specific m/z, known as a diagnostic ion. Diagnostic ions are used when part of a full structure is known and is potentially cleavable in the collision cell. QqTOF has the advantage of the TOF-MS being sensitive enough that Q1 can be set to guide all ions to the collision cell (turned "off" or acting as ion optics only) and still have enough mass accuracy to discriminate for the diagnostic ion. Figure 6-1 shows an example of the cleaving of a diagnostic ion from dimethylphenethylamine.

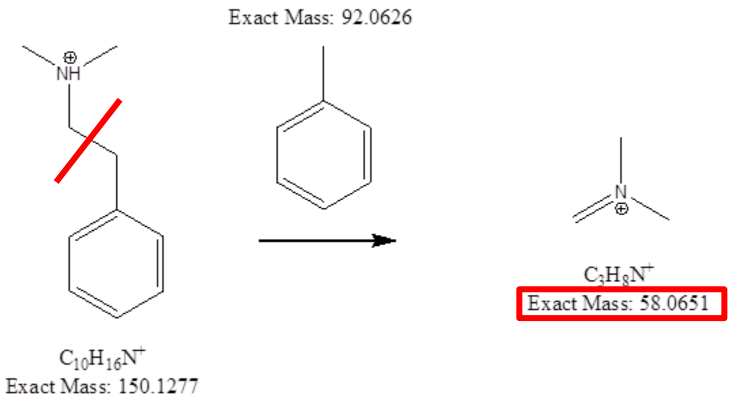

Figure 6-1 Predicted fragmentation pattern to produce a 58.0651 m/z ion and 92.0626 amu neutral loss for the model NDMA precursor, dimethylphenethylamine

Moreover, should the diagnostic fraction of the structure form a neutral loss that does not retain a charge and cannot therefore be directly detected, Q1 and Q3 in MS/MS can be set to filter a specific delta m/z (the neutral loss diagnostic fragment). The resulting ions detected are the parent and daughter ions. The neutral loss is removed by the vacuum pump. An example of a neutral loss from dimethylphenethylamine is shown in Figure 6-2. Although neutral loss scans have been in use since in MS/MS applications since at least 1976 (Dayringer *et al.*, 1976), unfortunately, Q1 in QqTOF is not able to scan on current instruments, and, therefore, neutral loss experiments are impossible directly and require manual examination of spectra.

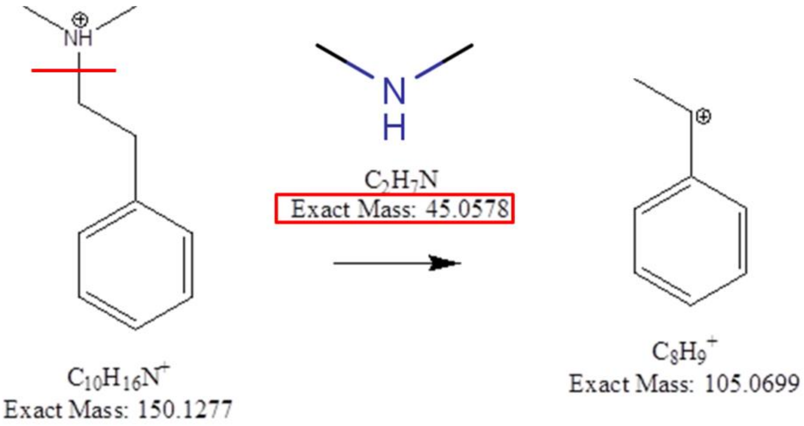

Figure 6-2 Predicted fragmentation pattern to produce a 45.0578 amu neutral loss from the model NDMA precursor, dimethylphenethylamine

The objective of this chapter is to circumvent the issue of conducting neutral loss diagnostic searches with QqTOF. This will combine the advantages of TOF-MS (high mass accuracy, high duty cycle and sensitivity) and of MS/MS (neutral loss searches).

6.2 Methods

Isolated samples produced in Chapter 5 were injected via Agilent 1290 UPLC (Agilent Technologies, Santa Clara, CA) onto a C_8 column for separation followed by an Agilent 6450 QqTOF equipped with electrospray Jet Stream ionization source. Because of the conclusion from Chapter 5, that NDMA precursors are probably tertiary amines, and because most tertiary amines will have a pK_a of greater than 6, we used a mobile phase of 0.1% formic acid in water (pH~2.7) and operated the ionization source in positive mode. This operation decision was based on finding tertiary amines and may have biased our findings. Organic matter that is not amenable to positive electrospray is neglected by this method. More information on the UPLC and MS conditions can be found in Section 7.6.

MassHunter v6.1 (Agilent Technologies, Santa Clara, CA) was used to collect and export the data. The MS spectra across the range of 50 to 1000 m/z was recorded and exported for elapsed time windows coinciding with the top 100 greatest area peaks. The start and end elapsed time (exported time window) of these exported spectra is determined by MassHunter and ultimately determined by the width (elution time) of the individual greatest 100 peaks by area. I was not necessarily interested in the greatest 100 peaks by area. However, these spectra contain the peak that flagged the specific time window for exportation (one of the 100 greatest area peaks) but also all other ions impacting the detector during the exported time. MassHunter did not allow for direct exportation of time resolved spectra and so I determined this to be the best alternative. Although this does not result in complete exportation of the spectra for the 30 minute run, it results incidentally in exportation of 100 spectra with time windows that collectively encompass approximately 75% of the total injection run time. See Figure 6-3 for an example of one exported spectra from one sample.

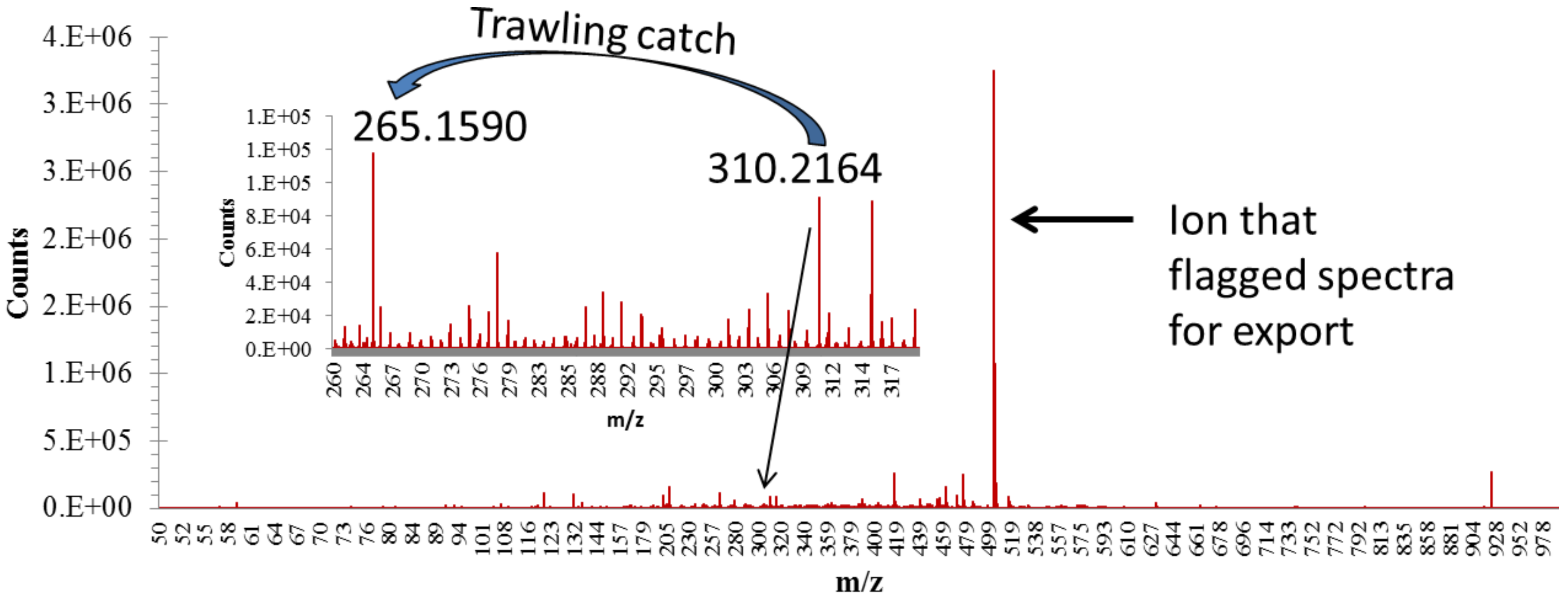

Figure 6-3 Example of spectra trawling and a catch that later was confirmed to be methadone. This spectra contains all peaks that eluted from 16.7 to 17.3 min of a 30 min injection run time. This time step was flagged for exportation because of the peak at ~500 m/z, which eluted during this time step and was one of the 100 greatest area peaks that eluted during the run. The trawler program was written in MATLAB® to search for exact neutral losses of 45.0578 amu and reported the 310.2164 m/z parent – 265.1590 m/z daughter ion pair here that was later confirmed to be methadone.

I wrote a MATLAB® program to search the 100 spectra of each of the associated 11 samples for neutral losses of exactly 45.0578 ±0.0005 amu. This mass represents the loss of a dimethylamine structure which was determined to be important to the formation of NDMA in Chapter 2. I call this program a trawler as it searches the entire spectra indiscriminately, including baseline noise, similar to a bottom trawl net using in commercial fishing. This structure can also be searched for by searching for 58.0651 m/z daughter ions (Figure 6-1), which the software and instrumentation were capable of doing without modification, and this is not the subject of this chapter. The mass error of 0.0005 amu was chosen is because it is the approximate mass accuracy of the instrument. The searches were achieved by moving through each of the exported m/z in the exported time window, calculating the neutral loss associated daughter ion mass (subtracting 45.0578 amu), and checking the spectra for the daughter ion m/z within the error window. Again, there were 100 exported time windows for each sample, meaning that each time window was relatively short (10ths of minutes) and so all ions at this stage were assumed to be associated due to similar elution times. As the program trawls the spectra, the daughter ion check (subtraction of 45.0578 amu and searching for daughter ions of the appropriate m/z) is skipped if the parent ion does not produce ion counts greater than 10,000. Hits are also disregarded if the daughter ion match is less than 10,000 ion counts. These threshold values were chosen because they are near the lower limit of signal to noise. The output of the program (the “catch”) is the exported ion number (1 to 100 number associated with the exported top 100 ions), parent/daughter ion m/z pairs, the calculated deviation from the exact neutral loss, and the ion count intensities for both ions. Using the 1 to 100 export number, a retention time can be determined by inspecting the export headers and further confirmatory experiments can be conducted. The trawler code was written for MATLAB® and is included as Appendix B but could be easily adapted to open source coding environments such as R because it contains only simple addition and subtraction (R Development Core Team, 2012).

6.3 Results

Trawling of samples isolated in Chapter 5 produced 331 hits that are yet to be further investigated. These catches are included as Appendix C. Notably, the initial exported spectra of the 11 samples contained 5.7 million ions and therefore distillation to ~300 ions was considered successful. Further distillation of the hits by removing duplicate reported parent/daughter ion pairs in each sample resulted in a total of 181 hits for the 11 samples (Figure 6-4). SW 5 is known to contain nearly 100% wastewater during low flow and therefore was expected to contain a high number of ion pair hits.

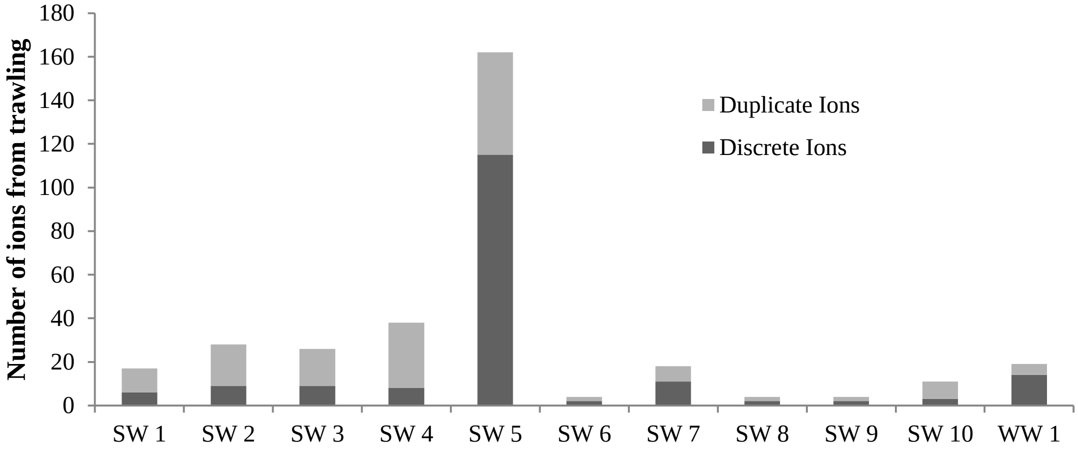

Figure 6-4 Total number of 45.0578 ±0.0005 amu neutral losses in isolated samples

Removal of duplicate parent/daughter ion pairs across samples resulted in 141 ion pairs to be investigated. An ion pair was considered a duplicate if another ion pair was within the error of the instrument (0.0005 amu). Further duplicate removal could be achieved by increasing this error limit and approximately 1/3 of the remaining hits are probably duplicates based on being very near this error threshold. Confirmation of duplicates could be investigated using manual inspection of the spectra and retention time. These 141 hits should be the first to be investigated as potential NDMA precursors including retention time match confirmation between parent and daughter ion pairs, and identifying the structures associated with the exact mass of the parent ion.

Matches are difficult to interpret without inspecting the spectra using the original data file produced by the instrument and the MassHunter software. The ability to rapidly inspect the spectra for other potential daughter ions, isotope ratios, etc. that give clues to the potential structure of a parent ion is invaluable in this process. Of the 181 discrete ion pairs caught during spectra trawling, I attempted to identify structures that match the exact mass of five compounds that occur the most frequently between samples.

Of the five, I found one potential match containing a tertiary amine by querying Chemspider (ChemSpider) for M+H with monoisotopic mass of 209.1287 and sorting the results by number of references. The results are sorted by number of associated references in Chemspider as this likely produces rough sorting by environmental relevance. Aminocarb was the match and is used worldwide as an insecticide. This peak is in 7 of 10 surface water samples isolated and is absent in the wastewater sample, which would be expected for an insecticide. I was not able to identify the other four most commonly occurring ion pairs because there were too many potential matches in

Chemspider to effectively sort and most did not contain tertiary amines. Further work to identify these compounds would involve MS/MS experiments to gain insight into ion fragmentation, isotope pattern spacing, fragment structural analysis, and other database extractions (Merk index) (Thurman *et al.*, 2005; Thurman and Ferrer, 2010). Investigation should be conducted using the distilled list of hits with duplicates removed and the MassHunter software. Ion hits could be prioritized by ion intensity, which might roughly correlate with concentration, assuming equal ionization efficiency.

One example of a hit that has been investigated thoroughly was the pharmaceutical methadone, which is the subject of Chapter 7. This is a good example of trawling, as methadone was discovered as a small peak that would have been near impossible to find by manual inspection of the full spectra (Figure 6-3). In brief, this compound was discovered initially as a 310.2164 m/z parent ion with a daughter ion of 265.1590 m/z corresponding to the loss of a dimethylamine structure (45.058 amu). The 310 exact mass was used to propose an elemental composition in the MassHunter software. The structure from MassHunter was $C_{21}H_{28}NO^{+}$. Because of the ionization source was in positive ionization with 0.1% formic acid in the eluent, the compound was assumed to be protonated and a proton was removed for database searches to identify the structure from the elemental composition. $C_{21}H_{27}NO$ was used to search the online database Chemspider (ChemSpider) and, when sorted again by the greatest number of associated references, resulted in the putative identification of the compound as methadone.

Subsequent experiments involved using Q1 to filter the wastewater sample ions, only allowing methadone to pass to the collision cell, and subsequent collisionally induced dissociation for fragmentation to identifiable daughter ions. Methadone was also confirmed using an authentic standard and retention time. More information about the confirmation of methadone is given in Chapter 7.

6.4 Conclusions

Although we are not the first to conduct neutral loss searches for a diagnostic loss, we believe we are the first to develop a MATLAB® program to search for neutral losses with a TOF-MS. The program takes advantage of the sensitivity of TOF-MS and was developed and used to flag neutral losses associated with the dimethylamine structure. 331 ions were identified as parent ions that likely produce the exact mass dimethylamine neutral loss that we believe is characteristic of NDMA precursors. These ions are potential NDMA precursors based on this loss and the next step should be to attempt to identify these compounds followed by NDMA yield tests in the presence of chloramines.

Because very few NDMA precursors have been identified in environmental water samples, it is not yet possible to account for the total NDMA formation of a sample by quantifying precursors present. Based on our first identification, methadone, these 331 ions may potentially close the gap between quantifiable NDMA precursors with known yields and the total NDMA formation of a water sample, which, combined with structural matches, might provide insight into potential drinking water NDMA formation mitigation strategies. Furthermore, the MATLAB® program can be used in other future applications to combine the advantages of neutral loss searches from MS/MS instruments and the mass accuracy and sensitivity of TOF-MS instruments.

7 Methadone Contributes to *N*-nitrosodimethylamine Formation in Surface Waters and Wastewaters during Chloramination

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7.1 Abstract

N-nitrosodimethylamine (NDMA) is a probable human carcinogen that forms in drinking water as a disinfection by-product. Several specific precursor chemicals present during chloramination are known but cannot account for the total observed NDMA formation potential (FP) in drinking waters. We discovered a pharmaceutical precursor of NDMA with high FP using a liquid chromatography/quadrupole/time-of-flight mass spectrometry (LC/QTOF-MS) screening procedure. The pharmaceutical methadone, which is used to mitigate heroin withdrawal symptoms and is also prescribed for chronic pain, contains a dimethylisopropylamine functional group that reacts to form high amounts of NDMA upon chloramination. In this study, methadone had a molar NDMA yield ranging from 23% to 70% dependent upon chloramine dose (1 to 150 mgCl$_2$/L) and was responsible for between 1 and 10% of NDMA FP in most raw surface waters in which it was detected and up to 62% of NDMA FP in wastewater. Samples with higher methadone concentrations had greater NDMA FP. We measured a median methadone concentration of 23 ng/L with a range of 1 to 2,256 ng/L among detections, which was consistent with high occurrence rates and environmental persistence for methadone in the published literature for surface waters and wastewaters. A literature review of methadone use, metabolism, and fate in the U.S. resulted in a prediction of low ng/L levels of methadone-associated NDMA FP at drinking water treatment plants (DWTPs) downstream of communities using methadone. Medicinal use of methadone potentially displaces and transforms the health risks associated with heroin use by individuals to possible cancer risk for populations served by downstream DWTPs. This work is among the first to contrast known public health benefits of pharmaceutical-taking patients

against the potential exposure of millions of people to physiologically-relevant levels of carcinogenic NDMA in chloraminated drinking water.

7.2 Introduction

N-nitrosodimethylamine (NDMA) is a disinfection by-product (DBP) of regulatory concern due to its carcinogenic potential and occurrence (Peto *et al.*, 1991; USEPA, 2006a). Health Canada, Massachusetts, and California have set regulatory limits, guidance limits, or notification levels in the 10 to 40 ng/L range (California Department of Public Health, 2013; Health Canada, 2011; Massachusetts Department of Energy and Environmental Affairs, 2004). NDMA forms in drinking water from a reaction between chloramines and predominantly unidentified organic nitrogen precursors, and these precursors appear to be strongly linked with the presence of treated wastewater (Krasner *et al.*, 2008; Krasner *et al.*, 2013). While several model compounds produce NDMA upon chloramination (Chang *et al.*, 2011; Kemper *et al.*, 2010; Le Roux *et al.*, 2012a; Selbes *et al.*, 2013; Shen and Andrews, 2011b), either their NDMA yields are low or the occurrence is too low at the point of chloramination to account for NDMA formation (Krasner *et al.*, 2013; Mitch and Sedlak, 2004). The only current options to remove NDMA precursors in drinking water treatment plants (DWTPs) are nonselective control strategies (e.g., activated carbon or pre-oxidation), which are potentially cost prohibitive or confounded by unintended consequences such as formation of other DBPs (Sedlak and von Gunten, 2011). Without knowledge of precursor chemical structures and characteristics, mitigation strategies for NDMA formation in DWTPs are difficult to optimize.

Current research regarding NDMA precursors is limited to applying chloramines to model compounds that contain organic nitrogen. Wastewater is well known to contain higher amounts of NDMA precursors (Krasner *et al.*, 2008), and thus there has been a significant effort to identify pharmaceutical and personal care products present in wastewater that are NDMA precursors (Shen and Andrews, 2011b). Other research has focused on agricultural runoff and led to the discovery that diuron, a herbicide, produces NDMA upon chloramination (Chen and Young, 2008). This approach has led to discovery of multiple NDMA precursors with a range of molar NDMA yields but the occurrence of such compounds in DWTP intakes is either unknown or not great enough to account for a significant fraction of the total NDMA formation potential (FP) of the water (Mitch and Sedlak, 2004). For example, ranitidine has high NDMA yield upon chloramination but no occurrence, and dimethylamine has high occurrence but is only responsible for low ng/L levels of NDMA due to low NDMA yield. However, both the occurrence of anthropogenic chemicals in the environment (Kolpin *et al.*, 2002) and the wastewater content in U.S. surface water are increasing (Rice *et al.*, 2013), and therefore it is likely that NDMA precursor loadings will consequently increase. In addition, 22% of the U.S. population was served with chloraminated drinking water in 2010, an increased from 19% in 2007 (Li, 2011). Thus, discovering NDMA precursors with moderate to high yield that are likely to occur in surface water could lead to targeted treatment strategies that reduce NDMA formation and thus cancer risk to end users of chloraminated drinking water.

Methadone is a pharmaceutical that contains organic nitrogen (tertiary amine) and is typically used to treat heroin addiction, but is becoming more commonly prescribed for chronic non-cancer pain and to mitigate withdrawal symptoms associated with prescription opiates (e.g., morphine) (Paulozzi *et al.*, 2012). In the U.S. in 2009, 4.4 million methadone prescriptions (approximately 1.5/100 U.S. persons) were issued, which includes only methadone distributed for pain relief and not to substance abuse treatment centers (Kenan *et al.*, 2012; Paulozzi *et al.*, 2012). In 2013, there were 330,308 persons (approximately 1/1,000 U.S. persons) being treated with methadone for substance abuse, which was 26% of all U.S. substance abuse clients (Substance Abuse and Mental Health Services Administration, 2014). The 2014 production quota of methadone in the U.S. was 31,875 kg, or approximately 274 mg day^{-1} 1000 U.S. persons^{-1} (Drug Enforcement Administration Office of Diversion Control, 2014). Methadone use is marginally lower in Europe, where use was reported as 0.3–232 (Boleda *et al.*, 2009), 138 (van Nuijs *et al.*, 2011), 148 (Terzic *et al.*, 2010) (estimated from concentrations in WWTPs), and 97 (Baker *et al.*, 2014) (National Health Service data) mg day^{-1} 1000 people^{-1}, in Spain, Belgium, Croatia, and the United Kingdom, respectively.

Approximately 28% of ingested methadone is excreted in the urine as unmetabolized drug (although this varies from 10-60% based on patient sex and urine pH) (Baselt and Casarett, 1971; Bellward *et al.*, 1977; Ferrari *et al.*, 2004; Inturrisi *et al.*, 1987; Leimanis *et al.*, 2012; Nilsson *et al.*, 1982). EPISuite modeling and occurrence data predict methadone removal in wastewater treatment plants (WWTPs) to be low (27% (USEPA, 2015) and 0 to 44% (Baker and Kasprzyk-Hordern, 2011; Berset *et al.*, 2010; Bijlsma *et al.*, 2012; Boleda *et al.*, 2009; Subedi and Kannan, 2014; Terzic *et al.*, 2010), respectively). Methadone removal in the environment is also predicted to be slow, having a predicted lifetime of several months (USEPA, 2015). Estimated NDMA FP from methadone in DWTPs downstream of WWTP effluents results in one to tens of ng/L NDMA, which is typical for DWTPs of this nature (See Health Implications). Pre-oxidation and granular activated carbon (GAC) remove methadone well in DWTPs (Subedi and Kannan, 2014), which is similar to what has been seen previously for NDMA FP reduction (Hanigan *et al.*, 2012; Krasner *et al.*, 2015). Methadone therefore likely has the characteristics (occurrence and environmental persistence) to be a precursor of importance to NDMA formation.

The goal of this research was to identify NDMA precursors in surface water and wastewater that have high occurrence and high NDMA molar yield. Our approach was to use liquid chromatography/quadrupole/time-of-flight mass spectrometry (LC/QTOF-MS) with accurate mass to identify NDMA precursors via neutral loss fragmentation of the dimethylamine structure, which may form NDMA upon chlorination. If successful, this approach will be useful to identify new NDMA precursors to suggest new treatment techniques or DWTP source water protection strategies. This paper details the approach and identifies methadone, a pharmaceutical that has not been previously reported as a precursor of NDMA in surface water and wastewater.

7.3 Materials and Methods

A list of reagent chemicals and a description of the analytical methods can be found in the supporting information (SI). Surface waters (n=10) and the secondary effluent of a wastewater treatment plant were collected from across the U.S. and Canada between August 2014 and February 2015. The wastewater plant treated 45,000 m^3/d (roughly 120,000 people at 378 L/d) and was selected because we have conducted research at this facility located near our laboratories for over a decade (Chen *et al.*, 2003;

Upadhyay *et al.*, 2011). Samples ranged in organic matter characteristics (dissolved organic carbon from 2.5 to 6 mgC/L and total dissolved nitrogen from 0.4 to 5.4 mgN/L) and in the potential contribution from upstream wastewater and agricultural sources. The sample locations are known to have relatively high NDMA FP (20 to 600 ng/L) and thus were expected to have high concentrations of NDMA precursors.

Samples were shipped overnight in coolers with ice packs within 24 hours of collection. Immediately upon arrival, samples were filtered with pre-combusted Whatman GF/D filters (2.7 µm nominal pore size, GE Healthcare, Piscataway, NJ) to remove colloids and particles that may impede solid phase extraction. The filtered samples were stored in a refrigerated (4°C) chamber for a maximum of one week before extraction/isolation.

NDMA FP tests for methadone yield and kinetics (details contained in the SI) were conducted on the filtered water or Milli-Q™ water. A method to capture and elute NDMA precursors was developed, and recovery of precursors into cation exchange (Oasis MCX) isolates ranged from 41 to 168% (coefficient of variance from 0.01 to 1.04). The details of this method are given in the SI and will be the subject of a future publication. One fraction of the isolate was reconstituted into Milli-Q™ water and chloraminated under FP conditions to determine recovery of bulk NDMA precursors (reconstituted NDMA FP / raw water NDMA FP = bulk precursor recovery). A second fraction was used for NDMA precursor identification by LC/QTOF-MS and methadone quantification by gas chromatography/mass spectrometry (GC/MS) and liquid chromatography/mass spectrometry (LC/MS). Further details regarding NDMA and methadone quantification as well as a description of the LC/QTOF-MS system can be found in the SI. A blank (Milli-Q™ water) was also isolated to confirm that methadone was not a contaminant leaching from the cation exchange resin, and none was found.

7.4 Results and Discussion

Discovery of a new pharmaceutical NDMA precursor: methadone. Methadone, as an NDMA precursor, was discovered in wastewater using a LC/QTOF-MS screening procedure for the presence of dimethylamine, with a diagnostic loss of 45.058 mass units corresponding to the loss of a dimethylamine structure from the molecule (Figure 7-1). Using data files from the instrument software that were modified with MATLAB®, it was possible to extract ions with the correct diagnostic ion loss of 45.058 from the sample. Further details of the MATLAB® procedure are given in Chapter 6. Using this procedure, an ion with mass of 310.2165 m/z was found in the water sample that had a dimethylamine loss (45.058). The ion gave a formula of $C_{21}H_{28}NO$ (Figure 7-1), which corresponds to over 800 possible structures in ChemSpider for the neutral molecule (ChemSpider). Several accurate mass tools were applied to help determine the structure and identify the unknown, including extraction of diagnostic ions (Ferrer and Thurman, 2012), MS/MS analysis (Ferrer and Thurman, 2012), isotope pattern mass spacing (Thurman and Ferrer, 2010), fragment structural analysis (Thurman *et al.*, 2005), and database extractions (Ferrer *et al.*, 2006). Figure 7-1 shows the results of the MS-MS analysis and structural fragments consistent with a putative methadone identification, which was later confirmed with a pure methadone standard by retention time and MS-MS analysis (Figure 7-4) with accurate mass. A more detailed explanation of the screening and MATLAB® procedure will be discussed in a later publication that presents instrumental analytical techniques for unknown NDMA precursors. Next was to confirm that the dimethylamine loss was consistent with a high NDMA formation potential.

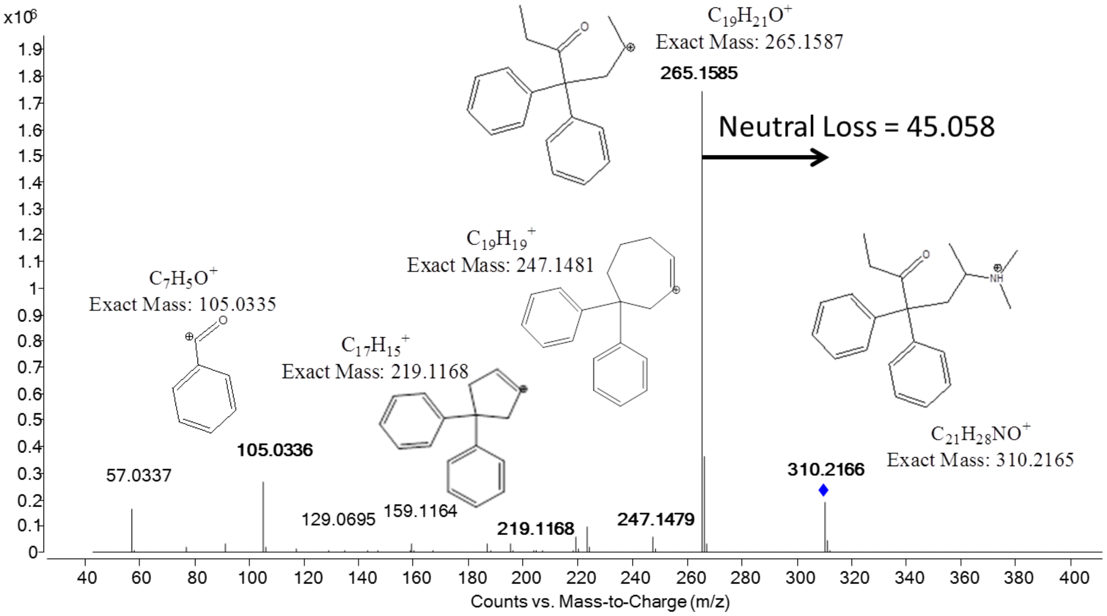


Figure 7-1 MS/MS analysis of wastewater sample with putative structures for methadone fragments, which matches MS/MS analysis of a pure standard with less than 1-ppm mass accuracy. Note the loss of a dimethylamine with a neutral loss of 45.058 mass units

NDMA formation yield and kinetics from methadone. After confirmation of methadone by the LC/QTOF-MS screening procedure, a methadone standard was purchased, added to Milli-Q™ water, and dosed with monochloramine for varying contact times to determine NDMA formation yield and kinetics (Figure 7-2). Methadone forms NDMA at low monochloramine doses (1 to 10 $mgCl_2/L$) and at doses typically used in NDMA FP tests (>10 $mgCl_2/L$). At a dose and contact time commonly used in NDMA FP studies (18 $mgCl_2/L$ for 72 hours), methadone had a molar yield of 60%. At this monochloramine dose, NDMA formation from methadone was moderately slow (Figure 7-2; $K_{app} = 0.035\ M^{-1}\ s^{-1}$ modeled using previously published methods (Zhang *et* *al.*, 2015a; Zhang *et al.*, 2015b)) and within the range of previously observed rates for NDMA formation in a wastewater-impacted surface water (Zhang *et al.*, 2015a; Zhang *et al.*, 2015b). As the monochloramine contact time increased from 0 to 72 hr, NDMA formation from methadone increased, but did not plateau at longer contact times, meaning that our estimate of 60% yield at 72 hr is potentially a conservative estimate with longer contact times.

In addition to the yield under FP conditions, we investigated whether monochloramine dose would affect the total NDMA formed. In Figure 7-2, we show that increasing monochloramine dose increased the NDMA yield of methadone (from 23 to 70% at doses of 1 to 150 mgCl_2/L), a phenomenon that has been similarly observed in other natural and engineered (wastewater) water sources recently by our team (Zhang *et al.*, 2015a; Zhang *et al.*, 2015b).

Methadone is one of only six compounds known to have a molar yield of NDMA in excess of 50% under 72 hr formation potential conditions; the five others are ranitidine (Shen and Andrews, 2011b), dimethylisopropylamine (Selbes *et al.*, 2013), 5-((Dimethylamino)methyl)furan-2-methanol (Le Roux *et al.*, 2012a), dimethylbenzylamine (Kemper *et al.*, 2010; Mitch *et al.*, 2009; Selbes *et al.*, 2013), and N,N-Dimethyl-1-(2-thienyl)methanamine) (Selbes *et al.*, 2013). The other five compounds have not been detected or have not been looked for in wastewater effluents, however published literature reports methadone occurs in both wastewater and surface water (Baker and Kasprzyk-Hordern, 2011; Berset *et al.*, 2010; Bijlsma *et al.*, 2012; Boleda *et al.*, 2009; Chiaia *et al.*, 2008; Mendoza *et al.*, 2014; Subedi and Kannan, 2014; Terzic *et al.*, 2010; Vazquez-Roig *et al.*, 2010; Zuccato *et al.*, 2008).

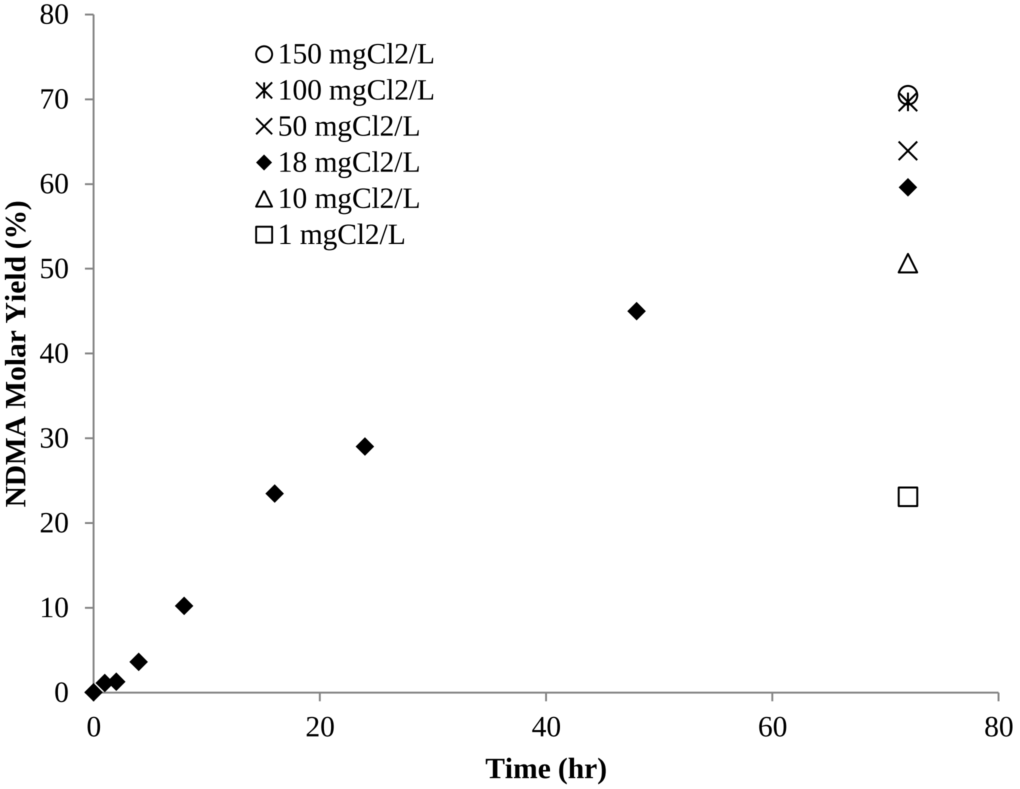


Figure 7-2 NDMA yield from methadone at various contact times and doses. The matrix was Milli-Q™ water borate buffered at pH 8. The data points shown are averages of duplicates with relative deviation <8%

Occurrence of methadone and contribution to NDMA formation. Organic matter from a secondary wastewater effluent sample was isolated using cation exchange (Oasis MCX) in triplicate to search for the DMA structure. After discovering methadone in extracts from a WWTP sample by LC/QTOF-MS (Section 4.1), we quantified methadone in the extracts by GC/MS and found that concentrations ranged from 32 to 2,256 ng/mL (Figure 7-3). Because methadone can degrade in the inlet of a GC (Galloway and Bellet, 1999), we used LC/MS to confirm our quantification, and the results agreed well. Furthermore, although our extraction method was similar to published methadone extraction procedures (Baker and Kasprzyk-Hordern, 2011; Zuccato *et al.*, 2008), our goal during method development was to screen samples for dimethylamine structures. Therefore, an isotopically labeled methadone was not used to quantify losses during solid phase extraction. Consequently, our estimations are likely conservative and inherently variable. When exposed to 18 mgCl$_2$/L monochloramine (the same as that used in our FP tests on the raw water), methadone had a 60% molar yield to NDMA at 72 hr. Using this yield, methadone contributed up to 323 ng/L (assuming 100% recovery across SPE) to the NDMA FP of this water, or up to 62% of the total NDMA formation potential of the non-methadone spiked reconstituted wastewater isolates (reconstituted NDMA FP of 525 ng/L for this extract). We note that two of the methadone extracts contributed 1 to 13% of NDMA formation with one extract contributing 62%.

We also isolated 10 surface water samples for DMA structure searches by LC/QTOF-MS, and methadone was quantifiable in five of these sample isolates (SW 3, 5, 6, 7, and 9 in Table 7-2). The contribution to NDMA FP ranged from <1 to 3% of the reconstituted isolates (Figure 7-3). In general, isolates with greater methadone concentrations formed more NDMA when reconstituted into Milli-Q™ water. One sample had unusually high NDMA FP in the raw water (>500 ng/L); this sample is known to be heavily impacted by wastewater and had the greatest contribution of NDMA FP from methadone, albeit still relatively low (1 to 3%). Five surface water samples had no detectable methadone.

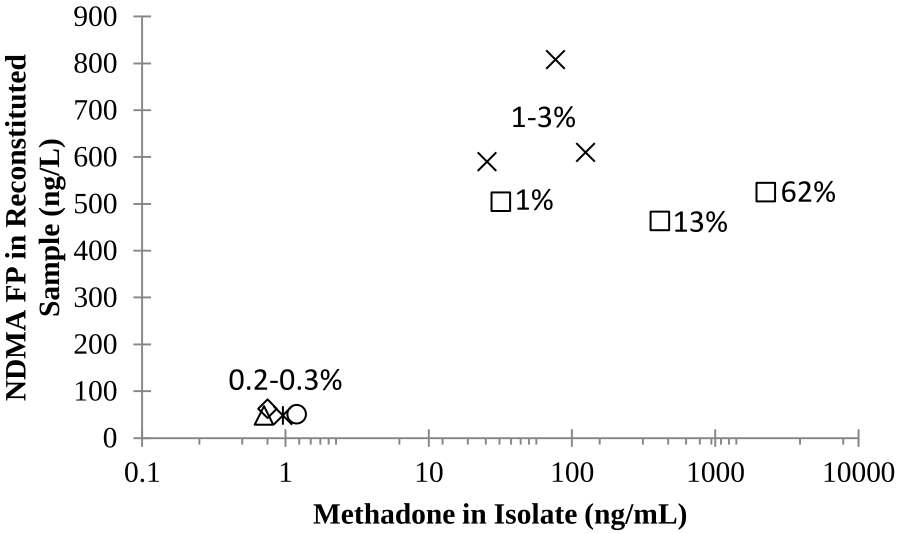


Figure 7-3 Percent contribution of methadone to NDMA FP in six water sources
Note: Methadone recovery across SPE was unknown. Squares and Xs show a wastewater and a surface water, respectively, with triplicate extractions and quantification (GC/MS). Other symbols represent four surface waters that were extracted in triplicate, but only a single sample was used for quantification (LC/MS).

Because our sampling campaign and methods were not initially developed to specifically identify and quantify methadone, we searched the literature for methadone occurrence data (Table 7-1). Available data regarding methadone occurrence are primarily from Europe with only two studies in the U.S. reporting concentrations. Methadone occurred in all WWTP influents except when the limit of quantification (LOQ) was insufficiently low (LOQ = 45 ng/L in one study for WWTP influent samples), and methadone was poorly removed through conventional WWTPs (37% (Boleda *et al.*, 2009), 42% (Berset *et al.*, 2010), 44% (Baker and Kasprzyk-Hordern, 2011), 0% (Bijlsma *et al.*, 2012), 0-16% (Subedi and Kannan, 2014), and 26% (Terzic *et al.*, 2010)). The finding that methadone is poorly removed in WWTPs agrees well with the predicted removal by EPISuite (27%) (USEPA, 2015). It should be considered that methadone is metabolized to 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP). This metabolite has been reported as two to three times more abundant in wastewater than the parent compound (Baker and Kasprzyk-Hordern, 2011; Berset *et al.*, 2010; Boleda *et al.*, 2009; Subedi and Kannan, 2014), and the NDMA FP of the metabolite EDDP is unknown, although it is likely to be low based on demethylation and cyclisation of the N. Methadone is generally ubiquitous in surface waters, occurring in all European samples except those of a state controlled park, and ranged in concentration from non-detectable to 55 ng/L. Only two studies published concentrations in the U.S.; both studies were from WWTPs and reported lower concentrations than Europe. Based on this literature review and a molar yield of 60%, the contribution to NDMA formation in surface and wastewater from methadone could be in the low ng/L and the hundreds of ng/L, respectively. We conclude that methadone is a potentially important precursor, as NDMA typically forms at roughly the same order of magnitudes as these preliminarily calculated values.

Table 7-1 Summary of methadone occurrence in surface water and WWTP influents (inf)

Water source	**Source type**	**Frequency >LOQ (*n*)[a]**	**Methadone occurrence (ng/L)**
Spain (Boleda *et al.*, 2009)	Surface	94% (32)	<0.04 – 18
United Kingdom (Baker and Kasprzyk-Hordern, 2011)	Surface	100% (6)	10/18[b]
Switzerland (Berset *et al.*, 2010)	Surface	97% (25)	<0.2 – 5
Northern and central Italy (Zuccato *et al.*, 2008)	Surface	100% (11)	0.2 – 10
Near Madrid, Spain (Mendoza *et al.*, 2014)	Surface	100% (14)	8 – 55
L'Albufera National Park in Spain (Vazquez-Roig *et al.*, 2010)	Surface	31% (16)	<0.01 – 0.84
Spain (Boleda *et al.*, 2009)	WWTP inf	100% (15)	3 – 1531
United Kingdom (Baker and Kasprzyk-Hordern, 2011)	WWTP inf	100% (7)	88/171[b]
Switzerland (Berset *et al.*, 2010)	WWTP inf	100% (5)	42 – 202
Netherlands (Bijlsma *et al.*, 2012)	WWTP inf	0% (32)	<45
New York State, U.S.A. (Subedi and Kannan, 2014)	WWTP inf	93% (14)	<LOQ[c] – 54.6
Czech Republic (Baker *et al.*, 2012)	WWTP inf	100% (14)	13 – 19
U.S.A. (Chiaia *et al.*, 2008)	WWTP inf	100% (7)	5 – 62
Zagreb, Croatia (Terzic *et al.*, 2010)	WWTP inf	100% (27)	25 – 94

[a] *n*: number of samples

[b] Mean/max are shown as no range was given.

[c] LOQ between 1 and 10 ng/L

Health implications. Methadone has clear benefits as a medicinal tool. However, it is poorly removed in WWTP (<50%), relatively persistent in the environment (months) (USEPA, 2015), and has the potential to contribute to the increased cancer risk associated with nitrosamines in chloraminated drinking water. For example, a community of 100,000 people could contain 1,500 chronic pain treatment and 100 substance abuse treatment methadone users (Kenan *et al.*, 2012; Paulozzi *et al.*, 2012; Substance Abuse and Mental Health Services Administration, 2014). Notably, the number of prescriptions of methadone to treat chronic pain is 1.5 orders of magnitude greater than for substance abuse treatment in the U.S. and potentially avoidable using other prescription drugs. At the minimum recommended dose of 7.5 mg/d (Paulozzi *et al.*, 2012), the community will consume 12 g/d of methadone, of which approximately 28% is excreted as the parent drug in urine (Baselt and Casarett, 1971; Bellward *et al.*, 1977; Ferrari *et al.*, 2004; Inturrisi *et al.*, 1987; Leimanis *et al.*, 2012; Nilsson *et al.*, 1982). These are conservative estimates of doses and excretion, and if applied to the total number of methadone users in the U.S. given in the introduction, only half of the U.S. production of methadone is accounted for. A typical wastewater production rate is 378 L day^{-1} $person^{-1}$, resulting in 90 ng/L methadone entering this theoretical WWTP, where it is partially removed (27%) (USEPA, 2015). If <10% is removed in the receiving stream with 40% dilution (Rice and Westerhoff, 2015) (non-WW origin), a downstream DWTP practicing chloramination could produce roughly 5 ng/L NDMA FP from methadone in the river (60% molar NDMA FP yield). Notably, this theoretical potable water treatment plant would form NDMA in concentrations that are typical of chloraminating DWTPs using wastewater impacted surface water as the water source (median of 35 ng/L in one study) (Guo and Krasner, 2009).

This is among the few examples showing a direct relationship between a pharmaceutical that improves human welfare and the formation of a carcinogen during drinking water disinfection. The closest example is a personal care product (triclosan) that has the potential to form trihalomethanes during chlorination, but the relative formation of trihalomethanes was concluded to be minor (Rule *et al.*, 2005). The medicinal use of methadone potentially displaces and transforms the health risks for individuals associated with heroin use and chronic pain to cancer risk for entire populations served by downstream DWTPs. The health risk associated with heroin use is high, and the risk associated with consumption of low levels of NDMA is relatively low but is spread across a greater population.

7.5 Acknowledgements

The authors gratefully acknowledge the support received from participating utilities and from the funding sources: The Water Research Foundation (Project #4499 managed by Djanette Khiari), the American Water Works Association Abel Wolman Fellowship, the Water Environment Federation Canham Graduate Studies Scholarship, and the Arizona State University Ira A. Fulton School of Engineering Dean’s Fellowship. The Center for Environmental Mass Spectrometry acknowledges Agilent Technologies, Inc., for instrument support, especially Jerry Zweigenbaum and Craig Marvin.

7.6 Supporting Information

Table 7-2 NDMA FP recovery after extraction of raw water samples

	Raw Water NDMA FP (ng)	Reconstituted NDMA FP (ng)	Recovery of NDMA FP (%)	Raw Water DOC (mgC/L)	Raw Water TDN (mgN/L)
SW 1	21 ±0.4	20 ±0.8	95	3.2	0.4
SW 1 (2nd sampling)	22 ±0.7	21 ±0.3	95	3.2	0.4
SW 2	36 ±1.8	29 ±1.2	81	5.3	0.4
SW 3	47 ±0.7	48 ±0.4	102	2.5	2.7
SW 4	97 ±4.6	57 ±3.3	59	6.0	2.7
SW 5	112 ±4.9	71 ±7.2	63	6.4	3.2
SW 6	546 ±3.0	599 ±9.9	110	6.9	4.3
SW7	122 ±9.2	50 ±8.1	41	4.5	4.8
SW8	40 ±2.1	67 ±69.5	168	4.4	0.5
SW9	111 ±2.6	49 ±1.7	44	4.7	4.6
SW10	40 ±1.5	28 ±5.1	70	4.3	0.5
WW 1	602 ±27.5	497 ±25.8	83	5.2	5.4

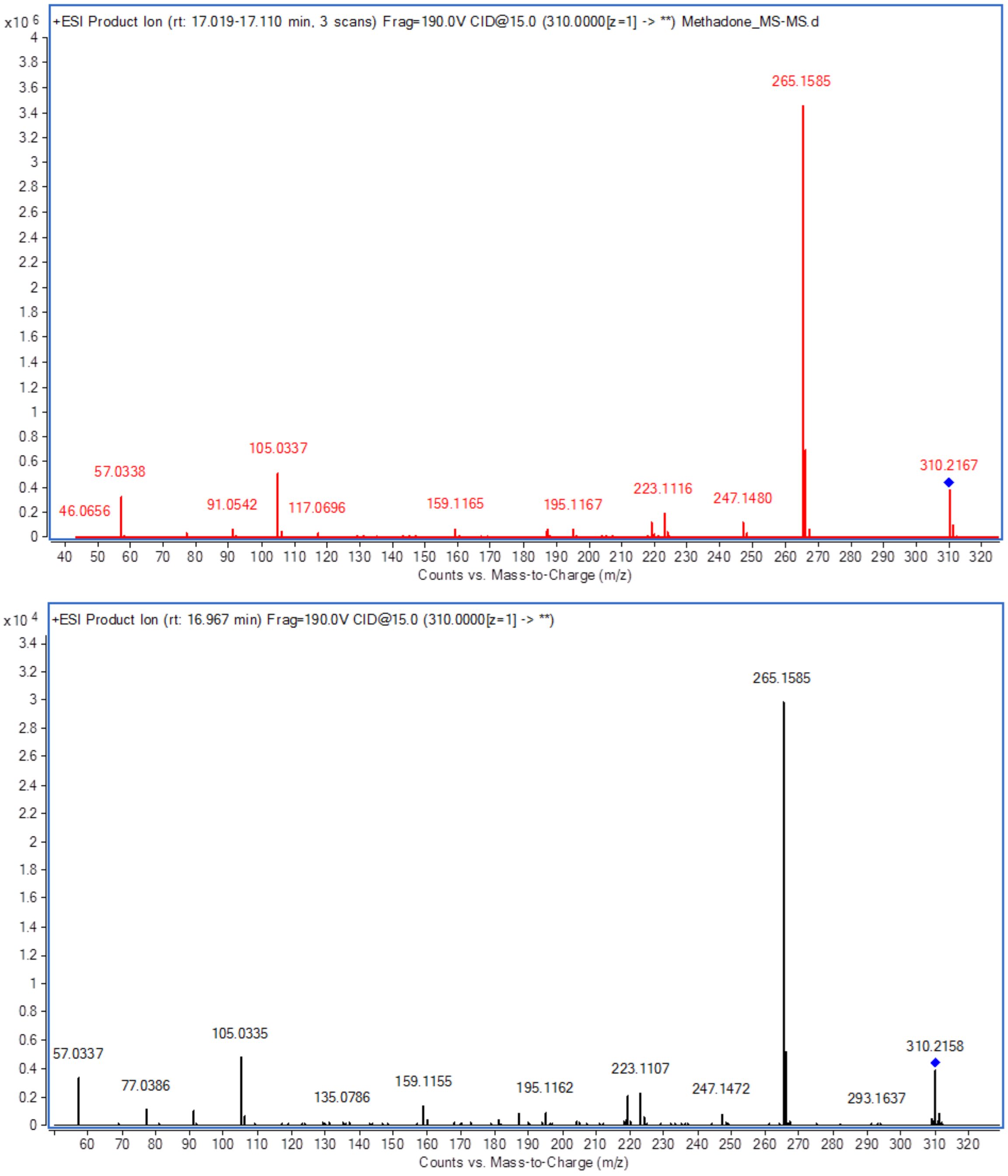


Figure 7-4 MS/MS spectra of methadone standard (top) and methadone discovered in wastewater (bottom)

Reagent chemicals. Methanol (MeOH) was purchased from Fisher Chemical (Fair Lawn, NJ). Sulfuric acid (H2SO4) was purchased from EMD Millipore. Reagent water used was either of HPLC grade (purchased from commercial sources) or was >18.2 MΩ-cm (Megohm-cm). Ascorbic acid, sodium hypochlorite, boric acid, and borax were purchased from Fisher Chemical. Sodium sulfate drying cartridges were from Agilent Technologies (Santa Clara, CA) and methadone, ammonium hydroxide (NH_4OH), formic acid, and sodium hydroxide were from Sigma Aldrich (St. Louis, MO). A NDMA standard was purchased from Supelco (Bellefonte, PA), and the isotopically labeled d6-NDMA standard was from Cambridge Isotopes (Tewksbury, MA). Oasis MCX (500mg) SPE cartridges were purchased from Waters (Milford, MA).

NDMA precursor isolation. NDMA precursors were concentrated as follows: 3.5 L of filtered sample was pH adjusted to 3 using sequential additions of ≤1M H2SO4. 1L of sample was pushed through Oasis MCX SPE cartridges in triplicate at 5 mL/min by an automated SPE system (Caliper Life Sciences Autotrace 280). SPE cartridges were first rinsed with 5 mL MeOH and 5 mL H_2O. After loading, the cartridges were dried for 30 min under a gentle flow of nitrogen gas. Methadone was eluted from the SPE cartridges with 10 mL of 5% NH_4OH in MeOH at a flow rate of 1.5 mL/min. The resulting concentrates were blown down under a gentle stream of nitrogen gas to a final volume of 1 mL (1,000 times concentrated). 500 µL of the extract was reconstituted into Milli-Q™ water and chloraminated under formation potential conditions to quantify bulk precursor recovery. For methadone calculations, we assumed recovery through the cation exchange process was 100% because no labeled isotope of methadone was used and because this results in a likely the most conservative estimate of methadone in the samples.

NDMA formation tests. Preformed monochloramine was prepared by slowly adding via burette 250 mL of a NaOCl solution to 250 mL solution of 10mM borate buffered (pH 8) NH_4OH solution. The final N:Cl_2 ratio was 1.2 and the monochloramine concentration in the stock solution was ~2,000 mgCl_2/L as measured by the indophenol colorimetric Monochlor F method (Hach Company, Loveland, CO).

500 mL sample was buffered with 10mM borate buffer (pH 8), and an appropriate amount of chloramine solution was added. After 72 hours in the dark at 25°C, the chloramines were quenched with 5 mM ascorbic acid, and 200 ng/L of the deuterated NDMA standard was added immediately. Samples were stored for less than two weeks at 4°C in the dark before extraction.

Solid phase extraction followed EPA Method 521.(Munch and Bassett, 2004) Activated carbon cartridges were washed successively with dichloromethane (DCM), MeOH, and HPLC grade water before being loaded at a rate of 5 mL/min. The columns were dried using compressed nitrogen gas and eluted with 5 mL of DCM. The extract was blown down to 1 mL using a gentle stream of nitrogen gas and transferred to a GC vial via Pasteur pipette. NDMA was quantified by GC/MS (ammonia chemical ionization) using an isotopically labeled standard to quantify losses during solid phase extraction. The details of the NDMA GC/MS method can be found elsewhere.(Hanigan *et al.*, 2012)

GC/MS analysis of methadone. The extract solution was analyzed using Gas Chromatography Mass Spectrometry on an Agilent 6890/5973 inert GC/MS system (Agilent, Santa Clara, CA). The system was equipped with an Agilent HP-5MS column (0.25mm x 30m×0.25µm, Agilent Santa Clara, CA). Helium was used as carrier gas at a constant flow rate of 1.2 mL/min. A generic temperature protocol (i.e., not optimized for methadone) was used in scan mode. In brief, 1 µL of sample was injected. The injector temperature was set at 300°C. The oven temperature started with a hold at 65°C for 10 minutes followed by an increase to 300°C and a final hold for 20 minutes at 300°C. The MS transfer line was set at 275°C, and the MSD was operated in electron impact mode and scanning from m/z 50 to 500 Da. Compound identification and quantification was performed using an authentic methadone standard.

LC/Q-TOF/MS screening procedure. The separation of the analytes was carried out using an UHPLC system consisting of vacuum degasser, thermostated autosampler, column compartment, and a binary pump (Agilent Series 1290, Agilent Technologies, Santa Clara, CA) equipped with a reverse phase C8 analytical column of 150 mm x 4.6 mm and a 3.5 µm particle size (Zorbax Eclipse XDB-C8). Column temperature was maintained at 25°C. The injected sample volume was 10 µL. Mobile phases A and B were water with 0.1% formic acid and acetonitrile, respectively. The optimized chromatographic method held the initial mobile phase composition (10% B) constant for 5 minutes, followed by a linear gradient to 100% B after 30 minutes. The flow rate used was 0.6 mL/min. A 10-minute post-run was used after each analysis. This UHPLC system was connected to an ultra-high definition quadrupole time-of-flight mass spectrometer model 6540 Agilent (Agilent Technologies, Santa Clara, CA) equipped with electrospray Jet Stream Technology, operating in positive ion mode, using the following operation parameters: capillary voltage 4000 V; nebulizer pressure 45 psig; drying gas 10 L/min; gas temperature 325ºC; sheath gas flow 11 L/min; sheath gas temperature 350ºC; nozzle voltage 1000 V; fragmentor voltage 190 V; skimmer voltage 45 V; and octopole

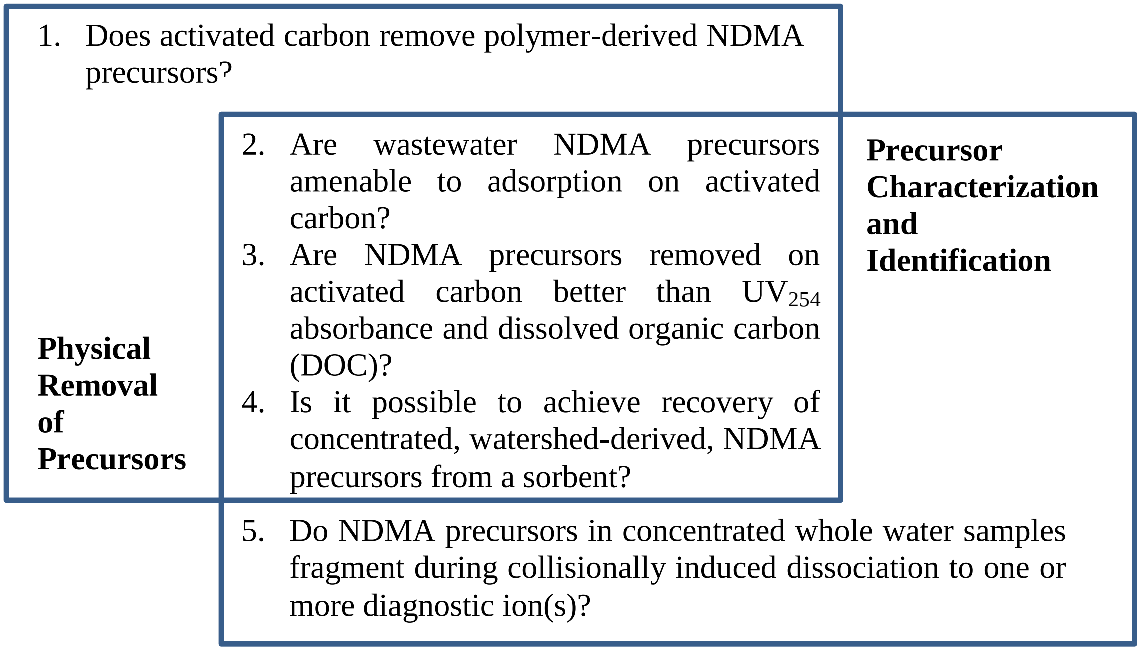
RF 750V. LC/MS accurate mass spectra were recorded across the range 50-1000 m/z at 2 GHz. The data recorded was processed with MassHunter software (version 6.1). Accurate mass measurements of each peak from the total ion chromatograms were obtained by means of an automated calibrant delivery system using a low flow of a calibrating solution (Calibrant Solution A, Agilent Technologies, Inc.), which contains the internal reference masses (purine m/z 121.0509 and HP-921 at m/z 922.0098). The instrument provided a typical mass resolving power of 30,000 at m/z 1522.

LC/MS/MS analysis of methadone. The separation of methadone in water samples was carried out using an HPLC system consisting of vacuum degasser, autosampler, and a binary pump (Agilent Series 1290, Agilent Technologies, Santa Clara, CA, USA) equipped with a reversed phase C_{18} analytical column of 50 x 2.1 mm and 1.8 µm particle size (Agilent Zorbax Eclipse Plus). Column temperature was maintained at 25°C. The mobile phases A and B were water with 0.1% formic acid and acetonitrile, respectively. Samples were injected (injection volume 15 µL) on to the column. Initial mobile phase composition was 10% B, held constant for 1.7 min, followed by a linear gradient to 100% B at a flow-rate of 0.4 mL/min, for a total run time of 10 min.

The HPLC system was connected to a triple quadrupole mass spectrometer Model 6460 Agilent (Agilent Technologies, Santa Clara, CA, USA) equipped with electrospray Jet Stream technology operating in positive ion mode, using the following operation parameters: capillary voltage 4000 V in positive and 3500V in negative; nebulizer pressure 45 psig; drying gas 10 L/min; gas temperature 250°C; sheath gas flow 11 L/min; sheath gas temperature 350°C; and nozzle voltage 0 V. The fragmentor voltage was 110V, and collision energies were optimized for methadone. Quantitation was performed on the main fragment ion at m/z 265 (collision energy 10V). Two qualifier ions at m/z 105 and 57 were used for unequivocal identification and confirmation of the compound by LC-MS-MS at a collision energy of 20V. The data recorded was processed with MassHunter software (Agilent Technologies).

8 Synthesis

This chapter incorporates findings from my dissertation with the existing literature to answer the guiding research questions proposed in Chapter 1 and shown in Figure 8-1. The overarching research question that guided the research was, **“What are the likely organic chemicals responsible for nitrosodimethylamine (NDMA) formation in water and how can they be removed?”**



1. Does activated carbon remove polymer-derived NDMA precursors?
2. Are wastewater NDMA precursors amenable to adsorption on activated carbon?
3. Are NDMA precursors removed on activated carbon better than UV_{254} absorbance and dissolved organic carbon (DOC)?
4. Is it possible to achieve recovery of concentrated, watershed-derived, NDMA precursors from a sorbent?
5. Do NDMA precursors in concentrated whole water samples fragment during collisionally induced dissociation to one or more diagnostic ion(s)?

Physical Removal of Precursors

Precursor Characterization and Identification

Figure 8-1 Research questions used to guide research in this dissertation aimed at identifying and the treatment of NDMA precursors.

8.1 Relative Importance of Watershed- vs Polymer-derived NDMA Precursors During Chloramination

In Table 8-1 I concluded from the literature (Chapter 2) that wastewater derived organic matter and amine-containing polymers are two of the most important groups of NDMA precursor chemicals. Polymers are used broadly and typically alongside chloramination to control trihalomethane (THM) formation, but are reactive in the formation of NDMA. Optimum THM precursor removal typically occurs at a metal salt (coagulant) dose higher (and thus lower pH) than is required for optimum turbidity removal and organic polymer is used to aid in the removal of turbidity under these conditions. I studied poly-diallyldimethyl ammonium chloride (polyDADMAC) almost exclusively because it is the most commonly used polymer during coagulation.

Table 8-1 Importance of different precursors for nitrosamine formation in drinking waters

Precursor	**Importance**
Amine-containing coagulation polymers	High
Effluent-impacted source waters	High
Pharmaceuticals and personal care products	Moderate/High
Distribution system materials	Moderate
Anion exchange resins	Moderate
Soluble microbial products	Limited
Agricultural chemicals	Limited
Bulk DON	Low
Algae	Low

Figure 8-2 shows NDMA formation potential (NDMA FP) from surface waters, wastewaters, and polyDADMAC samples in this dissertation. The relative contribution to NDMA formation from polyDADMAC at the highest dose typically seen in water treatment (0.4 mg/L active ingredient) contributes to a low amount of NDMA when compared to other watershed-derived precursors. In Figure 8-3, I show NDMA FP for all water samples in this dissertation normalized to dissolved organic carbon (DOC). In Figure 8-2 and Figure 8-3, I show that the NDMA FP of surface water is typically low and less variable than that of wastewater. PolyDADMAC forms more NDMA upon chloramination when normalized to the DOC of the resulting water but it should be noted that polyDADMAC dosing results in <0.3 mgC/L when applied at typical doses (<0.4 mg/L active ingredient). The focus of the majority of the research questions and work in this dissertation was on watershed- and wastewater-associated precursors due to their high variability and high occurrence. While polymer NDMA precursors can be removed by cessation of polymer use, a drinking water treatment plant has little control over the source water NDMA precursor loading.

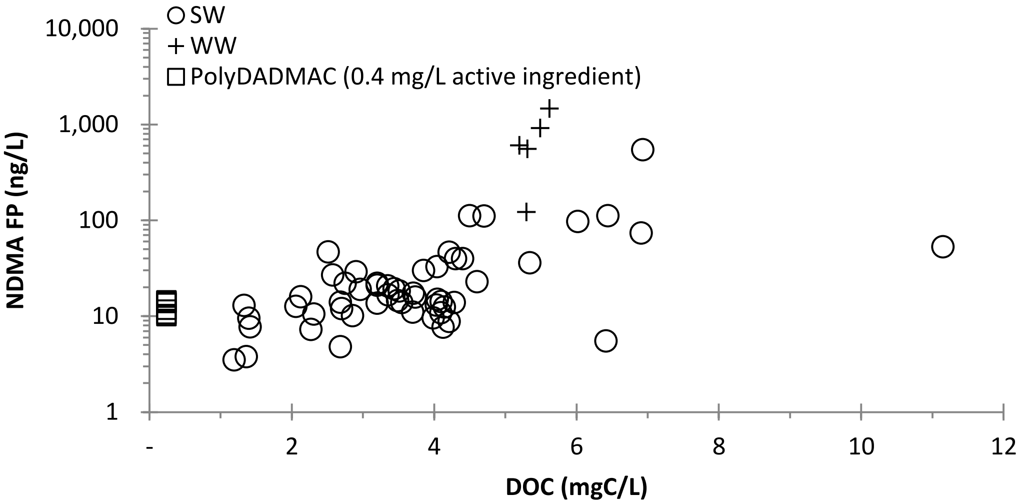


Figure 8-2 Summary of NDMA formation from 54 surface waters (SW), 5 wastewaters (WW), and 7 polyDADMAC samples in this dissertation

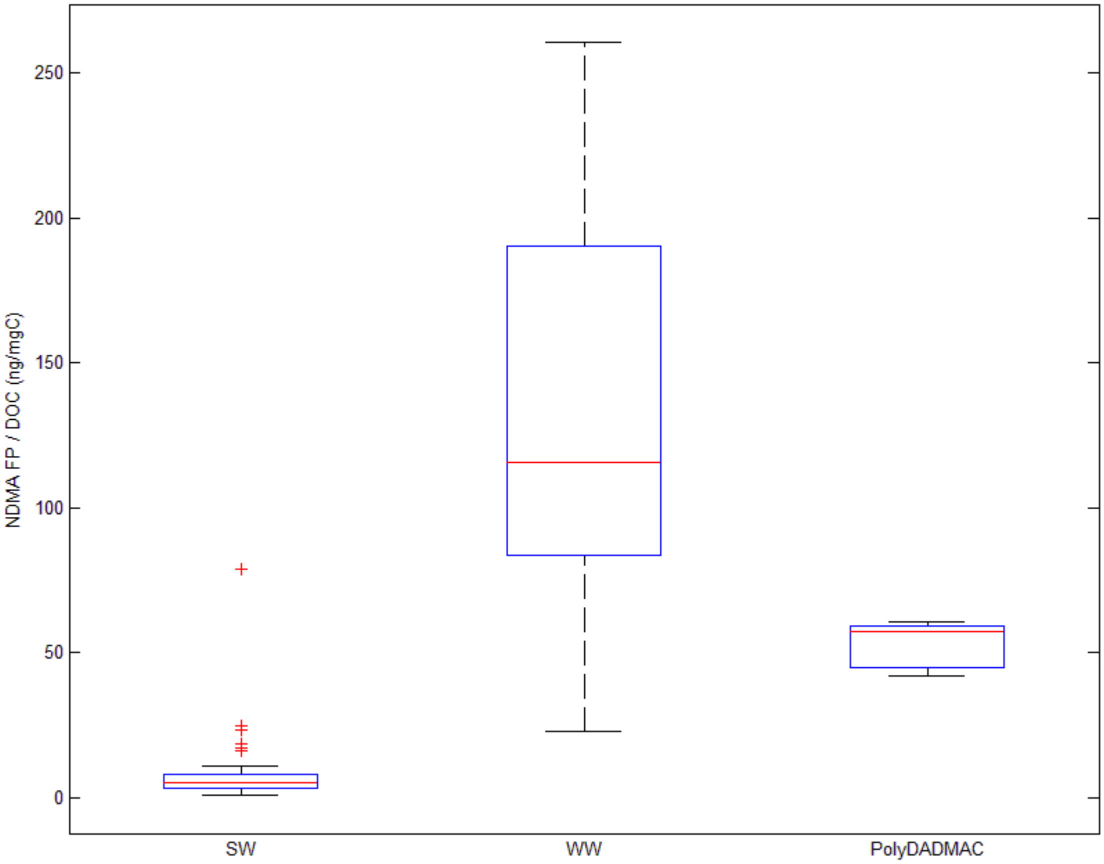


Figure 8-3 NDMA formation potential normalized to DOC content of 54 surface waters (SW), 5 wastewaters (WW), and 7 polyDADMAC samples in this dissertation. Central mark is the median, box is the 25th and 75th percentile, whiskers extend to ±2.7σ of the dataset, and individual points are outliers.

8.2 Polymer-associated NDMA Precursors

Does activated carbon remove polymer-derived NDMA precursors? Figure 8-4 shows that polymer-associated NDMA precursors were not sorbed by activated carbon. The dominant moiety in polyDADMAC is a positively charged amine group, which is responsible for bridging and settling negatively charged NOM during coagulation. Given that the polymer itself is positively charged at typical water treatment pH (pH 8 adjusted log K_{ow} [log D_{ow}]<<0 and decreases with increasing polymerization (Chemicalize.org, 2013)) and that electrostatic interactions have greater energy than hydrophobic interactions (Crittenden *et al.*, 2012), I did not expect physisorption to dominate.

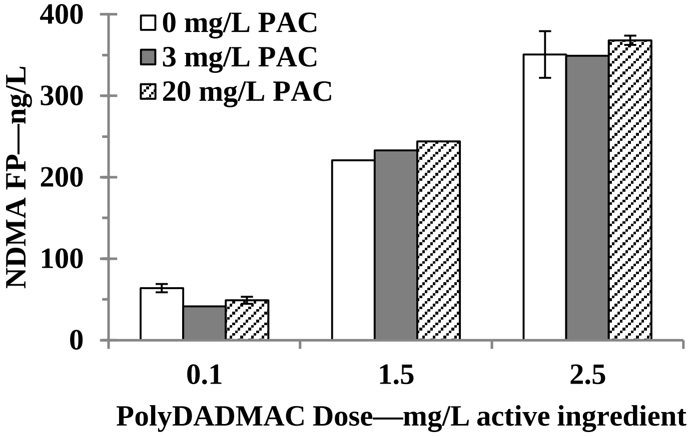
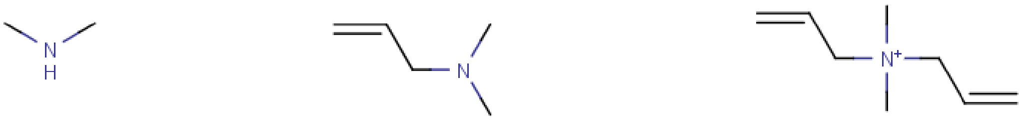
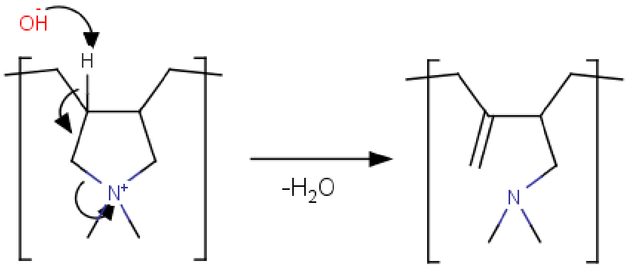


Figure 8-4 NDMA FP of polymer-associated precursors after exposure to PAC at bench scale. PAC was contacted for 1 hr in DI water at 100 rpm using a gang stirrer. Error bars show 1 SD of triplicate samples

However, recent work has suggested that contaminants in the polymer solution may be the source of NDMA formation rather than the polymer itself. Published literature suggests that the contaminants could be stoichiometric excesses of reactants used to manufacture polymers (dimethylamine, allyldimethylamine, DADMAC monomer, etc.) or degraded polymer itself (via Hofmann elimination) (Park *et al.*, 2009). These potentially NDMA reactive structures are shown in Figure 8-5. Notably, dimethylamine, allyldimethylamine, and DADMAC monomer have pH 8 Log D_{ow} of -2.64, -0.16, and -2.51, respectively. The degraded polymer pH 8 Log D_{ow} is difficult to determine because the degree of degradation and polymerization are unknown. The degraded monomer pH 8 Log D_{ow} is 0.78 and increases with polymerization but if any charged groups are still present (i.e., incomplete degradation), polarity increases and partitioning to water rather than octanol will dominate at pH >0 (Chemicalize.org, 2013). Compounds that are well removed by activated carbon typically have Log D_{ow} >1 (Westerhoff *et al.*, 2005) and therefore, based on modeled partitioning of these potential contaminants, I also expect poor sorption to activated carbon. The polymer itself and all known NDMA forming potential contaminants sorb poorly to activated carbon based on modeled partitioning, which agrees with my results that NDMA precursors in polymer solutions are poorly removed by activated carbon.



Dimethylamine Allyldimethylamine DADMAC monomer



Hoffmann elimination of polyDADMAC to form a tertiary amine

Figure 8-5 Potential NDMA forming contaminants in polyDADMAC solutions (adapted from Park *et al.* (2009)).

8.3 Watershed-associated NDMA Precursors

Watershed-associated NDMA precursors account for a greater contribution to NDMA formation than polymer precursors (Chapter 2). Therefore, it was my goal to find one or multiple mitigation options for watershed-associated NDMA precursors.

Are wastewater NDMA precursors amenable to adsorption on activated carbon? Early occurrence data suggested that some watershed-associated precursors could be removed by activated carbon (Farré *et al.*, 2011; Mitch *et al.*, 2009). In Chapters 3 and 4, I demonstrate that granular activated carbon (GAC) and powdered activated carbon (PAC) are capable of removal of wastewater-associated NDMA precursors. 50% to 75% of wastewater-associated precursors were removed from wastewater by GAC and PAC removed precursors well at doses achievable by drinking water treatment plants (Figure 8-6).

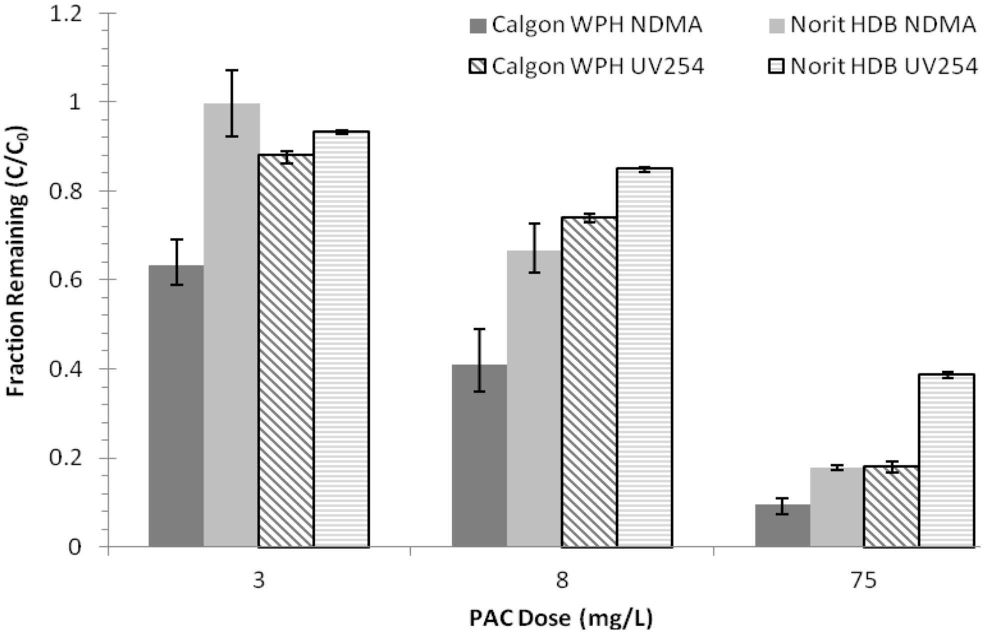


Figure 8-6 NDMA FP and UV_{254} absorbance reduction in a secondary wastewater effluent after treatment with bituminous (WPH)- and lignite (HDB)-based PACs. The control sample (no PAC) had a NDMA FP of 1470 ng/L and $UV_{254} = 0.11$ cm^{-1}

Table 8-2 shows all known model precursors from published literature. 51% of these model NDMA precursors have a pH 8 Log D_{ow} greater than 1, which is an indication of hydrophobicity and potential for sorption to activated carbon of these model NDMA precursors. The compounds with lower Log D_{ow} may also be potential NDMA precursors that sorbed from wastewater to the activated carbon in my studies because 1) Log D_{ow} is not a perfect predictor of sorption to activated carbon and, 2) to be present in the secondary effluent samples that was used for sorption studies, the precursor compound must not be removed entirely via sorption to biosolids during secondary treatment and thus, a slightly polar compound may have a greater likelihood of passing biological treatment. These compounds' modeled partitioning suggests that, if the model precursors are representative of real precursors, and the precursor compounds are not completely removed in the biosolids first, they are likely to be well removed by activated carbon based on many favorably partitioning to octanol at near neutral pH.

Table 8-2 Summary of known NDMA-forming chemicals to date (chloramination)

Relative NDMA FP Molar Yields	Compound Name*	NDMA FP Molar Yield	pH 8 Log D (Chemicalize.org, 2013)	Amine Structure
Very High (>75%)	Ranitidine^{Rx}	80–90% (Le Roux *et al.*, 2012c; Selbes *et al.*, 2013; Shen and Andrews, 2011a)	0.64	β-aryl tertiary
	N,N-Dimethylisopropylamine^{Ind}	84% (Selbes *et al.*, 2013)	-1.01	Tertiary
	5-((Dimethylamino)methyl)furan-2-methanol	82% (Le Roux *et al.*, 2012a; Selbes *et al.*, 2013)	-0.2	β-aryl tertiary
	2-Thenylamine, N,N-dimethyl-	78% (Selbes *et al.*, 2013)	1.07	β-aryl tertiary
	Methadone^{Rx}	60% (Hanigan *et al.*, 2015a)	3.86	Tertiary
High (10 to 75%)	*N,N*-Dimethylbenzylamine^{Ind}	20–84% (Kemper *et al.*, 2010; Mitch *et al.*, 2009; Selbes *et al.*, 2013)	0.89	β-aryl tertiary
	Dimethyl-1-(1H-pyrrol-2-yl)methanamine	25% (Selbes *et al.*, 2013)	-0.73	β-aryl tertiary
	DMP30^{Ind}	18-55% (Le Roux *et al.*, 2012a)	-1.49	3 X β-aryl tertiary groups
	Diphenylamine^{Ag}	15–20% (NDPhA) (Zhou *et al.*, 2009)	3.41	Secondary
Moderate (1 to 10%)	Doxylamine^{Rx}	9% (Shen and Andrews, 2011a)	2.04	Tertiary
	Minocycline^{Rx}	8% (Le Roux *et al.*, 2011)	-5.67	Tertiary
	Sumatriptan^{Rx}	7% (Shen and Andrews, 2011b)	-0.66	Tertiary
	Diethylamine^{Ind}	6% (Wang *et al.*, 2011c)	-1.98	Secondary
	Dimethyltert-butylamine	6% (Selbes *et al.*, 2013)	-1.23	Primary
	3-(Dimethylaminomethyl)indole	6% (Lee *et al.*, 2007a)	0.72	β-aryl tertiary
	Nizatidine^{Rx}	5% (Shen and Andrews, 2011b)	0.73	β-aryl tertiary
	4-dimethylaminoantipyrine	4% (Lee *et al.*, 2007a)	1.15	Tertiary
	Morpholine^{Ind,Ag}	4% (Wang *et al.*, 2011c)	-1.03	Secondary
	Diltiazem^{Rx}	2% (Shen and Andrews, 2011b)	2.33	Tertiary
	Doxepin^{Rx}	2% (Le Roux *et al.*, 2011)	2.08	Tertiary
	Dimethylaminoacetonitrile	2% (Selbes *et al.*, 2013)	-0.27	Tertiary
	Chlorpheniramine^{Rx}	2% (Shen and Andrews, 2011a)	2.10	Tertiary
	Dimethylamine^{Ind}	1–3% (Le Roux *et al.*, 2012a; Lee *et al.*, 2007a; Selbes *et al.*, 2013)	-2.64	Secondary
	Trimethylamine^{Ind}	1–2% (Lee *et al.*, 2007a; Selbes *et al.*, 2013)	-1.39	Tertiary
	3-Dimethylaminophenol	1% (Le Roux *et al.*, 2012a; Selbes *et al.*, 2013)	1.77	Tertiary
	Diuron^{Ag}	1% (Chen and Young, 2008; Le Roux *et al.*, 2011)	2.53	Tertiary amide
	Carbinoxamine^{Rx}	1% (Shen and Andrews, 2011b)	2.35	Tertiary
	Tetracycline^{Rx}	1% (Shen and Andrews, 2011b)	-6.78	Tertiary
	1-(dimethyl- amine) pyrrole	1.6% (Le Roux *et al.*, 2012a)	0.25	Tertiary
Low (<1 %)	*N,N*-Dimethylethylamine	<1% (Selbes *et al.*, 2013)	-1.21	Tertiary
	N,N-Dimethylbutylamine	<1% (Selbes *et al.*, 2013)	-0.28	Tertiary
	Dimethylaminoethanol^{Ind}	<1% (Lee *et al.*, 2007a; Selbes *et al.*, 2013)	-1.57	Tertiary
	Dimethylethylenediamine	<1% (Selbes *et al.*, 2013)	-2.43	Secondary
	2-Dimethylaminoethanethiol	<1% (Selbes *et al.*, 2013)	-0.43	Tertiary
	N,N-Dimethylaniline^{Ind}	<1% (Lee *et al.*, 2007a; Selbes *et al.*, 2013)	2.08	Tertiary
	4-Dimethylaminopyridine^{Ind}	<1% (Selbes *et al.*, 2013)	0.23	Tertiary

	2-Dimethylaminopyridine	<1% (Le Roux *et al.*, 2012a; Selbes *et al.*, 2013)	1.44	Tertiary
	2-Chloro-*N,N*-dimethylaniline	<1% (Selbes *et al.*, 2013)	2.69	Tertiary
	Dimethylphenethylamine^{Rx}	<1% (Selbes *et al.*, 2013)	0.92	Tertiary
	Tetramethylamine	<1% (Kemper *et al.*, 2010)	-3.97	Quaternary
	Benzyldimethyldodecylamine	<1% (Kemper *et al.*, 2010)	1.74	Quaternary
	Benzyldimethyltetradecylamine	<1% (Kemper *et al.*, 2010)	2.63	Quaternary
	Cetyltrimethylamine	<1% (Kemper *et al.*, 2010)	1.8	Quaternary
	Choline^{SMP}	<1% (Kemper *et al.*, 2010)	-4.66	Quaternary
	Tetrabutylamine	<1% (Kemper *et al.*, 2010)	1.32	Quaternary
	Benzyltributylamine	<1% (Kemper *et al.*, 2010)	1.72	Quaternary
	Cocamidopropyl betaine^{Rx}	<1% (Kemper *et al.*, 2010)	0.06	Quaternary
	Dimethyldithiocarbamate^{Ind}	<1% (Padhye *et al.*, 2013)	0.15	Tertiary
	Diethyldithiocarbamate	<1% (NDEA) (Padhye *et al.*, 2013)	0.86	Tertiary
	Dimethylformamide^{IND}	<1% (Lee *et al.*, 2007a)	-0.63	Tertiary
	3-*N,N*-DAPSIS^{Ind}	<1% (Chang *et al.*, 2011)	0.23	Quaternary
	Benzalkonium chloride^{IND,Rx}	<1% (Chang *et al.*, 2011)	2.63	Quaternary
	Thiram^{Ag,Rx}	<1% (Graham *et al.*, 1995)	2.73	Tertiary
	Mifepristone^{Rx}	<1% (Le Roux *et al.*, 2011)	5.13	Tertiary
	Isoproturon^{Ag}	<1% (Le Roux *et al.*, 2011)	2.57	Tertiary
	Trifluralin^{Ag}	<1% (Le Roux *et al.*, 2011)	4.6	Tertiary
	Azithromycin^{Rx}	<1% (Shen and Andrews, 2011b)	-0.08	Tertiary
	DEET^{Rx}	<1% (NDEA) (Shen and Andrews, 2011b)	2.5	Tertiary
	Lidocaine^{Rx}	<1% (NDEA) (Shen and Andrews, 2011b)	2.65	Tertiary
	Venlafaxine^{Rx}	<1% (Shen and Andrews, 2011b)	1.78	Tertiary
	Clarithromycin^{Rx}	<1% (Shen and Andrews, 2011b)	2.71	Tertiary
	Erythromycin^{Rx}	<1% (Shen and Andrews, 2011b)	2.06	Tertiary
	Roxithromycin^{Rx}	<1% (Shen and Andrews, 2011b)	1.89	Tertiary
	Amitriptyline^{Rx}	<1% (Shen and Andrews, 2011b)	3.05	Tertiary
	Escitalopram^{Rx}	<1% (Shen and Andrews, 2011b)	1.98	Tertiary
	Metformin^{Rx}	<1% (Shen and Andrews, 2011b)	-5.37	Pri/Sec/Tertiary
	Tramadol^{Rx}	<1% (Shen and Andrews, 2011b)	1.20	Tertiary
	Methylene blue	0.8 (Le Roux *et al.*, 2012a)	2.61	Tertiary
	2-(dimethyl- amine) pyridine	0.37 (Le Roux *et al.*, 2012a)	1.44	Tertiary
	Dimethyl-4-phenylenediamine	0.9 (Le Roux *et al.*, 2012a)	1.23	Tertiary
	6-(dimethyl- amine) fulvene	0.53 (Le Roux *et al.*, 2012a)	0.3232	β-aryl tertiary
	Diphenhydramine^{Rx}	<1% (Shen and Andrews, 2011b)	2.73	Tertiary

*superscripts indicate likely sources: Ind, industrial including pharmaceutical synthesis; Rx, pharmaceuticals; Ag, agriculture; SMP, soluble microbial product.

With integrated knowledge from both Chapter 3 and 4, I was able to characterize NDMA precursors. Although specific chemical structures were not yet identified in my wastewater and surface water samples, I was able to determine that some precursors are derived in the watershed and have hydrophobic groups. In addition, I determined that

NDMA precursors are well adsorbed to activated carbon, which lead to the next guiding question.

Are NDMA precursors removed on activated carbon better than UV_{254} absorbance and dissolved organic carbon (DOC)? Answering this question further helps to characterize NDMA precursors. UV_{254} and DOC are bulk organic matter measurements and based on my findings in Chapter 2, that NDMA precursors are probably trace organic matter, I did not expect them to behave the same as bulk organic matter during sorption. Trace organic matter typically adsorbs for greater GAC loading periods because the likelihood of interaction with an active sorption site increases when the adsorbate concentration is low. Furthermore, low molecular weight (MW) adsorbates (trace) can access more internal pore structure (micropores) of activated carbon that is unavailable to high MW compounds that sorb in meso and macropores. This is demonstrated in Figure 8-7, where NDMA precursors are sorbed 25% to 50% greater and for a longer loading period than bulk organic matter measured as DOC and UV_{254}.

In another case, I used DOC-expended GAC columns at a pilot-plant to sorb NDMA precursors and found that NDMA precursors were well removed in both DOC expended GAC treatment scenarios (>50%). Biodegradation has recently been shown to play a role in precursor removal on columns that have been in use for a long duration of time (Liao *et al.*, 2015) and biodegradation of precursor material may have played a part at the pilot-plant in this dissertation, where columns had been in use for >5 years.

Trace organic pharmaceuticals are also removed by activated carbon better than DOC (Redding *et al.*, 2009) and combined with information from Chapter 2 and Table 8-1, where several pharmaceuticals and personal care products are implicated as NDMA precursors, I further reinforced the conclusion that watershed-associated NDMA precursors are trace (low concentration, low molecular weight) organic matter. This lead to a new research question ultimately aimed at identifying NDMA precursors responsible for formation in drinking water.

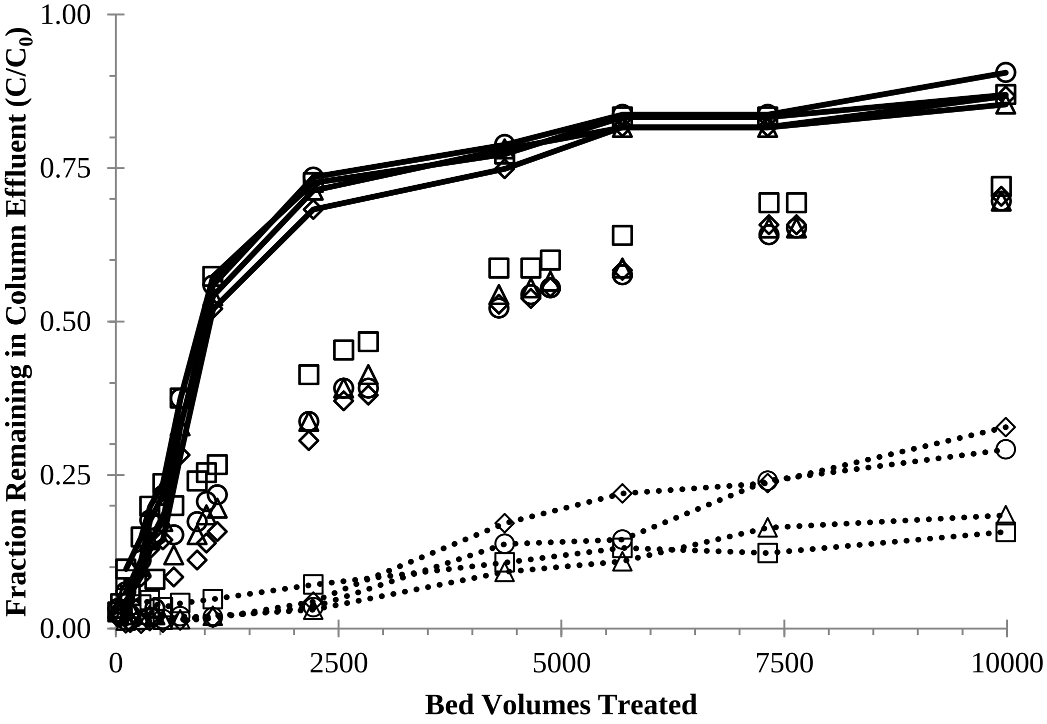


Figure 8-7 DOC and UV_{254} breakthrough in GAC packed beds using blended SW and secondary wastewater effluent
Note: Symbols and lines represent DOC breakthrough, whereas symbols alone represent UV_{254} breakthrough, and symbols with dashed lines represent NDMA FP precursor breakthrough with blends of SW and secondary effluent (WW) for GAC820 (◇ for 10% SW + 90% WW; △ for 50% SW + 50% WW; ☐ for 90% SW + 10% WW) or HD3000 (○ for 50% SW + 50% WW).

Is it possible to achieve recovery of concentrated, watershed-derived, NDMA precursors from a sorbent? The current state of identifying NDMA precursors had focused on model compounds that form NDMA in the lab with little regard for whether the precursors occur in the watershed and therefore whether they are or are not responsible for NDMA formation in drinking water (Le Roux *et al.*, 2012b; Padhye *et al.*, 2013; Shen and Andrews, 2011b). The greatest challenge in reducing the formation of DBPs by identifying and selectively removing specific organic precursor compounds is the identification of the compounds themselves. Assuming one mole of nitrogen in NDMA is derived in the precursor and one from monochloramine and that the precursors contain only one reactive N, a typical drinking water source water that produces 15 ng/L NDMA FP equates to a possible range of NDMA precursors concentration from 0.2 to 20.7 nM based on molar yields of precursors ranging from 1 to 100%. Because of this low predicted concentration of precursors and because of interferences from many other chemicals in typical environmental samples, precursor identification by optical spectrometry is unlikely. Mass spectrometry identifications are also unlikely due to interferences and therefore pre-concentration and isolation is needed. The notion that watershed-associated NDMA precursors are trace organic chemicals that adsorb to activated carbon was invaluable to answering this research question.

In Chapter 5, I used the conclusions from Chapters 3 and 4 (NDMA precursors sorb to GAC) to sorb and elute concentrated precursors based on hydrophobicity. Recovery from GAC was ~40% because of poor elution and eventually I moved on to develop a strategy based on the discovery from 2 that the important NDMA precursors are probably tertiary amines and ionize at low pH.

In Chapter 5, I describe the optimization of a method to isolate 1,000 fold concentrated precursors in an organic solvent amenable to mass spectrometry identification approaches. This demonstrated and further confirmed a conclusion from

Chapter 2, that NDMA precursors are probably tertiary amines based on their cation exchange sorption at low pH to ion exchange resin.

Initially, we attempted to sorb precursors using activated carbon. This resulted in sorption of >90% of precursors, but recovery in the eluent was poor. We tested other hydrophobic sorbents to target the moieties that controlled sorption in the activated carbon work in this dissertation and two cation exchangers to target a potential tertiary amine that we thought might be specific to NDMA precursors. The final method involved cation exchanging tertiary amines. While some samples had low initial NDMA FP, and additive errors in measurement of NDMA FP influenced their final recovery while others had poor recovery for unknown reasons. However, to some extent, precursors were isolated and concentrated for all samples, and identification of these is possible no matter the percent recovery. The true nature of this work was to understand NDMA precursors and this was achieved by this concentration method, which resulted in a median of 82% recovery of NDMA precursors across 12 natural water samples.

Do NDMA precursors in concentrated whole water samples fragment during collisionally induced dissociation to one or more diagnostic ion(s)? Armed with the concept that the NDMA precursors responsible for NDMA formation were tertiary amines, I designed mass spectrometry experiments based on predicted collisionally induced fragmentation to identify the precursors. The first prediction is shown in Figure 8-8. I used model NDMA precursors from previous literature of tertiary amine reactivity (Chapter 2) for fragmentation pattern predictions and later confirmed them using time-of-flight mass spectrometry (TOF-MS). In Figure 8-8, I predicted cleaving of the tertiary amine at the carbon α to the nitrogen to form a 58.0651 m/z ion. By searching for this ion and inspecting higher molecular weight ions in the spectra at the same retention time, I was able to identify NDMA precursors such as venlafaxine. This work was a strong collaboration with the University of Colorado, Center for Environmental Mass Spectrometry and is not part of this dissertation, but I will be a co-author on the resulting manuscript.

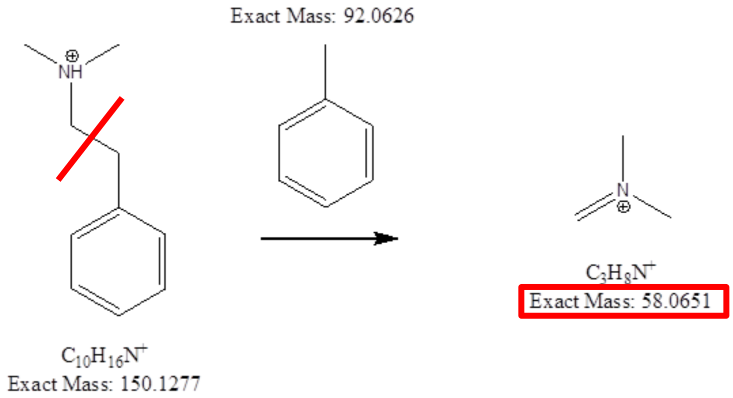


Figure 8-8 Predicted fragmentation pattern to produce a 58.0651 m/z ion and 92.0626 amu neutral loss for the model NDMA precursor, dimethylphenethylamine

Upon further inspection of the TOF-MS spectra of this model compound and others with similar tertiary amine structures, I realized that some potential precursors were likely to fragment at the N itself, forming an R group ion that was dependent on the original structure (Figure 8-9). Because I did not know the structure of this R group and because it would have been different for each NDMA precursor, I searched the TOF-MS spectra for the neutral loss amine rather than the ion. TOF-MS is not currently capable of conducting explicit neutral loss experiments (q1 unable to scan and no software to search full spectra) and therefore I developed a MATLAB® program capable of searching the exported spectra from the instrument. Because I believed I had concentrated mostly tertiary amine containing NDMA precursors in Chapter 5, I searched only for tertiary amines using my TOF-MS methods in Chapters 6 and 7 and thus was able to identify methadone as a significant contributor to NDMA formation in wastewater and surface water. Methadone and dimethylamine are the only two known precursors to occur in concentrations responsible for significant fractions of NDMA formation (Hanigan *et al.*, 2015a; Mitch and Sedlak, 2004).

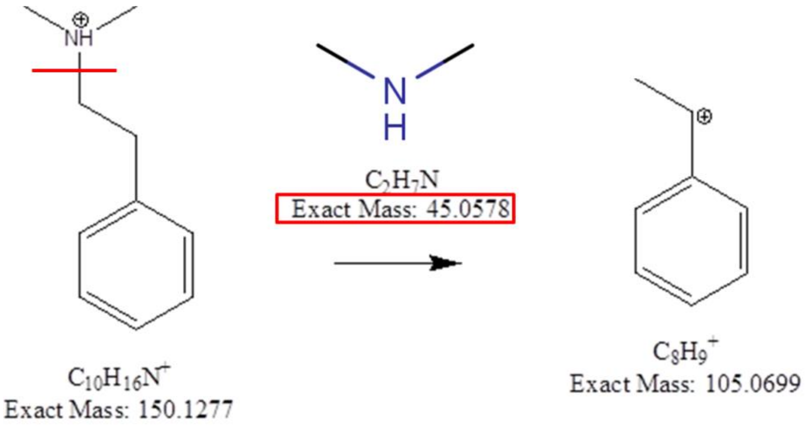


Figure 8-9 Predicted fragmentation pattern to produce a 45.0578 amu neutral loss from the model NDMA precursor, dimethylphenethylamine

To date, only the wastewater sample from Chapter 5 has been investigated thoroughly using these two diagnostic ion methods, although I have collected TOF-MS spectra for 11 other samples. Potential hits from 58.0651 m/z searches that are yet to be confirmed with authentic standards are: amitriptyline (isomeric to methadone and I see two peaks at this retention time), O-desmethyltramadol (tramadol metabolite), 3-hydroxymorphinan (dextromethorphan metabolite), venlafaxine, O-desmethylvenlafaxine (venlafaxine metabolite).

Spectra trawling for the 45.0578 amu neutral loss as described in Chapter 6 resulting in approximately 300 catches. Of the 300 catches, I attempted to identify structures that match the exact mass of five m/z that occur the most frequently across samples. Matches are difficult to interpret without inspecting the actual spectra but one potential match containing a tertiary amine was found for 209.1287 m/z. Aminocarb was the match and is used worldwide as an insecticide. This peak was in 7 of 10 surface water samples isolated and was absent in the wastewater sample, which would be expected for an insecticide. I was not able to identify the other four most commonly occurring m/z catches.

8.4 Summary

Table 8-3 summarizes the answers to the research questions posed. Polymer-derived precursors were not amenable to removal by activated carbon while watershed-derived were better removed than DOC and UV_{254}. A method was developed to isolate NDMA precursors and diagnostic ions were searched for in these isolates.

Table 8-3 Summary of research questions and answers

Research Question	**Answer**
Does activated carbon remove polymer-derived NDMA precursors?	No; polymer-associated NDMA formation was statistically unchanged after activated carbon treatment.
Are wastewater-associated NDMA precursors amenable to adsorption on activated carbon?	Yes; wastewater-associated NDMA formation decreased 50 to 75% when treated with activated carbon.
Are NDMA precursors removed on activated carbon better than UV_{254} absorbance and DOC?	Yes; DOC and UV_{254} breakthrough occurred in GAC columns at ~2,000 bed volumes while wastewater-derived NDMA precursors did not break through in >10,000 bed volumes.
Is it possible to achieve recovery of concentrated, watershed-derived, NDMA precursors from a sorbent?	Yes; after extensive optimization of a recovery method, >70% recovery was achieved in 7 of 11 surface and wastewater samples.
Do NDMA precursors in concentrated whole water samples fragment during collisionally induced dissociation to one or more diagnostic ion(s)?	Yes; tertiary amine containing structures fragmented to 58.0651 m/z ions and to 45.0578 amu neutrals.

Figure 8-10 shows the steps taken in Chapters 2, 3, 4, 5, 6 and 7 to arrive at the answers to these research questions. Although the individual steps are specific to NDMA, minor changes in this method could aid in the identification of other poorly characterized disinfection by-product precursors (e.g. haloacetonitriles, halonitromethanes, halobenzoquinones). Specifically, the method could be adapted by altering the physical chemistry used to concentrate the precursors (e.g. C_{18} instead of cation exchange) and modifications to the diagnostic ion search.

Figure 8-11 shows the overall contribution of these steps to the current state of NDMA precursor science. I cannot yet account for the total NDMA formation in most waters, because many watershed-derived NDMA precursors remain unidentified, but I believe this work has outlined the methodology to identify a majority of the precursors responsible for formation in drinking waters. Some precursors likely remain unidentified as exact mass hits from spectra trawling in Appendix C and further work to identify these will be conducted in the near future. This method along with specifics from the respective chapters in this dissertation could aid in the rapid identification of NDMA and other disinfection by-product precursors and have a profound impact on the risk of disinfection by-products to human health.

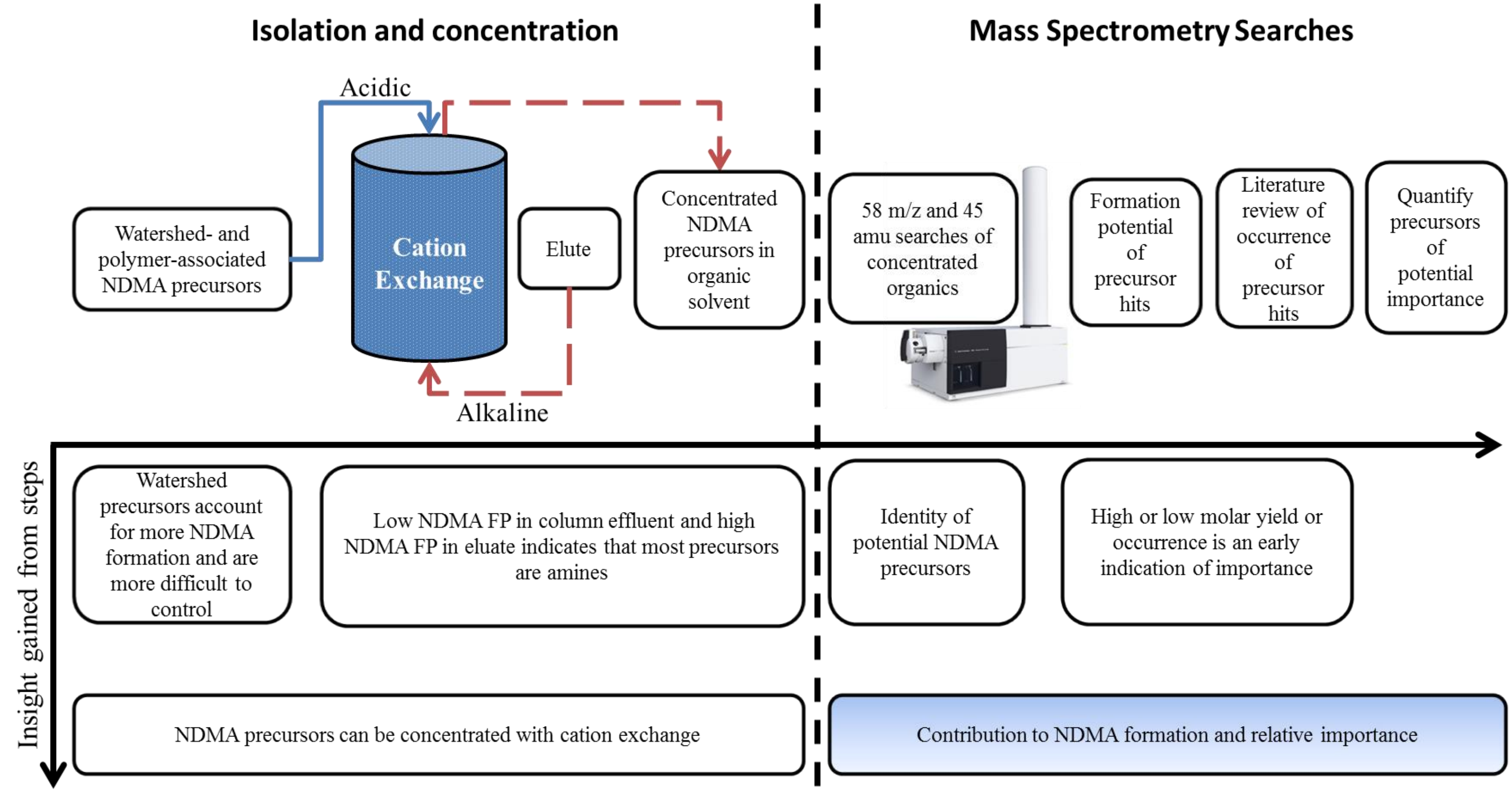


Figure 8-10 Steps in procedure to identify NDMA precursors to improve their control

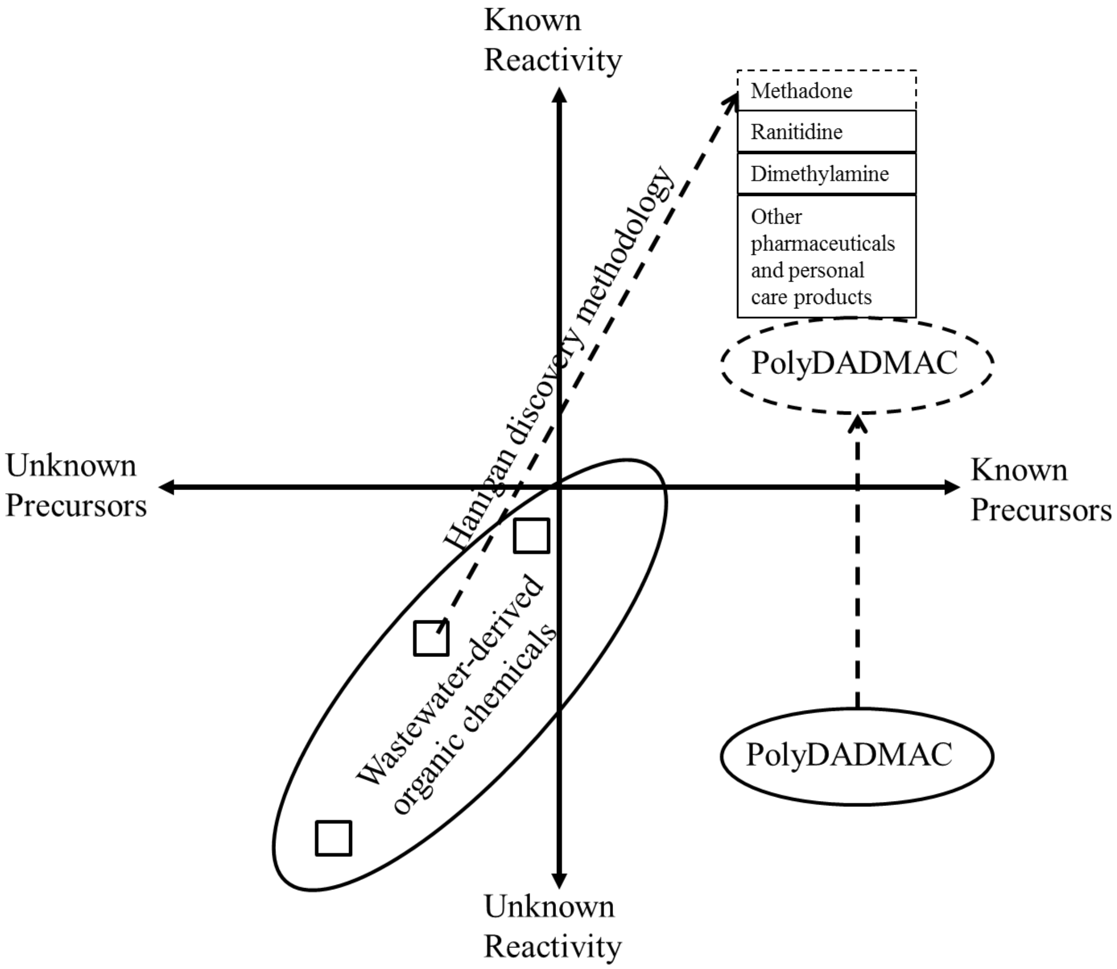


Figure 8-11 Dissertation contribution to NDMA precursor discovery and reactivity. Dashed lines represent my contribution to the state-of-the-science

9 Conclusions and Recommendations for Future Research

The objective of this chapter is to summarize the conclusions of individual chapters and provide guidance for future research. The overarching research question for this dissertation was, "**What are the likely organic chemicals responsible for nitrosodimethylamine (NDMA) formation in water and how can they be removed?"**

9.1 Conclusions

Chapter 2 – Formation, Precursors, Control, and Occurrence of Nitrosamines in Drinking Water: A Review

- Polymer use and watershed organic chemicals are the most important contributors to NDMA formation in drinking water. Bulk organic matter (dissolved organic carbon) forms low levels (<2 ng/L) of NDMA upon chloramination.
- Tertiary amines are the most important NDMA precursors based on yield during chloramination.

Chapter 3 – Contribution and Removal of Watershed and Cationic Polymer *N*-nitrosodimethylamine Precursors

- Polymer-associated precursors are not removed by activated carbon.
- Watershed-associated NDMA precursors are removed 60% to 80%, removal is rapid (<15 min for powdered activated carbon), and percent removal is independent of the initial precursor loading.

Chapter 4 – Adsorption of *N*-nitrosodimethylamine Precursors by Powdered and Granular Activated Carbon

- NDMA precursor removal was always greater than dissolved organic carbon and UV_{254} absorbing matter. NDMA precursors act like trace organic chemicals that access the pore structure of activated carbon that is unavailable to bulk organic matter.
- 10% to 30% of NDMA precursors are not amenable to adsorption to activated carbon, no matter the dose or contact time.

Chapter 5 – Optimizing Isolation of Organic Bases from Water Helps to Identify *N*–nitrosodimethylamine Precursors

- Cation exchange at pH 3 sorbs precursors well and elution using 5% NH_4OH in methanol resulted in a median of 82% recovery for 10 surface waters and one wastewater sample.
- Recovery with cation exchange indicates that most NDMA precursors in surface and wastewater are probably tertiary amines that are protonated at acidic pH.

Chapter 6 – Hanigan Neutral Ion Fragment Trawler

- Quadrupole time of flight mass spectrometry is not capable of conducting neutral loss scans due to hardware and software limitations.
- Spectra were exported and a MATLAB® program was developed to take advantage of the increased sensitivity of time of flight mass spectrometry and to incorporate neutral loss scans that are typically conducted on less sensitive quadrupole mass spectrometers.
- 181 parent ion/daughter pairs that had a neutral loss matching that of a tertiary amine (45.0578 amu) were discovered in 12 samples by the program.

- Most parent/daughter pairs are yet to be investigated thoroughly but one investigated pair was methadone, a pharmaceutical, and another may be aminocarb, a pesticide.

Chapter 7 – Methadone Contributes to *N*-nitrosodimethylamine Formation in Surface Waters and Wastewaters during Chloramination

- Methadone was putatively identified by a 45.058 amu neutral loss during trawling of exported spectra and confirmed by retention time and inspection of collisionally dissociated daughter ions.
- In a literature review, methadone occurred ubiquitously in Europe and in wastewater in the U.S. Methadone occurred in 50% of our extracted surface waters and in the only wastewater extracted at concentrations between 1 and 2556 ng/L among detections.
- Methadone has a molar NDMA yield of 23% to 70% when exposed to monochloramine, dependent on monochloramine dose. Methadone was previously unidentified as a NDMA precursor and this finding confirmed that our trawling for 45.0578 amu neutral losses is capable of identifying new NDMA precursors.
- Methadone may be responsible for physiologically relevant concentrations of NDMA in finished drinking waters. When metabolism, excretion pathways, removal in wastewater treatment plants and surface waters, and surface water dilution were taken into account, methadone may account for ~5 ng/L NDMA formation at drinking water treatment plants downstream of communities of 100,000 people. Increasing population of the upstream community increases

the usage (by mass) of methadone and therefore this may be a conservative estimate of the contribution of methadone to drinking water NDMA formation.

9.2 Recommendations for Future Research

Reducing the occurrence of NDMA in drinking water is important to reduce the risk of cancer associated with consuming disinfected drinking water. However, reducing the occurrence of NDMA should not be done at the expense of forming other disinfection by-products. Changes from monochloramine to other non-selective oxidants are unlikely to obey this rule because all oxidants produce by-products when they oxidize organic matter present ubiquitously in treated drinking water. Therefore, the goal should be to selectively remove or inactivate disinfection by-product precursors, including NDMA precursors. The other possibility is to cease introduction of the precursor into the source water before disinfection (e.g., coagulation polymers, pharmaceuticals, agricultural chemicals, and/or other anthropogenic chemicals).

All three mitigation strategies rely on detailed knowledge of the precursors that are reactive in forming NDMA. Although many model compounds have been identified as NDMA precursors, only two watershed-derived precursors have known occurrence in drinking water. One is dimethylamine which is ubiquitous as a biological by-product but not reactive enough in forming NDMA to be responsible for meaningful formation. The other is methadone, which was discovered during work conducted as part of this dissertation. Although polymers are known to contribute to NDMA formation, it not clear what the precursor material(s) in the polymer solution is (e.g., polymer itself or manufacturing contaminants). Clearly, there is a need to continue to identify individual precursors that are present in drinking water treatment plant influents and this dissertation provides the foundation for such work. Following the identification of precursors, mitigation strategies that do not produce disinfection by-products should be researched. This means that pre-oxidation, which was previously shown to reduce the formation of NDMA, is not a good candidate because it forms other by-products.

Without specific knowledge of NDMA precursor structures, the possibility still exists to use non-selective removal strategies such as activated carbon to remove NDMA precursors. This is studied in detail in this dissertation and proved to be a robust strategy to remove unknown NDMA precursors. Activated carbon is known to also remove bulk organic carbon which serves as the source material for other disinfection by-product precursors. However, activated carbon is relatively expensive due to the embedded energy and therefore other nonselective removal strategies that are yet to be investigated in depth (i.e., biologically activated carbon) might be more cost effective and should be of interest. Finally, all *disinfection* by-products are products of *disinfection*, and therefore the greatest opportunity for protecting public health might come from relying less on oxidation disinfection in concert with retaining the final biological stability of the finished water (pathogen inactivation).

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APPENDIX A

FORMATION, PRECURSORS, CONTROL, AND OCCURRENCE OF NITROSAMINES IN DRINKING WATER: A REVIEW

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A-1 Abstract

This review summarizes major findings over the last decade related to nitrosamines in drinking water, with a particular focus on *N*-nitrosodimethylamine (NDMA), because it is among the most widely detected nitrosamines in drinking waters. The reaction of inorganic dichloramine with amine precursors is likely the dominant mechanism responsible for NDMA formation in drinking waters. Even when occurrence surveys found NDMA formation in chlorinated drinking waters, it is unclear whether chloramination resulted from ammonia in the source waters. NDMA formation has been associated with the use of quaternary amine-based coagulants and anion exchange resins, and wastewater-impaired source waters. Specific NDMA precursors in wastewater-impacted source waters may include tertiary amine-containing pharmaceuticals or other quaternary amine-containing constituents of personal care products. Options for nitrosamine control include physical removal of precursors by activated carbon or precursor deactivation by application of oxidants, particularly ozone or chlorine, upstream of chloramination. Although NDMA has been the most prevalent nitrosamine detected in worldwide occurrence surveys, it may account for only ~5% of all nitrosamines in chloraminated drinking waters. Other significant contributors to total nitrosamines are poorly characterized. However, high levels of certain low molecular weight nitrosamines have been detected in certain Chinese waters suspected to be impaired by industrial effluents. The review concludes by identifying research needs that should be addressed over the next decade.

A-2 Introduction

As a low-cost control option for the Trihalomethane (THM) Rule (McGuire and Meadow, 1988), chloramines are increasingly used to control the formation of THMs, haloacetic acids (HAAs), and other halogenated disinfection by-products (DBPs) (Diehl *et al.*, 2000), and were selected as best available technology for consecutive systems in the Stage 2 DBP Rule (USEPA, 2006b). However, chloramination is associated with the formation of nitrosamines, which are emerging by-products of health and regulatory concern (Mitch *et al.*, 2003a). The U.S. Environmental Protection Agency's (USEPA's) Integrated Risk Information System database indicates for 6 nitrosamines that drinking water concentrations in the low ng/L level are associated with a 10^{-6} lifetime excess cancer risk. Accordingly, California's Department of Public Health (CDPH) set 10 ng/L notification levels for 3 nitrosamines (California Department of Public Health, 2013), and California's Office of Environmental Health Hazard Assessment (OEHHA) set a 3 ng/L public health goal for *N*-nitrosodimethylamine (NDMA) (OEHHA, 2006). The USEPA included 6 nitrosamines in the Unregulated Contaminant Monitoring Rule 2 (UCMR2) (USEPA, 2006a) and 5 on the Contaminant Candidate List 3 (CCL3) (USEPA, 2009). USEPA will make a preliminary regulatory determination for nitrosamines in 2013 and, if they intend to regulate, will propose in 2016. With the increasing reliance of utilities on chloramination, it is critical to identify options to control the formation of nitrosamines down to potentially low ng/L levels, while maintaining compliance with other DBP and microbial pathogen regulations.

The aim of this review is to provide a state-of-the-science assessment, based primarily upon the last 5 to 10 years of published literature, on critical nitrosamine formation mechanisms and precursors, methods for nitrosamine control by precursor removal or destruction, and nitrosamine occurrence.

A-3 Nitrosamine Formation Mechanisms

Pathways and precursors for the formation of nitrosamines during drinking water treatment were recently reviewed, together with precursors and formation pathways for other nitrogenous DBPs (Shah and Mitch, 2012). Nitrosamine formation pathways are summarized and updated here, and their importance relative to drinking water treatment is discussed (Table A–1).

Nitrosamine formation during chloramination. Early mechanistic research suggested nitrosamine formation by a reaction between monochloramine and organic amine precursors (Choi and Valentine, 2002; Mitch and Sedlak, 2002). Subsequent mechanistic research indicated that monochloramine was not a significant precursor; nearly all nitrosamine formation could be explained via reactions involving the low concentrations of dichloramine (i.e., ~5%) that always coexist with monochloramine under typical chloramination conditions according to the equilibrium (Schreiber and Mitch, 2006a):

$$2\ NH_2Cl + H^+ \leftrightarrow NHCl_2 + NH_4^+$$

Briefly, the nucleophilic attack of unprotonated secondary amines on dichloramine forms a chlorinated unsymmetrical dialkylhydrazine intermediate (e.g., Cl-UDMH), which is then oxidized by dissolved oxygen to the corresponding nitrosamine. The reaction occurs slowly (i.e., days), indicating that nitrosamines should accumulate within chloraminated distribution systems (Mitch *et al.*, 2003a; Mitch *et al.*, 2003b). Additional studies with model precursors, described later, demonstrated that tertiary and quaternary amines also serve as nitrosamine precursors. Molar yields of NDMA from most model secondary and tertiary amines were ~2% (Mitch and Sedlak, 2004), and were an order of magnitude lower for quaternary amines (Kemper *et al.*, 2010). However, yields from chloramination of tertiary amines containing a β-aromatic ring (e.g., ranitidine) were up to ~90% (Shen and Andrews, 2011b). Formation increased with pH due to the increasing prevalence of the active unprotonated form of the amines. Application of chloramines to authentic source waters indicated that NDMA formation increases with temperature (Krasner *et al.*, 2012a). Because this pathway relates to the predominant association of nitrosamine formation with chloramine disinfection, this reaction pathway is likely the most important pathway for drinking water treatment.

Recent mechanistic research suggests that bromide catalyzes the formation of NDMA during chloramination (Le Roux *et al.*, 2012a; Luh and Marinas, 2012). The formation of bromochloramine (NHBrCl) by monochloramine oxidation of Br^- has been suggested (Luh and Marinas, 2012). As Br^- is a better leaving group than Cl^-, Cl-UDMH is the expected intermediate. The reason for the promotion of NDMA formation remains unclear. Regardless, the increase in NDMA formation upon spiking of a limited number of authentic waters with bromide and treatment with relevant exposures of free chlorine or ozone for pre-oxidation followed by chloramines for post-disinfection usually was only significant for bromide concentrations ≥ 500 μg/L (Shah *et al.*, 2012). Evaluation of additional waters is needed to confirm that bromide promotion generally is only important for high-bromide waters.

Ozonation. While ozonation of typical secondary amine precursors may form NDMA, yields are low (i.e., 0.02%) (Andrzejewski *et al.*, 2008; Yang *et al.*, 2009).

However, for a limited subset of precursors containing hydrazine (e.g., unsymmetrical dimethylhydrazine and semicarbazides) or sulfamide (e.g., *N*,*N*-dimethylsulfamide functionalities) functional groups, yields could be > 50% (Kosaka *et al.*, 2009; Schmidt and Brauch, 2008; Shen and Andrews, 2011b; Von Gunten *et al.*, 2010). The reactions are rapid (i.e., < 1 h) and, in the case of sulfamides, bromide catalysis was significant at concentrations as low as 15 μg/L (Von Gunten *et al.*, 2010). The occurrence of *N*,*N*-dimethylsulfamide, a degradation product of the fungicide tolylfluanide, resulted in NDMA formation in excess of 10 ng/L upon ozonation in several German drinking water treatment plants (Schmidt and Brauch, 2008). Similarly, NDMA formation exceeded 10 ng/L after ozonation in several drinking water plants near Tokyo due to the presence of semicarbazide anti-yellowing agents (Kosaka *et al.*, 2009). To our knowledge, no similar instances of nitrosamine formation due to ozonation have been reported in United States drinking waters. While this pathway is potent at promoting nitrosamine formation, its importance is restricted to utilities with source waters containing significant concentrations of certain industrial or agricultural precursors.

Chlorination of nitrite-containing waters. Mechanistic research indicated that chlorination of nitrite in the presence of nitrosamine precursors can cause nitrosamine formation (Choi and Valentine, 2003; Schreiber and Mitch, 2007a). Formation has been attributed to the formation of a dinitrogen tetraoxide (N_2O_4) intermediate, which can nitrosate or nitrate amines. The reaction is rapid (i.e., < 1 h), but the yields are approximately two orders of magnitude lower than for the chloramination pathway. This pathway has been implicated in nitrosamine formation in chlorinated wastewater effluents and recreational waters (Shah and Mitch, 2012; Walse and Mitch, 2008).

However, limited research involving spiking of up to 140 μg N/L nitrite into authentic surface waters suggests that this pathway is unimportant in drinking waters (Shah *et al.*, 2012). Likewise, in distribution systems experiencing nitrification, there was (in general) no increase in NDMA formation compared to other sites without nitrification (Krasner *et al.*, 2012c). The low importance is likely due to the low concentrations of nitrosamine precursors, low nitrosamine yields by this pathway and rare co-occurrence of free chlorine and significant nitrite concentrations. An unexplored area where this reaction may prove important is where free chlorine is applied to nitrifying sections of chloraminated distribution systems to boost chloramine residuals; the substantial nitrite concentrations (i.e., up to 1 mg N/L) that can be observed in such systems may compete with residual ammonia to enable nitrite reaction with free chlorine, and potentially promote nitrosation. However, limited bench-scale testing of this hypothesis did not result in any significant impact (Krasner *et al.*, 2012c).

Breakpoint chlorination. Mechanistic research suggested that nitrosamine formation may increase up to four-fold during breakpoint chlorination (Schreiber and Mitch, 2007b). The reaction was rapid (<1 h), and appeared to derive from the formation of reactive nitrogen species formed during chloramine decay at the breakpoint. However, this enhancement was observed at a limited range of chlorine to ammonia molar ratios near 1.7:1 (8.6:1 weight ratio), where negligible residual chlorine was measured. With a sufficient chlorine dosage to maintain a free chlorine residual (e.g., 2:1 molar ratio), the enhancement in NDMA formation was not significant. In a range of authentic waters, NDMA formation was found to be significant in the region approaching breakpoint in highly wastewater-impacted drinking waters, but not in waters where polyDADMAC was the major source of precursors (Krasner *et al.*, 2012a). This pathway is unlikely to be important for drinking water treatment, except where utilities fail to achieve a free chlorine residual during breakpoint chlorination, or where blending of chlorinated and chloraminated waters (e.g., in consecutive systems) results in poorly-controlled breakpoint chlorination.

Catalytic formation on activated carbon. Mechanistic research demonstrated that activated carbon can catalyze the formation of nitrosamines from secondary amines at low yields (<0.3%) under aerobic conditions (Padhye *et al.*, 2011b). The mechanism likely involves formation of reactive nitrogen species on activated carbon surfaces by fixation of nitrogen gas from air. The relevance of this mechanism to tertiary or quaternary amine precursors for nitrosamines has not yet been demonstrated. Formation during sample analysis by activated carbon solid phase extraction (EPA Method 521) may be more important than during activated carbon treatment of drinking water because of the greater contact of the cartridges with air during drying of the cartridge between extraction and elution. This pathway did yield nitrosamine artifacts when EPA Method 521 was applied to the analysis of nitrosamines in aqueous samples associated with carbon sequestration from power plant exhaust gases that contained millimolar levels of secondary amines (Dai *et al.*, 2012). However, the combination of the low yields of the reaction from secondary amine precursors and the low importance in drinking waters of secondary amines as precursors for those nitrosamines evaluated by EPA Method 521 (Gerecke and Sedlak, 2003; Mitch and Sedlak, 2004) suggests that this pathway is unlikely to be important for drinking water treatment.

UV or sunlight photolysis. At 290-400 nm, sunlight photolysis of nitrite forms reactive nitrogen species, including nitrosating species (Lee *et al.*, 2007a). With mM concentrations of secondary amine precursors, yields were ~0.02%, likely due to competing sunlight photolysis of nitrosamines at λ = 300-350 nm. At the low NDMA precursor and nitrite concentrations in drinking waters supplies, this pathway is probably unimportant. Similarly, ultraviolet (UV) (254 nm) treatment of chlorinated secondary amines in the presence of monochloramine increased nitrosamine concentrations at UV fluence relevant to recreational water treatment (Soltermann *et al.*, 2013). However, this mechanism is unlikely to be important for drinking waters due to the low prevalence of secondary amines.

Table A–1 Summary of nitrosamine formation pathways in drinking water

Mechanism	**Features**	**Importance**
Chloramination	• Dichloramine as the active reagent • Formation over days • Yields ~2% for most secondary/tertiary amines but >50% for amines with β-aromatic groups • Bromide catalysis for high bromide concentrations (>500 μg/L)	High
Ozonation	• Rapid formation (<1 h) • Bromide catalysis important for 15 μg/L bromide • Importance restricted to source waters impaired by hydrazines/sulfamides	Limited
Chlorine-nitrite	• Formation of the nitrosating and nitrating species, N_2O_4. • Rapid reaction (<1 h) but yields 2 orders of magnitude lower than for chloramination • Low importance due to low concentrations of nitrosamine precursors, low yields and limited co-occurrence of chlorine and high nitrite concentrations	Limited
Breakpoint chlorination	• Formation of nitrosating species from chloramine decay reactions at the breakpoint • Rapid enhancement of nitrosamine formation • Importance limited to poorly-controlled breakpoint chlorination scenarios where no significant free chlorine residual is achieved (mixing of chlorinated and chloraminated waters in consecutive systems?)	Low
Activated carbon	• Formation of nitrosating species from nitrogen gas on activated carbon surfaces • Restricted to secondary amine precursors • Low importance due to low concentrations of secondary amine precursors	Low
Photolysis	• Sunlight photolysis of nitrite or UV photolysis of secondary chloramines • Low importance due to low concentrations of nitrite and secondary amines, low yields (<0.3%) and photolysis of nitrosamine products	Low

A-4 Nitrosamine Precursors

This section describes the state of knowledge of the relative importance of different types of bulk and trace level organic precursors for nitrosamines potentially present or added to drinking waters (Table A–2).

Development of FP and SDS tests. Most previous research on nitrosamine precursors has used formation potential (FP) tests. The FP test maximizes nitrosamine formation using much higher monochloramine doses than applied during drinking water treatment. The first NDMA FP test applied preformed monochloramine at a 140-mg/L dose for 10 days (Mitch *et al.*, 2003b). More recently, a "reactivity" based method was developed, in which chlorine was added at three times the total organic carbon (TOC) concentration of the sample (on a mass basis with Cl_2) and sufficient ammonia to (typically) reach a Cl_2/N mass ratio of 3:1 (Krasner *et al.*, 2004; Krasner *et al.*, 2007), where the ammonia was added first. Samples were held at pH 8 at 25°C for 3 days. This method has been used for treated wastewaters, reclaimed waters, watershed, and drinking water samples (Krasner *et al.*, 2009b; Krasner *et al.*, 2012b). However, previous work (Krasner *et al.*, 2012b) generated NDMA from drinking water sources using FP tests, even when no NDMA is reported from actual treatment, illustrating that FP tests are used to represent precursor loading rather than formation under typical conditions.

Optimization of treatment and disinfection, necessary for continued use of chloramination for DBP control, must be performed under realistic conditions. In recent work (Krasner *et al.*, 2012a; Shah *et al.*, 2012), realistic simulated distribution system (SDS) and uniform formation condition (UFC) tests for nitrosamine and halogenated DBP formation were developed. The UFC test involves a chlorine dose sufficient to leave

~2.5 mg/L as Cl_2 residual after 3 minutes, ammonia addition to achieve a Cl_2/N weight ratio of 4.75:1, and a reaction in the dark for 3 days at pH 8 and 25°C, all intended to mimic a "standard" set of realistic chloramination conditions. Alternatively, SDS tests match actual site-specific plant operating conditions. Bench-scale SDS tests of treated water yielded NDMA, THM, and HAA levels that closely matched observed formation in the corresponding distribution systems (Krasner *et al.*, 2011), indicating that the SDS test is suitable for exploring treatment and control research.

Nitrosamine formation from chloramination of model precursors. Chloramination is the major cause of nitrosamine formation in North American drinking waters, and amines are expected to be the major source of precursors during chloramination. Amides, the other major category of organic nitrogen precursors, react orders of magnitude more slowly than amines with chloramines, due to the electron-withdrawing carbonyl groups adjacent to the nitrogen (Mitch and Sedlak, 2004; Walse and Mitch, 2008). Although nitrosamine formation from amides is low over short chloramine contact times, the slow release of secondary amines from certain amides by hydrolysis can form significant concentrations of nitrosamines over timescales of ~1 week (Mitch and Sedlak, 2004). Examples include the solvent dimethylformamide and the herbicides dimethyldithiocarbamate and diuron (Chen and Young, 2008; Mitch and Sedlak, 2004; Padhye *et al.*, 2013).

Although primary amines can be nitrosated, primary nitrosamines decay nearly instantaneously, releasing nitrogen gas and a carbocation. Thus primary nitrosamines have not been isolated (Ridd, 1961). Most mechanistic research has addressed secondary amines (Choi and Valentine, 2002; Mitch and Sedlak, 2002; Schreiber and Mitch, 2006a;

Shah and Mitch, 2012), which can directly form stable secondary nitrosamines. While most research has focused on NDMA formation from dimethylamine (DMA), other secondary amines can form their corresponding nitrosamines upon chloramination(Schreiber and Mitch, 2006b).

Tertiary amines may also serve as significant precursors. Upon exposure to chlorine, tertiary amines decay nearly instantaneously and quantitatively to release an aldehyde and a secondary amine capable of forming a stable secondary nitrosamine upon subsequent chloramination (Mitch and Schreiber, 2008). There was no regioselectivity regarding which of the alkyl substituents on the tertiary amines were eliminated as the aldehyde. Similar reactions pertain to chloramination of tertiary amines, although the conversion of the tertiary amine to a secondary amine was slower due to the lower reactivity of chloramines compared to chlorine. The net result is that nitrosamine yields from most tertiary amines during chloramination are comparable to those from secondary amines (i.e., ~2%).

However, a subset of tertiary amines, where one of the alkyl substituents contained an aromatic group in the β-position to the nitrogen (e.g., a benzyl functional group), exhibit far higher yields of NDMA during chloramination (Le Roux *et al.*, 2011; Shen and Andrews, 2011a; Shen and Andrews, 2011b). Such functional groups are observed in certain pharmaceuticals. For example, ranitidine, the active component in the antacid Zantac®, formed NDMA at yields of 60-90% (Le Roux *et al.*, 2011; Shen and Andrews, 2011a; Shen and Andrews, 2011b). These higher yields suggest that these tertiary amines can form nitrosamines without proceeding through a secondary amine intermediate, although the specific pathway is unclear.

Although the positive charge on quaternary amines hinders reactions with chloramines, model quaternary amines formed NDMA at yields ~0.2%, likely via pathways involving degradation of quaternary amines to secondary amines initiated by radicals (Kemper *et al.*, 2010; Padhye *et al.*, 2010). As indicated below, quaternary amines are important functional groups in personal care products (e.g., shampoos), and materials used for drinking water treatment (e.g., cationic coagulation polymers and certain anion exchange resins).

NDMA formation from bulk organic matter. While bulk organic matter analytical parameters (TOC, UV_{254}) and other precursors (bromide) or operating conditions (chlorine dose, pH, temperature) can be used to predict the formation of regulated DBPs across a range of waters, no such relationships were found between dissolved organic nitrogen (DON), nitrite, ammonia or bromide and the formation of ng/L levels of NDMA (Chen and Westerhoff, 2010). Average DON levels in drinking waters are on the order of 0.2 mg N/L (200,000 ng N/L), which equates to dissolved organic carbon (DOC)/DON ratios of ~18/1 (Lee and Westerhoff, 2006). To produce 50 ng/L of NDMA requires only ~500 ng N/L of precursor amines, assuming 2% molar yield, or on the order of only 0.25% of the average DON in source waters. This perhaps explains why bulk measurements of DON in different water sources may not be good surrogates for NDMA precursors. However, within a watershed, DON may correlate with NDMA FP, if correlations exist between bulk DON and the subset of NDMA precursors.

Just as hydrophobic organic acids (i.e., humic substances) were shown to contribute the most towards THM formation, efforts to compare the reactivity of different bulk organic matter fractions towards NDMA formation have been forged. NDMA formation from organic matter isolates in the presence of monochloramine requires one nitrogen atom in organic matter to react with inorganic nitrogen in chloramines, based upon $^{15}N\text{-}NH_2Cl$ experiments (Mitch *et al.*, 2009). Generally, the hydrophilic fractions tended to form more NDMA than hydrophobic fractions, and base fractions tend to form more NDMA than acidic fractions when normalized to a carbon basis (Chen and Valentine, 2007). NDMA yields (ng NDMA FP/mg DOC) ranged from 22 to 78 in one study (Chen and Valentine, 2007), but after accounting for the contribution of each fraction to the total DOC of the river water, the low reactivity of the hydrophobic acid fraction still accounted for nearly 70% of the NDMA FP . However, Dotson *et al*. (2009) found that hydrophobic acids had no reactivity to form NDMA. Additional studies with isolates from multiple surface waters and wastewaters, confirmed a trend for isolates with greater nitrogen enrichment (base and colloid fractions) having higher NDMA yields (Lee *et al.*, 2007b)). The base fractions were the most reactive, with yields of up to 6 ng/mg DOC (Dotson *et al.*, 2009). The reactivity of wastewater effluents was substantially higher than that of algal-impacted waters. Despite representing <3% of the DOC in bulk waters, the base fraction accounted for ~60% of the NDMA in a wastewater effluent.

In another study, the vast majority of DON in bulk wastewater effluent organic matter and the NDMA FP were hydrophilic in nature (Pehlivanoglu-Mantas and Sedlak, 2008). Low molecular weight compounds, capable of passing through a 1000 Da ultrafilter, contained >60% of the NDMA precursors in wastewater effluents (Pehlivanoglu-Mantas and Sedlak, 2008). In separate research, NDMA formation from different size fractions of organic matter indicated that colloidal material produced

NDMA – perhaps from sorbed trace organic chemicals – otherwise, <2,500 Da material yielded NDMA (Krauss *et al.*, 2010).

Origin of NDMA precursors in source waters. Treated wastewater effluent organic matter (EfOM) generally contains higher levels of NDMA FP than drinking water NOM, including eutrophic water supplies (Bond *et al.*, 2011; Krasner *et al.*, 2008; Krasner *et al.*, 2009a; Nawrocki and Andrzejewski, 2011; Russell *et al.*, 2012). In many cases, the fraction of wastewater effluent in drinking water sources, based upon the levels of wastewater indicators, such as boron, the anticonvulsant primidone or the artificial sweetener sucralose, correlated well with NDMA FP in drinking water sources (Krasner *et al.*, 2008). EfOM from a biological WWTP includes soluble microbial products (SMPs) (Barker and Stuckey, 1999), where laboratory-generated SMPs from activated sludge were found to contribute to the formation of NDMA (Krasner *et al.*, 2008). However, organic matter isolates from SMPs had lower NDMA FP yields than bulk wastewater EfOM (Dotson *et al.*, 2009). The particular association of NDMA formation and municipal wastewater effluents suggests that anthropogenic chemicals may be important.

One study of Chinese source waters and drinking waters examined the occurrence of nine nitrosamines and their corresponding secondary amines (Wang *et al.*, 2011c). Secondary amine concentrations ranged from 0.1 to 4 μg/L in these waters, which were likely impaired by industrial effluents. Although secondary amines can be important precursors in certain waters heavily impacted by specific industrial effluents, in most natural waters (Gerecke and Sedlak, 2003) or municipal wastewaters (Mitch and Sedlak, 2004), dimethylamine concentrations were not sufficient to explain NDMA formation.

Trimethylamine concentrations in wastewater effluents also were insufficient to explain NDMA formation (Mitch and Schreiber, 2008). However, tertiary amines are common functional groups in anthropogenic chemicals and, as noted above, most form nitrosamines at yields comparable to secondary amines. A subset of β-aryl tertiary amines formed NDMA at significantly higher yields, such as pharmaceuticals like ranitidine. Such pharmaceuticals are microconstituents of wastewater-impacted waters, but may explain a significant fraction of NDMA formation if they form NDMA at high yields upon chloramination. However, in a survey of wastewater-impacted surface waters, ranitidine was only detected with a frequency of 1.2% and the maximum concentration was at the 10 ng/L detection limit (Kolpin *et al.*, 2002). A decomposition by-product of ranitidine was also shown to have a high yield to form NDMA (Le Roux *et al.*, 2012b), but it is unclear whether such by-products occur in significant concentrations in source waters.

Alternatively, although NDMA yields from quaternary amines in FP assays were ~0.2% (Kemper *et al.*, 2010), quaternary amines are macroconstituents of monomers and polymers in an array of consumer products (e.g., shampoos). However, their concentrations in wastewater-impacted waters are unknown, due to the difficulty of quantifying polymer concentrations.

Contribution of water treatment materials towards NDMA formation.

Cationic polymers. Many cationic treatment polymers (e.g., polyamines, polyDADMAC) used as coagulant or dewatering aids in drinking water treatment can degrade and release NDMA precursors (Bolto, 2005; Kohut and Andrews, 2003; Najm and Trussell, 2001; Wilczak *et al.*, 2003). In one study, the age of polymer feed stocks was not shown to affect NDMA FP (Kohut and Andrews, 2003). Chlorination of backwash water from filters fed with polyDADMAC-coagulated water formed elevated levels of NDMA (Wilczak *et al.*, 2003). There has been considerable research into the residuals and removal of polyelectrolytes used in water treatment (Bolto and Gregory, 2007). Unfortunately, techniques to monitor residuals after coagulation have detection limits on the order of μg/L, and these are likely inadequate to monitor for ng/L levels of NDMA FP. Nonetheless, FP tests can provide sufficient information on polymer impacts (Krasner *et al.*, 2012b).

Polyamines produced more NDMA than polyDADMAC, and the highest levels of NDMA were found around pH 8 during chloramination (Park *et al.*, 2009). For polyamines, the tertiary amines terminating polymer chains were mostly responsible for NDMA formation, while degradation of the quaternary amine ring in polyDADMAC, which lacks tertiary amines, accounted for the NDMA formation (Park *et al.*, 2009). Accordingly, for polyamines, lower molecular weight polymers produced more NDMA than higher molecular weight forms, and NDMA formation was unaffected by the molecular weights of polyDADMAC polymers (Park *et al.*, 2009). During ozonation, degradation of the quaternary ammonium ring of polyDADMAC by hydroxyl radicals produced dimethylamine, which can form NDMA during subsequent chloramination (Padhye *et al.*, 2011a). Used as an alternative polymer, polyacrylamide resulted in substantially less NDMA FP than polyDADMAC (Labernik *et al.*, 2010), in accordance with its lack of dimethylamine functional groups.

Anion-exchange resins. Anion exchange units use strong (quaternary amine) or weak (tertiary amine) base polymeric resins. Fresh trimethylamine- and tributylamine-based type 1 and dimethylethanolamine-based type 2 anion exchange resins released NDMA and their corresponding nitrosamines (e.g., *N*-nitrosodibutylamine from tributylamine-based resins), likely due to shedding of manufacturing impurities (Kemper *et al.*, 2009). The extent of such shedding was highly variable among commercially available resins (Singer and Flower, 2012). The resins can also degrade over time releasing organic precursors that might contribute to formation of their corresponding nitrosamines within distribution systems when chloramines are applied downstream (Nawrocki and Andrzejewski, 2011). Higher levels of nitrosamine precursors were observed after regeneration cycles, and particularly after periods of flow interruption, where the resins were bathed in stagnant water (Singer and Flower, 2012). In full-scale anion exchange treatment systems, shedding of precursors declined after multiple regeneration cycles (Krasner *et al.*, 2012a; Singer and Flower, 2012). Exposure of resins to chlorinated tap water produced NDMA in the effluents (Kimoto *et al.*, 1980; Najm and Trussell, 2001). When magnetic ion exchange resin (MIEX) was used to treat 3 wastewater effluents, NDMA FP increased from 156-287 to 266-344 ng/L, whereas the increase for 3 drinking waters was from 10-12 to 14-18 ng/L (Gan and Karanfil, 2012). A similar increase was not observed in deionized water treated with MIEX. The mechanism for greater formation is not well understood, but it was found that increasing wastewater content increased NDMA FP after MIEX treatment. Because cation exchange resins do not use amine-functional groups they did not release NDMA or NDMA precursors (Kemper *et al.*, 2009).

Distribution system synthetic materials. Recent field and bench-scale studies show that certain rubber seals and gaskets in potable water systems can be a source of

NDMA in chloraminated water systems (Morran *et al.*, 2011a; Teefy *et al.*, 2011). The vulcanization process of rubber production is known to release NDMA (Incavo and Schafer, 2006; Spiegelhalder and Preussmann, 1982)). While PVC pipe materials were relatively unreactive in forming NDMA in chlorinated or chloraminated water, rubber components (pipe rubber ring joint lubricant [in the form of water-soluble gel]; natural rubber seal rings, ethylene propylene diene terpolymers and styrene-butadiene rubber) leached NDMA in chlorine-free water and formed NDMA after chloramination (Morran *et al.*, 2011a). Periods of stagnation resulted in significant increases in NDMA levels. There was no apparent relationship between NDMA release and exposed surface area or newer versus older exposed materials. NDMA levels resulting from sealing ring leaching, on the order of 10 to 25 ng/L, would undermine any NDMA-reduction processes at the water treatment plant (Morran *et al.*, 2011a). In another study, elevated NDMA levels were observed in a potable water distribution storage tank that was equipped with temporary gaskets (ethylene propylene diene monomer M class rubber; NSF/ANSI 61 certified for drinking water use) (Teefy *et al.*, 2011), and the gaskets were determined to be the source of NDMA and other nitrosamines (N-nitrosodibutylamine [NDBA] and N-nitrospiperidine [NPIP]).

Table A–2 Importance of different precursors for nitrosamine formation in drinking waters

Precursor	Importance
Amine-containing coagulation polymers	High
Effluent-impacted source waters	High
Pharmaceuticals and personal care products	Moderate/High
Distribution system materials	Moderate
Anion exchange resins	Moderate
Soluble microbial products	Limited
Agricultural chemicals	Limited
Bulk DON	Low
Algae	Low

A-5 Removal of Nitrosamines and their Precursors

Nitrosamine removal can occur by sorption to activated carbon or UV photolysis within drinking water plants. However, due to the slow kinetics of nitrosamine formation during chloramination, nitrosamine formation continues within chloraminated distribution systems. Because nitrosamines can continue to form in distribution systems unless the precursors have been removed or transformed, the discussion will focus on removal of nitrosamine precursors (Table A–3).

Coagulation and polymer optimization. Coagulation using four different German waters at multiple ferric chloride dosages concluded that <10% removal occurred of NDMA, N-nitrosodiethylamine (NDEA) or N-nitrosopyrrolidine (NPYR) FP (Sacher *et al.*, 2008). Alum coagulation (40 or 80 mg/L) of a wastewater-dominated river showed <10% removal of NDMA FP (Krasner *et al.*, 2008). Likewise, lime softening had no significant impact on NDMA FP (Mitch *et al.*, 2009). It has been shown that the majority of NDMA precursors are <1 kDa and that this fraction of NOM is poorly removed by coagulation (Xu *et al.*, 2011).

Coagulation, due to the frequent inclusion of amine-based cationic polymers, typically increases NDMA FP (Bond *et al.*, 2011). One study involving 3 treatment plants (typically 2 sampling events each) found that NDMA FP increased by 43 to 82% at plants using polyDADMAC and was not changed (±18%) at the plants that did not use a cationic polymer (Krasner *et al.*, 2012b). High polymer doses can leave residual polymer in the effluent (Novak and Montgomery, 1975; Novak and Langford, 1977). One bench-scale study found polyDADMAC residual in all samples in which it was used as a coagulant alone, at concentrations of at least 100 µg/L. When polyDADMAC and alum were used concurrently, detection of polyDADMAC after filtration was reduced, indicating a need for polymer dose optimization (Becker *et al.*, 2004). For example, the dosage of coagulant could be raised to compensate for a reduction in polyDADMAC dosage in order to maintain good turbidity removal and filter run lengths (Labernik *et al.*, 2010).

Physical adsorption of nitrosamine precursors. Because they are fairly hydrophilic (e.g., $K_{OW} = 0.27$ for NDMA) (ATSDR, 1989; Mitch *et al.*, 2003b), nitrosamines sorb poorly to activated carbon. Furthermore, chloramines are typically added after activated carbon treatment, so nitrosamines will normally not be present in drinking waters treated by activated carbon. Because adsorption of nitrosamines after formation is not feasible, sorption can only be applied for the removal of nitrosamine precursors. Although research regarding sorption of precursors is in its infancy, one study has shown 50% NDMA FP reduction in 3 of 4 surface waters exposed to powdered activated carbon (PAC; Calgon F300) at a dose of just 5 mg/L (Sacher *et al.*, 2008). A PAC dose of 20 mg/L produced reductions of 90% or greater. However, the water was in contact with PAC for 7 d in both cases to assure that adsorption equilibrium was established, whereas in conventional treatment water is only in contact with PAC for hours.

NDMA FP was reduced in a municipal wastewater effluent by both PAC and granular activated carbon (GAC) (Hanigan *et al.*, 2012). PAC reduced NDMA FP after a 4 hour contact time by 37 and 59% at doses of 3 and 8 mg/L, respectively. Using GAC at a 10 min simulated empty bed contact time to treat a mixture of 90% surface water and 10% wastewater, NDMA FP breakthrough was less than 20% after 10,000 bed volumes. For both GAC and PAC treatments, removal of NDMA FP exceeded removal of DOC and UV, surrogate measures for traditional DBP precursors, including THMs. Similarly, pilot- and full-scale studies using GAC demonstrated 60-80% reduction in NDMA FP in surface waters (Hanigan *et al.*, 2012). Farré *et al.* (2011) found that NDMA FP was reduced from 250 to 50 ng/L using pilot-scale biologically active carbon (BAC) columns at a wastewater reuse facility. Biologically active sand filtration removed precursors poorly, suggesting the importance of adsorption onto the BAC.

For specific trace organic compounds which may produce NDMA upon chloramination, sorption affinity can be inferred from octanol-water partitioning coefficients, but this is increasingly difficult for higher molecular weight compounds with acid or base functional groups (Redding *et al.*, 2009). Low molecular weight amine precursors sorb poorly to GAC. For example, the Freundlich parameters for dimethylamine were K_f = 0.92 mg/g and 1/n = 0.84 (Hwang *et al.*, 1994). In a GAC pilot-plant study, it was shown that several pharmaceutical precursors of NDMA sorbed well to BAC (Farré *et al.*, 2011). Even the most poorly absorbed compound, roxithromycin, was reduced ~98% across BAC. However, in another study some pharmaceuticals that would sorb readily to activated carbon from deionized water were poorly removed from surface waters (e.g., <1% removal of carbinoxamine after 24 h), presumably due to competition for sorption sites from other organic constituents (Hanigan *et al.*, 2012).

Nitrosamine precursor removal by riverbank filtration. Riverbank filtration has been shown in Europe to remove nitrosamine precursors via biodegradation (Sacher *et al.*, 2008). Recently, riverbank filtration was shown to be effective at a site in the U.S. (Krasner *et al.*, 2012d). Travel time varied from ~21 to 90 days. The riverbank filtration-treated water was diluted somewhat (~30%) by local groundwater. Based upon this dilution factor, the true removal of TOC was ~30%, and the removal of NDMA FP was 64%. Thus, NDMA precursors appeared to be better removed than the bulk NOM.

Pre-oxidation of nitrosamine precursors. Previous research has demonstrated that pre-oxidation of waters with chlorine, ozone, chlorine dioxide, permanganate, ferrate, hydrogen peroxide, and even sunlight are capable of reducing NDMA formation during subsequent chloramination by deactivating NDMA precursors (Charrois and Hrudey, 2007; Chen and Young, 2008; Lee *et al.*, 2007a; Lee *et al.*, 2008). To evaluate precursor deactivation under drinking water-relevant conditions, recent research evaluated the reduction in NDMA formation in authentic waters associated with combinations of pre-oxidants (chlorine, ozone, chlorine dioxide, and low or medium pressure UV) applied at exposures relevant to 3-log removal of *Giardia* at 5°C with post-chloramination conducted under conditions relevant to drinking water distribution (Shah *et al.*, 2012). Ozone was the most effective of the four pre-oxidants, generally achieving 50% reduction in NDMA formation for exposures ≤ 0.4 mg•min/L, roughly 20% of the exposure range relevant to *Giardia* control. Chlorine achieved similar results at exposures ~70 mg•min/L, nearly half that relevant to *Giardia* control. Chlorine dioxide and UV treatment were relatively ineffective over exposures relevant to disinfection. However, reductions in NDMA precursors of ~30% were observed for UV fluence relevant to advanced oxidation (~1000 mJ/cm^2). In some waters, chlorine promoted NDMA formation at low exposures, but formation declined again at higher exposures. In other waters, chlorine dioxide promoted NDMA across the range of exposures.

Maximum precursor deactivation by free chlorine is anticipated at pH ~8.5–9, where there is maximum co-occurrence of the active oxidant (HOCl, $pK_a = 7.5$) and the reactive deprotonated amine precursors (pK_a ~10-11) (Lee and von Gunten, 2010). Krasner and colleagues (2008) evaluated the impact of pH and temperature on NDMA formation on various drinking waters, where there was a 3-min free chlorine contact time before ammonia addition. In many waters, they observed at pH 8 or 9 that there was more NDMA formation at 5°C than at 25°C. To clarify these trends, these researchers varied the pre-chlorination and post-chloramination temperatures. The results indicated that nitrosamine formation increased with temperature during post-chloramination. However, precursor deactivation increased with temperature during pre-chlorination. In some waters, the reduction in precursor deactivation at 5°C enabled higher nitrosamine formation overall than at 25°C, despite the slower formation during post-chlorination. At pH 7, such a temperature effect was not observed, most likely due to poor precursor deactivation over this short chlorination time resulting from the low prevalence of deprotonated amines.

Unfortunately, increasing pre-oxidant exposures for control of NDMA formation promotes the formation of regulated and unregulated DBPs associated with each pre-oxidant, including THMs, HAAs, and chloral hydrate for chlorine; bromate, chloropicrin, and chloral hydrate for ozone; chlorite for chlorine dioxide; and chloropicrin and chloral hydrate for medium pressure UV treatment (Shah *et al.*, 2012). For the application of each pre-oxidant at ~60-100% of the exposures relevant to *Giardia* control to different waters, the median concentrations of regulated by-products did not exceed relevant maximum contaminant levels (MCLs), but these values were exceeded in some waters. Because ozone was able to deactivate precursors effectively at low exposures relevant to disinfection, its use for NDMA control may minimize these risk tradeoffs associated with the formation of other by-products. For example, bromate was never detected at >3 μg/L when 8 waters were pre-ozonated at exposures that reduced NDMA formation by 50% after post-chloramination. While similar studies have not yet been conducted for other pre-oxidants, the results of previous research suggest that permanganate, ferrate, hydrogen peroxide, and sunlight would be less effective for NDMA precursor deactivation than ozone and chlorine (Chen and Young, 2008; Lee *et al.*, 2008).

Modification of method of chloramine application. Based upon the dichloramine pathway for nitrosamine formation during chloramination, the addition of chlorine prior to ammonia was suggested to reduce nitrosamine formation during chloramination by preventing the occurrence of high chlorine to ammonia molar ratios at the point of chlorine injection, and thereby minimizing dichloramine formation (Schreiber and Mitch, 2005). This technique was successfully pilot-tested at a municipal wastewater recycling plant (Mitch *et al.*, 2005). It was also pilot tested at a drinking water plant (Krasner *et al.*, 2008). The order of addition of chlorine and ammonia at pilot scale often had no impact. However, when there was an effect, chlorine added first resulted in less NDMA formation.

Destruction of nitrosamines by UV treatment. UV treatment is the most widely practiced method for destroying nitrosamines at reuse facilities (Mitch *et al.*, 2003b). Because a UV fluence of ~1,000 mJ/cm^2 is required for a log order reduction in NDMA (Sharpless and Linden, 2003), UV treatment for nitrosamine destruction is more expensive than for disinfection. While effective for destruction of nitrosamines, UV treatment at fluence near 1,000 mJ/cm^2 is only partially effective at destruction of nitrosamine precursors (see above). Because chloramines are usually applied after UV treatment at drinking water treatment plants, there would generally be no nitrosamines present to destroy and, moreover, there would be formation of nitrosamines in the chloraminated distribution system. Nonetheless, UV treatment to destroy nitrosamines was designed for a drinking water treatment plant on an effluent-dominated river, where there were nitrosamines in the river water (Swaim *et al.*, 2006).

Table A–3 Importance of drinking water unit processes to control NDMA formation

Treatment	**Features**	**Importance**
Polymer Optimization	• Reduction in polyDADMAC dosage can reduce, but not eliminate NDMA formation.	High
Precursor Pre-Oxidation	• Involves risk tradeoffs because increasing pre-oxidant exposure promotes the formation of DBPs associated with each pre-oxidant. • Ozone most effective, followed by chlorine • UV treatment only partially effective at advanced oxidation process fluence • Chlorine dioxide relatively ineffective	High
Alternative Polymer	• Nearly all cationic polymers currently in use will contribute to nitrosamine formation because they are amine-based. Epi-DMA polymers are more potent precursors than polyDADMAC. Polyacrylamide has much less precursors than polyDADMAC.	High
Activated Carbon	• Activated carbon is more efficient at removing NDMA precursors than TOC in limited studies. • The ability to remove precursors for other nitrosamines is limited to one study in China.	High
Riverbank Filtration	• Limited evidence shows that riverbank filtration can remove NDMA precursors.	Moderate
Modify Chloramination Protocol	• Minimizes dichloramine, the active inorganic chloramine for promoting nitrosamine formation • Involves a hydraulic mixing phenomenon. Needs more pilot- or full-scale testing to characterize importance.	Moderate
Biofiltration	• Biofiltration may remove NDMA precursors, but can also increase NDMA formation by transforming some precursors into more potent forms.	Low or Moderate
UV Treatment	• Full-scale applications ongoing for hazardous waste treatment and wastewater recycling applications • Destroys nitrosamines, but only modest destruction in nitrosamine precursors (see pre-oxidation). Nitrosamine formation would continue from remaining precursors within chloraminated distribution system.	Low
Anion Exchange	• Anion exchange resins can increase nitrosamines. • The ability of anion exchange resins to remove nitrosamine precursors is unclear.	Low
Coagulation and Softening	• Neither process significantly removes NDMA precursors.	Low

A-6 Nitrosamine Occurrence and Detection

Occurrence surveys in North America. In line with expectations from known formation pathways, most studies have found that NDMA formation is more associated with chloramination than with chlorination (Boyd *et al.*, 2011; Mitch *et al.*, 2009; Russell *et al.*, 2012) (Table A–4). Systems with high plant effluent NDMA (>50 ng/L) typically used chloramines as the primary rather than secondary disinfectant (Russell *et al.*, 2012), reflecting the potential for precursor deactivation by strong pre-oxidants. Due to the long time-scales of nitrosamine formation, plants with long in-plant chloramine contact times (e.g., 12-18 hr) tended to have higher NDMA in the plant effluent than those with short (e.g., 0.5-2 hr) contact times (Krasner *et al.*, 2012d), and NDMA concentrations tend to increase throughout chloraminated distribution systems (Krasner *et al.*, 2009a; Krasner *et al.*, 2012c; Krasner *et al.*, 2012d; Liang *et al.*, 2009; Valentine *et al.*, 2005).

In the largest study, the USEPA UCMR2 (~1,200 systems), NDMA was detected (>2 ng/L) in 34% of chloramine plant effluents, but only 3% of chlorination plant effluents (Russell *et al.*, 2012). When detected in chlorinated plant effluents, NDMA may have been derived from the source waters (Boyd *et al.*, 2011). Alternatively, NDMA formed as a result of chlorination may be attributable to high source water ammonia concentrations (e.g., 0.7-1.9 mg N/L (Tugulea *et al.*, 2008)), as chlorination of ammonia-containing waters can lead to effective chloramination. This occurs if the chlorine dose is insufficient to lead to breakpoint chlorination, which requires 7.6 mg/L of Cl_2 per mg/L as N of ammonia (White, 1999).

NDMA was the most commonly detected specific nitrosamine. On the rare occasions when other nitrosamines were detected, NDMA concentrations tended to be higher. In the UCMR2, four other nitrosamines (NDEA, NPYR, NDBA, N-nitrosomethylethylamine [NMEA]) were detected at least once, but each at less than 1% occurrence (Russell *et al.*, 2012). However, the minimum reporting levels for many of the non-NDMA nitrosamines were relatively high (3-7 ng/L) and may have precluded their detection. In another North American study, *N*-nitrosodiphenylamine (NDPhA)—which was not in UCMR2—was detected in 5 of 38 systems (at 0.2 – 1.8 ng/L) (Boyd *et al.*, 2011). N-nitrosomorpholine (NMOR)—which also was not in UCRM2—occurred less frequently than NDMA, but fairly frequently compared to other nitrosamines (Boyd *et al.*, 2011; Shah *et al.*, 2012). However, it is unclear whether it formed as a DBP or was present as a contaminant. NMOR occurred frequently in wastewaters (Krasner *et al.*, 2009a; Schreiber and Mitch, 2006b), and may impact downstream drinking water utilities (Krasner *et al.*, 2008). When various combinations of pre-oxidants and chloramines were applied to source waters, NDMA frequently formed, while NMOR concentrations rarely increased above levels measured in the source waters (Shah *et al.*, 2012).

Worldwide occurrence. Nitrosamine occurrence surveys have been performed in the United Kingdom, as chloramination was uncommon in other parts of Europe. In England and Wales, only three of 41 surveyed plants had detectable NDMA, and the concentrations were always below 6 ng/L (Dillon *et al.*, 2008). In another study in the UK (Templeton and Chen, 2010), NDMA was barely above the method detection limit (0.9 ng/L) in a few isolated samples in one distribution system. In Scotland, NDMA was only found at one works, which used chloramines, of seven surveyed (Goslan *et al.*, 2009). Low NDMA occurrence in the UK was not surprising, as chloramine plants in the UK typically operated with a set (e.g., 30 min) pre-chlorine contact time and low (i.e., 0.5

mg/L as Cl_2) chloramine concentrations (Templeton and Chen, 2010). None of the source waters in the Templeton and Chen (2010) study were directly impacted by wastewater, and the use of amine-based coagulant polymers is not believed to be widespread in the UK (Dillon *et al.*, 2008).

Nitrosamine occurrence in Australia was relatively high, due to the high prevalence of chloramination, wastewater recycling, and effective chloramination resulting from high source water ammonia concentrations. One study (Newcombe *et al.*, 2012) detected NDMA in 75% of chloraminated waters and 37% of these detections had NDMA concentrations >10 ng/L (Table A–5). NDMA was detected in 88% of chlorinated recycled wastewaters, and 33% of chlorinated drinking waters. NMOR was also detected at >10 ng/L in 42% of the chlorinated recycled wastewaters. In Western Australia, relatively high incidences of NDMA in chlorinated water (33%) were observed, possibly due to high source water ammonia concentrations (Liew *et al.*, 2011).

In recent surveys of Chinese waters, nitrosamines occurred frequently (Table A–6), often due to contamination from industrial and domestic wastewaters (Wang *et al.*, 2011a; Wang *et al.*, 2011b). Compared to other countries, nitrosamines other than NDMA have been more frequently detected in China. NPYR, NMOR, and NPIP were detected at relatively high concentrations in treated Chinese waters (at one city, maximum concentrations were 16, 16, and 8 ng/L, respectively), and their concentrations varied seasonally (Wang *et al.*, 2011a; Wang *et al.*, 2011b). A study on Chinese source waters found detectable levels of seven nitrosamines in surface waters (Table A-7), with concentrations >5 ng/L on average for NDMA, NDEA, NMOR, NPIP, and NDBA (Ma *et al.*, 2012). The other two nitrosamines, NPYR and N-nitrosodipropylamine (NDPA), were detected on average at up to 2.8 and 1.7 ng/L, respectively. In Japan, NDMA was detected in raw waters at up to 4.3 ng/L, but NDMA concentrations were generally lower in finished drinking water, because chlorination was almost exclusively used in Japan (Asami *et al.*, 2009). However, NDMA was detected at 10 ng/L in the effluent of an ozone plant, as the source water contained anti-yellowing agents, which were found to be a NDMA precursor during ozonation (Kosaka *et al.*, 2009). NDMA was detected in distribution systems in Singapore, but was shown to occur at relatively low concentrations (1.1-6.4 ng/L) (Zhang *et al.*, 2010).

Occurrence of other nitrosamines. Recently an assay was developed to measure the molar concentration of total *N*-nitrosamines (TONO) for drinking water applications (Dai and Mitch, 2013; Kulshrestha *et al.*, 2010). Briefly, it involved extraction of 1-L samples by continuous liquid-liquid extraction with ethyl acetate, concentration to 0.4 mL, and analysis by injection into a heated reaction chamber containing a tri-iodide reducing solution to break the N-N bond. Nitric oxide (NO) liberated from *N*-nitrosamines was purged from the chamber with a stream of nitrogen gas into a chemiluminescent detector specific to NO. When used in conjunction with analysis of specific *N*-nitrosamines by EPA Method 521, the TONO assay indicated to what extent NDMA or other measured nitrosamines constitute the total *N*-nitrosamine pool. Specific *N*-nitrosamines, including NDMA, constituted ~5-10% of the TONO pool in recreational waters and drinking waters. The identity of the other components of the TONO was unclear. However, the TONO assay provided a boundary on the size of this pool, and helped place the importance of NDMA, the predominant specific *N*-nitrosamine detected in recreational waters (Walse and Mitch, 2008) or drinking waters (see above) in perspective. Interestingly, algal-derived organic matter was an insignificant precursor for EPA Method 521 *N*-nitrosamines during chloramination, but a potent precursor for other, uncharacterized *N*-nitrosamines, as measured using the total *N*-nitrosamine assay. These results suggest that *N*-nitrosamines may be relevant to a wider array of source waters than previously thought. One possible group of other nitrosamines in water could be those derived from alkaloids (Bull *et al.*, 2006) and it has been speculated that tobacco-specific nitrosamines may exist in water (Andra and Makris, 2011).

Table A–4 NDMA occurrence (ng/L) in various nationwide surveys in North America

Survey	Reference	(Primary/) Secondary Disinfectant	Sample Location	NDMA (ng/L)				
				Minimum	Median	75th Percentile	90th Percentile	Maximum
U.S. and Canada	(Krasner, 2009)	Chlorine	Plant eff.	ND	ND	ND	1.0	2.4
“	“	“	Dist. syst.	ND	ND	1.1	1.2	1.9
“	“	Chloramines	Plant eff.	ND	ND	1.4	3.3	6.6
“	“	“	Dist. syst.	ND	1.7	2.8	4.9	22
“ GW w/AXR*	“	Chlorine	Plant eff.	20	25	26	---	30
“	“	“	Dist. syst.	10	12	---	---	24
Canada and U.S.	(Boyd *et al.*, 2011)	Chlorine	Source	ND	2.1	4.2	---	9.4
“	“	“	Plant eff.	ND	4.0	5.3	---	17
“	“	“	Dist. syst.	ND	ND	9.0	---	20
“	“	Ozone/chlorine	Source	ND	ND	ND	---	4.7
“	“	“	Plant eff.	ND	ND	2.5	---	3.5
“	“	“	Dist. syst.	ND	ND	6.3	---	12
“	“	Chloramines	Source	ND	ND	ND	ND	4.7
“	“	“	Plant eff.	ND	7.5	14	24	29
“	“	“	Dist. syst.	ND	4.9	10	---	130
U.S.	(Mitch *et al.*, 2009)	Chlorine	Plant eff.	ND	ND	ND	ND	ND
“	“	Chloramines	Plant eff.	ND	ND	3.3	10	20
U.S.	(Krasner *et al.*, 2012d)	Chloramines	Source	ND	ND	ND	ND	ND
“	“	“	Plant eff.	ND	5	8	---	17
“	“	“	Dist. syst.	1.8	12	14	---	16
U.S.	(Russell *et al.*, 2012)†	Chlorine	Plant eff.	ND	ND	ND	ND	62
“	“	“	Dist. syst.	ND	ND	ND	ND	85
“	“	Chloramines	Plant eff.	ND	ND	ND	4.9	470
“	“	“	Dist. syst.	ND	ND	3.8	8.2	630

*Groundwater with anion exchange resin

†Based on UCMR2; assumes non-detects are equal to zero

Table A–5 NDMA occurrence in Australian drinking water (Newcombe *et al.*, 2012)

	<3 ng/L	**3-10 ng/L**	**11-25 ng/L**	**26-75 ng/L**
Chlorinated drinking water	67%	25%	4%	4%
Chloraminated water— all results	25%	39%	18%	19%
Chloraminated water—May - July	47%	26%	21%	5%
Chloraminated water—Nov. - Jan.	17%	38%	12%	33%
Chloraminated water—Apr. - June	7%	57%	21%	14%

Table A–6 Nitrosamine occurrence (ng/L) in China (Wang *et al.*, 2011a; Wang *et al.*, 2011b)

City	**Location**	**NDMA**	**NMOR**	**NPYR**	**NPIP**	**NMEA**	**NDPA**	**NDPhA**
T	Raw water	ND	3.5	ND	ND	ND	ND	ND
“	Disinf. eff.	12	2.5	2.4	ND	ND	ND	ND
“	Distribution	10-21	5.9-12	3.4-6.3	ND	ND	ND	ND
B	Distribution	ND-3.0	ND	6.0-13	5.0-23	ND	ND	ND-6.0
G	Raw water	ND	ND	ND	ND	ND	ND	ND
“	Disinf. eff.	21	ND	ND	4.7	4.5	36	ND
“	Distribution	22-36	ND	ND	4.7-7.5	2.9-3.1	54-79	ND
W	Raw water	ND	ND	ND	4.1	ND	ND	ND
“	Disinf. eff.	12	ND	ND	12	ND	ND	ND
“	Distribution	12-20	---	---	---	---	---	---
D	Distribution	7-8	---	---	---	---	---	---

Table A–7 Nitrosamine occurrence (ng/L) in Jialu River basin, China (Ma *et al.*, 2012)

Water-Statistic	**NDMA**	**NDEA**	**NMEA**	**NPYR**	**NMOR**	**NPIP**	**NDPA**	**NDBA**
GW-freq.	77%	67%	0%	13%	23%	0%	10%	93%
GW-ave. conc.	9.8 ±12.7	6.4 ±13.0	ND	0.3 ±0.2	0.3 ±0.5	ND	0.1 ±0.1	4.0 ±3.2
SW-freq.	98%	97%	0%	95%	95%	23%	61%	100%
SW-ave. conc.	31.7 ±49.5	19.5 ±16.8	ND	2.8 ±2.7	5.5 ±6.0	7.3 ±34.1	1.7 ±2.4	6.2 ±4.6

A-7 Summary, Research Needs and Conclusions

Mechanistic studies and results from occurrence studies suggest that the most important mechanism for nitrosamine formation during disinfection is the chloramination of amine precursors (Table A–1). In one study conducted in Canada, where NDMA formation was associated with chlorinated systems, ammonia was present in source waters, such that these systems were effectively practicing chloramination. Mechanistic studies have indicated that yields of NDMA from chloramination of most secondary and tertiary amines are ~2%, but can be >80% for certain tertiary amines with β-aryl functional groups. Wastewater-impaired source waters exhibit NDMA precursors, suggesting the importance of anthropogenic constituents. Specific precursors have not been characterized in wastewater-impaired waters, but could include either tertiary amine-based microconstituents forming NDMA at high yield, or quaternary amine-based macroconstituents of consumer products forming NDMA at low yields. Quaternary amines also serve as the predominant functional groups in common drinking water cationic coagulation polymers and anion exchange resins, that have proven to be important nitrosamine precursors. Mechanistic studies have also demonstrated that NDMA can form at yields >50% during ozonation of a limited subset of tertiary amine precursors, but associations between ozonation of source waters and NDMA formation have not yet been found in the U.S.

Of the nine specific nitrosamines targeted in occurrence surveys, NDMA generally was the nitrosamine detected at highest frequency. Other specific nitrosamines were rarely detected, except in certain industrially-impacted source waters. Additionally, when anion exchange resins contained functional groups other than dimethylamine, alternative nitrosamines or their precursors were released (e.g., *N*-nitrosodiethylamine from diethylamine-based resins). However, limited total *N*-nitrosamine data suggest that NDMA is a minor component of the total *N*-nitrosamine pool, and that current methods may ignore important *N*-nitrosamines.

The effectiveness of UV treatment for nitrosamine destruction has been demonstrated for wastewater recycling operations (Table A–3). However, UV treatment is substantially less effective at destroying nitrosamine precursors, especially at fluence levels used for disinfection. UV is unlikely to be useful at nitrosamine control at drinking water treatment plants, because NDMA formation happens slowly within chloraminated distribution systems. However, it may be effective if significant nitrosamine concentrations occur in source waters.

Avoiding chloramination may solve a NDMA problem. However, there are reasons for employing chloramines, including reducing halogenated DBP formation. Where utilities practice chloramination for secondary disinfection, two promising approaches may reduce nitrosamine exposure. First, nitrosamine precursors can be deactivated upstream of chloramination by strong pre-oxidants. Over oxidant ranges applied typically for disinfection, the order of effectiveness of oxidants for NDMA precursor destruction was ozone > chlorine >> chlorine dioxide ≈ UV. However, each oxidant forms DBPs. Accordingly, reduction in the formation of nitrosamines must be balanced against increased formation of halogenated DBPs. Second, nitrosamine precursors can be physically removed before chloramination. Recent research suggests that PAC or GAC may be more effective at removing NDMA precursors than at removing the bulk NOM. However, this has not been observed in all cases, so more research is needed in this area.

NDMA formation has been associated with the occurrence of amines in wastewater-impacted source waters and the use of amine-based cationic coagulation polymers and anion exchange resins. An alternative strategy for chloraminating utilities is to avoid precursors. Utilities could blend source waters to minimize wastewater impacts. Utilities could optimize the cationic polymer dose to minimize applied doses. Unfortunately, nearly all cationic polymers and anion exchange resins currently available are amine-based. However, polyacrylamide has less NDMA precursors than polyDADMAC. Over the longer term, development or use of non-amine-based treatment polymers is desirable.

Any modifications to water treatment plant operations could influence the efficiency of plant operations, affect the formation of other DBPs, or alter pathogen control. PolyDADMAC and certain anion exchange resins are important sources of nitrosamines and/or nitrosamine precursors. However, polyDADMAC is widely employed for sedimentation, sludge dewatering, filtered water turbidity control, and filter run time lengthening. Similarly, anion exchange resins are widely employed for control of nitrate and arsenic. If pre-oxidation is required to transform nitrosamine precursors prior to chloramine addition, then the formation of regulated (e.g., bromate from ozonation, THMs/HAAs from chlorination, chlorite from chlorine dioxide), and non-regulated (e.g., halonitromethanes from ozone or medium pressure UV treatment) halogenated DBPs will increase. Use of PAC or GAC could be used to reduce precursors for nitrosamines, but will increase the cost of water treatment.

Research needs. Research needs and timeframes in which to accomplish them are summarized in Table A–8. A first need is improved occurrence surveys. Previous surveys have broadly outlined the range of concentrations of specific nitrosamines, particularly NDMA, in drinking waters. However, most surveys have sampled insufficiently to provide adequate spatial and temporal coverage (seasonal, year-to-year, event-driven).

Additionally, insufficient water quality and operational data have been collected to enable strong conclusions to be drawn regarding the factors responsible for nitrosamine formation. For example, it is likely that the nitrosamine formation measured in many chlorinated water systems resulted from effective chloramination due to moderate ammonia concentrations in the source water. However, information on ammonia concentrations and chlorine doses are usually lacking in order to determine if breakpoint was achieved. In addition, information on wastewater impacts or polymer usage and pre-oxidation schemes were often not available in most occurrence surveys.

Another research need is to better define the nitrosamine precursor pool. While polyDADMAC and anion exchange resins have been identified as potentially important NDMA precursors, the importance of these precursors for overall NDMA occurrence has only been quantified in limited studies. Additionally, wastewater-impacted source waters have been shown as an important source of NDMA precursors. Based upon model precursor work, certain pharmaceuticals and micro- and macroconstituents of personal care products have been suggested as contributors to the association between NDMA formation and wastewater impact. However, the significance of specific precursors for NDMA in wastewater-impacted water supplies has not yet been quantified. Identifying precursors could aid in controlling them at their source or provide insight into treatment process design to remove precursors.

A third research need is to further characterize the importance of materials within distribution systems or plumbing systems as nitrosamine precursors. The formation or release of nitrosamines from rubber- or plastic-based products in distribution systems could be significant, and methods to screen these materials are essential. Related to the relative importance of nitrosamine exposure from drinking water and food, further research is needed on the potential for nitrosamine formation to occur by the use of disinfected tap water to prepare food. If dermal nitrosamine exposure is an important human exposure route, reactions between chloraminated water and detergents or shampoos may be important.

A fourth need is the development, refinement, and widespread implementation of the TONO assay and characterization of unidentified nitrosamine constituents. As the USEPA is interested in regulating nitrosamines as a group, one possibility is the use of the TONO assay for nitrosamine monitoring. Additionally, the TONO assay could be used in occurrence and treatment studies to evaluate NDMA as a surrogate for the total nitrosamine pool. Advantages of TONO over EPA Method 521 include that it is potentially simpler to operate, requires less expensive instrumentation, and captures the full *N*-nitrosamine pool (compared to ~5% for EPA Method 521). Further characterization of the TONO pool in drinking waters would include data on their size and hydrophobicity, toxicity, and fate and transport. Additionally, it is important to understand the association of precursors with different source water types (e.g., pristine, wastewater-impacted, algal-impacted), and the ability of different treatment units to remove their precursors. Evaluating these issues is important for understanding whether modifications to treatment schemes (e.g., polymer evaluations, activated carbon addition, use of pre-oxidants) to minimize exposures to specific nitrosamines (e.g., NDMA) minimizes or exacerbates exposures to other nitrosamines.

Several treatment options (e.g., pre-oxidation, activated carbon treatment) have been identified at laboratory-scale and in limited full-scale applications. These need to be further validated at pilot- and full-scale over a wide range of raw water and seasonal variations. These validations should also characterize tradeoffs associated with unit process efficiency, pathogen inactivation, and the formation of other DBPs resulting from these modifications. Additionally, the cost implications of these modifications should be evaluated. These research needs can be divided into the following three groups. First, the chemical addition sequence and reaction times during chloramination, free chlorine systems with occasional raw water ammonia influences, and the use of polyDADMAC should be optimized. Second, existing treatment alternatives to oxidize precursors (e.g., ozone, chlorine dioxide) and physical removal of precursors (PAC, GAC) should be evaluated. Third, new treatment processes or treatment trains specifically aimed at removing/transforming nitrosamine precursors within water treatment plants or post-formed nitrosamines within distribution systems, and the use of alternative polymers that do not contribute (significant levels) of nitrosamine precursors should be developed.

Conclusions. The discovery of halogenated byproducts of chlorine disinfection in the 1970s forced regulators and utilities to seek to balance the acute risks associated with pathogen exposure against the chronic risks associated with lifetime exposures to potentially carcinogenic chemical byproducts. Use of chloramination for secondary disinfection has increased in the United States, Canada, UK, Australia, and China to minimize the formation of regulated halogenated byproducts associated with chlorination, yet chloramination has been found to promote the formation of other potentially carcinogenic byproducts, including nitrosamines. One approach to this problem, favored in northern Europe, is to reduce or minimize disinfectant application and byproduct precursors using activated carbon or other technologies to remove dissolved organic matter and produce biostable water. This approach has not been targeted in the United States and other countries due to concerns over cost. It is likely that disinfection in the United States and elsewhere will seek to minimize the overall risks of exposure to pathogens, and byproducts from primary (e.g., chlorine and ozone) and secondary (i.e., chloramination) disinfectants.

A-8 Acknowledgements

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Table A–8 Relative timeframes for research needs

Research Need	**Timeframe for Research**
Improved occurrence surveys	2 years
Characterize specific precursors in wastewater-impacted waters	3 years
Characterize contribution of distribution system materials	3 years
Develop, refine, and use a total N-nitrosamine assay for drinking waters	2 years
Optimize protocols for addition of chloramine reagents	2-5 years
Optimize protocols for chlorinating ammonia-containing source waters	2-5 years
Optimize application of amine-based coagulant polymers (e.g., polyDADMAC)	2 years
Evaluate pre-oxidation of precursors at pilot and full-scale	<2 years
Evaluate activated carbon removal of nitrosamine precursors at pilot and full-scale	<2 years
Develop alternative polymers that are not amine-based	2 years
Develop new treatment processes specific to nitrosamines	5-10 years

APPENDIX B

MATLAB® CODE TO CONDUCT NEUTRAL LOSS SEARCHES

Notes: First import *.csv from MassHunter to Matalb by dragging and dropping (also can use command uiimport). Other importation notes are contained in CSVToArray. Once the file is imported, run CSVToArray on the imported data. S is the output. Run NeutralLossAllCompounds on S. If a neutral loss other than dimethylamine is desired, change the line is the script, “Neutral=45.0578”. This could also be included as an input if it is to be changed regularly.

Other notes are generally contained in the code itself as comments. If file is too big for uiimport, uiimport will not work for files this size. Use:

fileID=fopen('FileNameHere.csv')

A=textscan(fileID,'%f %f %f','Delimiter',',','CommentStyle','#','CollectOutput','1')

B=cell2mat(A);

%Now B is the matrix to use as input to CSVToArray

File: CSVToArray.m

```
function CSVToArray(input)

%takes CSV files from Mass Hunter with 2 lines of header information
per
%exported compound. When importing the CSV, remove all non numeric rows
%Usage - CSVToArray(inputmatrix)
%where input is matrix with all imported data
%Output is S

a=input(1,1);
i=0;
b=0;
S=zeros
c=1;

for i=1:length(input(:,1)) %Runs through the length of the imported
matrix
    a=input(i,1);  %sets spectra ident to a
    if a==0 %Checks if ident is the first in a set (first data point
for a compound)
       b=b+1 %adds 1 to new matrix ident if a new compound
```

```
        c=1; %resets row ident for new compound
    end
    S(b,c,1)=input(i,1);
    S(b,c,2)=input(i,2);
    S(b,c,3)=input(i,3);
    c=c+1;
end
assignin('base','S',S)
```

File:NeutralLossAllCompounds.m

```
function
NeutralLossAllCompounds(inputdata,error,MinIntensityParent,MinIntensity
Product)
%input is datafile with TOF spectra occurring at T~=elution time of 1
of top peaks
%Use CSVToArray to import data
%error is acceptable error + or - from neutral loss



%Usage Example - NeutralLossAllCompounds(Input,.0004,10000,10000)
%Neutral loss m/z search is set below by the variable

%output table "Results" Has header "Compound ID", "Parent Ion m/z",
"Parent
%ion intensity", "Product ion m/z", "product ion intensity",
"difference
%between parent and product ion m/z"

Neutral=45.0578;
a=0;
Results=zeros

for k=1:length(inputdata(:,1,1)) %k is compound number
    k
    for i=1:length(inputdata(k,:,2))
        Parent=inputdata(k,i,2); %sets the parents ion m/z
        if inputdata(k,i,3)>MinIntensityParent %checks if the parent
ion intensity is greater than the input threshold
            for j=1:length(inputdata(k,:,2))
                Product=inputdata(k,j,2); %sets product ion
                if Product<Parent &&
(inputdata(k,j,3))>MinIntensityProduct %checkcs is product ion m/z is
less than parent and if product ion meets threshold
                    if (Neutral-error)<=(Parent-Product) && (Parent-
Product)<=(Neutral+error) %if parent-product is within error or
netural, next
                        a=a+1; %Xaxis chart ident
                        Results(a,1)=k; %first column is compound ident
and then below is move data from original file into results table
                        Results(a,2)=Parent;
                        Results(a,4)=Product;
                        Results(a,3)=inputdata(k,i,3);
```

```
                        Results(a,5)=inputdata(k,j,3);
                        Results(a,6)=Parent-Product;

                    end
                end
            end
        end
    end
end
assignin('base','Results',Results)
```

APPENDIX C

MATLAB® OUTPUT OF NEUTRAL LOSS SEARCH FOR POTENTIAL DIMETHYLAMINE CONTAINING COMPOUNDS IN ISOLATED SAMPLES

Water Source	Parent Ion M/Z	Parent Ion Intensity	Product Ion m/z	Product Ion Intensity	m/z Loss	Retention Time (min)
SW 1	185.1291	1.8E+04	140.0716	1.6E+04	45.0575	3.460-3.521
	237.1593	5.5E+04	192.1019	3.3E+04	45.0574	
	254.1859	5.7E+04	209.1286	1.5E+04	45.0573	
	185.1291	2.0E+04	140.0716	1.8E+04	45.0575	3.460-3.521
	237.1593	6.1E+04	192.1019	3.6E+04	45.0574	
	254.1859	6.4E+04	209.1286	1.7E+04	45.0573	
	185.1291	1.7E+04	140.0716	1.6E+04	45.0575	3.460-3.521
	237.1593	5.3E+04	192.1019	3.2E+04	45.0574	
	254.1859	5.5E+04	209.1286	1.5E+04	45.0573	
	185.1291	1.5E+04	140.0716	1.4E+04	45.0575	3.460-3.521
	237.1593	4.7E+04	192.1019	2.8E+04	45.0574	
	254.1859	4.8E+04	209.1286	1.3E+04	45.0573	
	350.3049	1.5E+04	305.2475	1.7E+04	45.0574	27.626-27.746
	484.3993	1.2E+04	439.3417	1.2E+04	45.0576	29.791-29.875
	484.3993	1.2E+04	439.3417	1.3E+04	45.0576	29.899-30.031
	484.3992	1.3E+04	439.3417	1.3E+04	45.0575	29.935-30.031
	440.3732	2.8E+04	395.3154	1.4E+04	45.0578	30.055-30.224
SW 2	190.1071	1.0E+04	145.0495	3.3E+04	45.0576	2.361-2.470
	183.1130	1.9E+04	138.0556	2.7E+04	45.0574	2.361-2.770
	183.1129	3.6E+04	138.0555	5.2E+04	45.0574	2.410-2.518
	190.1069	1.3E+04	145.0496	2.9E+04	45.0573	
	183.1129	2.7E+04	138.0556	3.8E+04	45.0573	2.385-2.518
	190.1070	1.0E+04	145.0496	2.6E+04	45.0574	
	183.1129	3.1E+04	138.0554	4.4E+04	45.0575	2.434-2.518
	183.1129	3.7E+04	138.0554	5.1E+04	45.0575	2.458-2.518
	183.1129	1.4E+04	138.0554	2.4E+04	45.0575	2.482-2.614
	209.1283	1.6E+04	164.0706	1.5E+04	45.0577	3.468-3.504
	237.1592	7.5E+04	192.1019	3.0E+04	45.0573	
	254.1858	7.3E+04	209.1283	1.6E+04	45.0575	
	263.1401	1.0E+04	218.0822	1.5E+04	45.0579	
	209.1283	1.7E+04	164.0706	1.6E+04	45.0577	3.468-3.504
	237.1592	8.0E+04	192.1019	3.2E+04	45.0573	
	254.1858	7.8E+04	209.1283	1.7E+04	45.0575	
	263.1401	1.1E+04	218.0822	1.6E+04	45.0579	
	185.1285	1.6E+04	140.0711	1.5E+04	45.0574	3.468-3.528
	209.1284	1.4E+04	164.0708	1.4E+04	45.0576	

	237.1592	7.0E+04	192.1019	2.7E+04	45.0573	
	254.1859	7.3E+04	209.1284	1.4E+04	45.0575	
	185.1285	1.6E+04	140.0711	1.5E+04	45.0574	3.468-3.528
	209.1284	1.4E+04	164.0708	1.4E+04	45.0576	
	237.1592	7.0E+04	192.1019	2.7E+04	45.0573	
	254.1859	7.3E+04	209.1284	1.4E+04	45.0575	
	168.1382	1.6E+04	123.0803	1.2E+04	45.0579	16.158-16.459
	168.1382	1.7E+04	123.0805	1.1E+04	45.0577	16.711-16.940
	484.3992	1.4E+04	439.3416	1.2E+04	45.0576	29.907-30.015
SW 3	190.1071	1.0E+04	145.0495	3.3E+04	45.0576	2.361-2.470
	183.1130	1.9E+04	138.0556	2.7E+04	45.0574	2.361-2.770
	183.1129	3.6E+04	138.0555	5.2E+04	45.0574	2.410-2.518
	190.1070	1.0E+04	145.0496	2.6E+04	45.0574	2.385-2.518
	183.1129	3.1E+04	138.0554	4.4E+04	45.0575	2.434-2.518
	183.1129	3.7E+04	138.0554	5.1E+04	45.0575	2.458-2.518
	183.1129	1.4E+04	138.0554	2.4E+04	45.0575	2.482-2.614
	209.1283	1.6E+04	164.0706	1.5E+04	45.0577	3.468-3.504
	237.1592	7.5E+04	192.1019	3.0E+04	45.0573	
	254.1858	7.3E+04	209.1283	1.6E+04	45.0575	
	263.1401	1.0E+04	218.0822	1.5E+04	45.0579	3.468-3.504
	209.1283	1.7E+04	164.0706	1.6E+04	45.0577	
	237.1592	8.0E+04	192.1019	3.2E+04	45.0573	
	254.1858	7.8E+04	209.1283	1.7E+04	45.0575	3.468-3.528
	263.1401	1.1E+04	218.0822	1.6E+04	45.0579	
	185.1285	1.6E+04	140.0711	1.5E+04	45.0574	
	209.1284	1.4E+04	164.0708	1.4E+04	45.0576	3.468-3.528
	237.1592	7.0E+04	192.1019	2.7E+04	45.0573	
	254.1859	7.3E+04	209.1284	1.4E+04	45.0575	
	185.1285	1.6E+04	140.0711	1.5E+04	45.0574	16.158-16.459
	209.1284	1.4E+04	164.0708	1.4E+04	45.0576	16.711-16.940
	237.1592	7.0E+04	192.1019	2.7E+04	45.0573	29.907-30.015
	254.1859	7.3E+04	209.1284	1.4E+04	45.0575	
	168.1382	1.6E+04	123.0803	1.2E+04	45.0579	
	168.1382	1.7E+04	123.0805	1.1E+04	45.0577	
	484.3992	1.4E+04	439.3416	1.2E+04	45.0576	
SW 4	209.1288	1.4E+04	164.0711	2.0E+04	45.0577	3.442-3.502
	231.1702	4.2E+04	186.1128	1.1E+05	45.0574	
	209.1288	1.3E+04	164.0712	1.8E+04	45.0576	3.418-3.502
	231.1702	3.6E+04	186.1128	1.0E+05	45.0574	

	209.1288	1.4E+04	164.0711	1.9E+04	45.0577	3.442-3.502
	231.1702	4.0E+04	186.1128	1.1E+05	45.0574	
	209.1287	1.5E+04	164.0709	2.0E+04	45.0578	3.466-3.502
	231.1701	4.7E+04	186.1127	1.3E+05	45.0574	
	209.1289	1.4E+04	164.0710	1.9E+04	45.0579	3.466-3.526
	231.1701	4.4E+04	186.1127	1.2E+05	45.0574	
	209.1287	1.6E+04	164.0709	2.2E+04	45.0578	3.466-3.502
	231.1701	5.2E+04	186.1127	1.4E+05	45.0574	
	245.1852	1.0E+04	200.1271	1.3E+04	45.0581	
	209.1289	1.4E+04	164.0710	1.8E+04	45.0579	3.466-3.526
	231.1701	4.1E+04	186.1127	1.1E+05	45.0574	
	209.1287	1.4E+04	164.0709	1.8E+04	45.0578	3.466-3.502
	231.1701	4.3E+04	186.1127	1.2E+05	45.0574	
	209.1289	1.6E+04	164.0710	2.2E+04	45.0579	3.466-3.526
	231.1701	4.9E+04	186.1127	1.4E+05	45.0574	
	245.1853	1.0E+04	200.1273	1.3E+04	45.0580	
	209.1287	1.6E+04	164.0709	2.1E+04	45.0578	3.466-3.502
	231.1701	5.0E+04	186.1127	1.4E+05	45.0574	
	245.1852	1.0E+04	200.1271	1.3E+04	45.0581	
	209.1289	1.4E+04	164.0710	2.0E+04	45.0579	3.466-3.526
	231.1701	4.4E+04	186.1127	1.2E+05	45.0574	
	185.1285	1.7E+04	140.0708	1.4E+04	45.0577	3.466-3.550
	209.1289	1.2E+04	164.0709	1.7E+04	45.0580	
	231.1702	3.6E+04	186.1128	9.9E+04	45.0574	
	209.1287	1.5E+04	164.0709	2.0E+04	45.0578	3.466-3.502
	231.1701	4.9E+04	186.1127	1.3E+05	45.0574	
	472.3632	2.1E+04	427.3055	3.9E+04	45.0577	25.454-25.623
	472.3632	2.2E+04	427.3055	3.9E+04	45.0577	25.466-25.623
	428.3371	2.1E+04	383.2795	4.2E+04	45.0576	25.635-25.779
	428.3371	2.1E+04	383.2795	4.3E+04	45.0576	25.635-25.767
	484.3998	1.2E+04	439.3421	1.1E+04	45.0577	29.809-29.881
	440.3732	2.6E+04	395.3157	1.1E+04	45.0575	29.941-30.025
	484.3997	1.2E+04	439.3419	1.1E+04	45.0578	
	440.3735	2.8E+04	395.3158	1.1E+04	45.0577	30.049-30.193
SW 5	183.1141	4.9E+04	138.0564	6.9E+04	45.0577	2.446-2.662
	195.1131	2.0E+04	150.0554	6.0E+04	45.0577	
	196.1414	1.0E+04	151.0838	2.0E+04	45.0576	
	307.2222	1.5E+04	262.1641	1.5E+04	45.0581	
	195.1135	2.0E+04	150.0557	7.1E+04	45.0578	2.518-2.759

	257.1521	1.1E+04	212.0947	2.1E+04	45.0574	
	179.1177	1.1E+04	134.0601	8.4E+04	45.0576	2.939-3.132
	215.1391	2.1E+04	170.0812	9.7E+04	45.0579	
	227.1392	2.6E+04	182.0816	4.0E+04	45.0576	
	179.1177	1.8E+04	134.0602	9.9E+04	45.0575	2.915-3.156
	215.1391	3.2E+04	170.0813	1.1E+05	45.0578	
	227.1393	3.3E+04	182.0816	5.3E+04	45.0577	
	195.1129	7.4E+04	150.0555	4.7E+04	45.0574	3.444-3.577
	197.1259	4.0E+04	152.0680	5.9E+04	45.0579	
	199.1449	2.4E+04	154.0872	3.7E+04	45.0577	
	209.1289	4.4E+04	164.0711	3.8E+04	45.0578	
	218.1363	2.1E+04	173.0786	3.5E+04	45.0577	
	291.2275	1.2E+04	246.1695	3.5E+04	45.0580	
	354.2033	1.5E+04	309.1453	1.5E+04	45.0580	
	197.1286	1.9E+04	152.0706	2.1E+04	45.0580	4.407-4.707
	223.1448	2.7E+04	178.0866	2.0E+04	45.0582	
	237.1592	1.3E+04	192.1017	2.0E+04	45.0575	
	253.1552	2.8E+04	208.0970	2.5E+04	45.0582	
	326.1578	1.0E+04	281.0998	4.4E+04	45.0580	9.495-9.795
	296.1843	1.1E+04	251.1265	3.0E+04	45.0578	10.096-10.276
	310.1622	1.1E+04	265.1047	2.2E+04	45.0575	10.746-10.878
	310.1625	1.1E+04	265.1047	2.2E+04	45.0578	10.733-10.878
	296.1829	1.2E+04	251.1255	1.8E+05	45.0574	10.974-11.203
	308.1484	1.8E+04	263.0906	1.3E+04	45.0578	
	382.2204	1.0E+04	337.1627	2.9E+04	45.0577	
	282.1908	1.4E+04	237.1329	4.0E+04	45.0579	11.046-11.215
	308.1856	1.2E+04	263.1279	2.6E+04	45.0577	
	326.1582	1.5E+04	281.1002	1.3E+04	45.0580	11.515-11.744
	338.1944	1.3E+04	293.1365	4.6E+04	45.0579	
	382.1834	1.2E+04	337.1255	2.3E+04	45.0579	
	266.1733	1.3E+04	221.1151	6.5E+04	45.0582	11.515-11.720
	308.1477	1.3E+04	263.0896	1.4E+04	45.0581	
	326.1581	1.3E+04	281.1001	1.1E+04	45.0580	
	338.1944	1.1E+04	293.1362	4.0E+04	45.0582	
	354.1887	1.2E+04	309.1311	3.6E+04	45.0576	11.624-11.780
	244.1687	2.2E+05	199.1106	1.0E+04	45.0581	11.864-12.033
	238.1418	1.2E+04	193.0841	1.3E+04	45.0577	11.864-12.201
	244.1683	2.6E+05	199.1102	3.4E+04	45.0581	
	247.1426	5.9E+04	202.0849	7.6E+04	45.0577	

	308.1467	2.5E+04	263.0892	1.7E+04	45.0575	
	324.1767	1.6E+04	279.1191	6.1E+04	45.0576	
	340.1710	1.7E+04	295.1135	6.7E+04	45.0575	
	366.2259	1.4E+04	321.1679	2.4E+04	45.0580	
	380.2400	1.0E+04	335.1822	1.9E+04	45.0578	
	244.1675	2.9E+05	199.1094	2.2E+04	45.0581	11.972-12.105
	206.1527	2.0E+04	161.0946	1.0E+04	45.0581	12.069-12.297
	244.1684	3.9E+04	199.1104	2.9E+04	45.0580	
	247.1429	6.9E+04	202.0851	9.4E+04	45.0578	
	338.1570	1.4E+04	293.0995	1.6E+04	45.0575	
	366.2259	1.2E+04	321.1684	2.1E+04	45.0575	
	382.1835	1.6E+04	337.1257	2.6E+04	45.0578	
	382.2188	1.1E+04	337.1610	4.2E+04	45.0578	
	408.1987	1.6E+04	363.1412	1.5E+04	45.0575	
	226.1422	1.5E+04	181.0840	1.3E+04	45.0582	12.297-12.538
	324.2139	1.2E+04	279.1562	1.9E+04	45.0577	
	338.1574	1.6E+04	293.0993	1.5E+04	45.0581	
	338.1926	1.3E+04	293.1348	4.7E+04	45.0578	
	384.1978	1.2E+04	339.1398	3.5E+04	45.0580	
	416.2180	1.7E+04	371.1604	1.3E+04	45.0576	
	452.2230	1.2E+04	407.1654	2.0E+04	45.0576	
	226.1422	1.1E+04	181.0841	1.1E+04	45.0581	12.333-12.550
	338.1930	1.0E+04	293.1348	3.8E+04	45.0582	
	390.1851	1.2E+04	345.1275	2.6E+04	45.0576	
	416.2181	1.4E+04	371.1605	1.0E+04	45.0576	
	452.2233	1.0E+04	407.1656	1.7E+04	45.0577	
	308.1828	1.2E+04	263.1252	2.6E+04	45.0576	12.333-12.598
	336.1785	1.3E+04	291.1206	2.4E+04	45.0579	
	452.2232	1.3E+04	407.1654	2.2E+04	45.0578	
	250.1793	2.9E+04	205.1219	1.2E+04	45.0574	12.550-12.754
	320.1485	1.0E+04	275.0903	1.0E+04	45.0582	
	322.1630	1.2E+04	277.1054	1.7E+04	45.0576	
	352.2093	1.2E+04	307.1514	6.8E+04	45.0579	
	368.2038	1.6E+04	323.1459	6.7E+04	45.0579	
	368.2030	1.2E+04	323.1455	5.2E+04	45.0575	12.514-12.887
	250.1788	1.9E+04	205.1209	1.2E+04	45.0579	12.730-12.959
	280.1896	1.5E+04	235.1317	1.1E+04	45.0579	
	310.1623	2.2E+04	265.1046	2.2E+04	45.0577	
	350.1950	1.3E+04	305.1371	3.5E+04	45.0579	

	368.2033	1.2E+04	323.1451	5.3E+04	45.0582	
	380.2018	1.3E+04	335.1443	3.5E+04	45.0575	
	382.1845	1.1E+04	337.1263	1.4E+04	45.0582	
	250.1788	1.9E+04	205.1206	1.1E+04	45.0582	12.814-12.947
	280.1894	1.6E+04	235.1315	1.0E+04	45.0579	
	350.1950	1.1E+04	305.1371	3.4E+04	45.0579	
	380.2024	1.2E+04	335.1446	2.9E+04	45.0578	
	410.2136	1.4E+04	365.1561	2.6E+04	45.0575	
	364.1754	1.0E+04	319.1174	1.4E+04	45.0580	13.187-13.332
	260.1998	1.2E+05	215.1417	3.0E+04	45.0581	13.668-13.837
	278.2107	4.3E+05	233.1527	1.2E+04	45.0580	
	280.1527	1.0E+04	235.0946	1.5E+04	45.0581	
	296.1827	1.3E+04	251.1253	3.0E+04	45.0574	
	396.1994	1.1E+04	351.1412	2.4E+04	45.0582	
	180.1728	1.2E+04	135.1147	1.2E+04	45.0581	13.753-14.005
	278.2100	4.7E+05	233.1521	1.3E+04	45.0579	
	308.1817	1.0E+04	263.1242	3.8E+04	45.0575	
	364.2077	1.0E+04	319.1498	2.8E+04	45.0579	
	392.2055	1.7E+04	347.1475	2.2E+04	45.0580	
	164.1428	1.5E+04	119.0847	3.7E+04	45.0581	13.933-14.234
	248.1626	1.1E+04	203.1044	2.2E+04	45.0582	
	250.1784	1.2E+04	205.1207	1.9E+04	45.0577	
	254.2106	1.5E+04	209.1526	1.2E+04	45.0580	
	276.1946	1.2E+04	231.1371	1.4E+04	45.0575	
	292.1537	1.2E+04	247.0957	1.1E+04	45.0580	
	350.2293	1.1E+04	305.1716	2.2E+04	45.0577	
	354.1882	1.1E+04	309.1306	3.1E+04	45.0576	
	366.1888	1.8E+04	321.1308	4.0E+04	45.0580	
	378.1891	1.7E+04	333.1313	2.9E+04	45.0578	
	382.2185	1.1E+04	337.1605	5.3E+04	45.0580	
	396.2338	1.0E+04	351.1761	6.9E+04	45.0577	
	250.1785	1.1E+04	205.1206	1.7E+04	45.0579	13.897-14.198
	254.2105	1.4E+04	209.1525	1.1E+04	45.0580	
	276.1948	1.1E+04	231.1369	1.3E+04	45.0579	
	312.1775	1.4E+04	267.1198	2.3E+04	45.0577	
	350.2294	1.1E+04	305.1716	2.0E+04	45.0578	
	366.1889	1.7E+04	321.1307	3.9E+04	45.0582	
	494.2682	1.1E+04	449.2101	3.4E+04	45.0581	
	510.2636	1.0E+04	465.2054	1.3E+04	45.0582	

	164.1426	1.0E+04	119.0848	2.1E+04	45.0578	14.029-14.162
	317.1403	1.2E+04	272.0828	1.9E+04	45.0575	
	164.1426	1.1E+04	119.0848	2.4E+04	45.0578	14.029-14.186
	366.1890	1.2E+04	321.1312	2.7E+04	45.0578	
	164.1425	1.0E+04	119.0848	2.5E+04	45.0577	14.053-14.222
	348.1799	1.1E+04	303.1218	2.0E+04	45.0581	
	422.2141	1.1E+04	377.1564	2.6E+04	45.0577	14.246-14.438
	250.1793	1.6E+04	205.1212	2.4E+04	45.0581	15.148-15.437
	294.2054	1.7E+04	249.1474	3.3E+04	45.0580	
	304.1497	1.0E+04	259.0918	1.4E+04	45.0579	
	350.2293	1.1E+04	305.1712	2.9E+04	45.0581	
	253.1778	1.6E+04	208.1196	2.2E+04	45.0582	15.449-15.761
	376.2127	2.1E+04	331.1548	1.6E+04	45.0579	
	422.2150	1.7E+04	377.1569	3.0E+04	45.0581	
	253.1777	1.4E+04	208.1195	2.4E+04	45.0582	15.521-15.797
	306.1698	1.1E+04	261.1116	1.8E+04	45.0582	
	362.1947	1.4E+04	317.1367	2.4E+04	45.0580	
	368.2049	1.2E+04	323.1467	5.3E+04	45.0582	
	422.2153	1.3E+04	377.1571	2.5E+04	45.0582	
	424.2282	1.2E+04	379.1707	3.4E+04	45.0575	
	450.2458	1.5E+04	405.1881	3.5E+04	45.0577	
	477.2844	3.4E+04	432.2269	1.6E+04	45.0575	
	456.2801	8.8E+04	411.2223	1.3E+04	45.0578	16.627-16.736
	168.1377	2.6E+04	123.0798	2.0E+04	45.0579	16.615-16.832
	324.2146	1.1E+04	279.1564	5.0E+04	45.0582	16.772-17.253
	420.2341	2.1E+04	375.1767	4.9E+04	45.0574	
	450.2456	1.6E+04	405.1878	4.3E+04	45.0578	
	458.2484	1.2E+04	413.1905	2.6E+04	45.0579	
	562.3305	2.0E+04	517.2729	3.6E+04	45.0576	
	372.2190	1.1E+04	327.1610	1.3E+04	45.0580	17.289-17.445
	266.1728	1.0E+05	221.1151	1.1E+04	45.0577	17.650-18.023
	507.3317	1.3E+04	462.2743	1.4E+04	45.0574	17.650-18.023
	530.3423	2.1E+04	485.2841	1.3E+04	45.0582	17.987-18.227
	518.3031	1.7E+04	473.2451	1.2E+04	45.0580	18.720-19.202
	588.3824	1.6E+04	543.3245	2.7E+04	45.0579	19.334-19.562
	416.2404	1.0E+04	371.1823	1.4E+04	45.0581	19.454-19.755
	578.3522	1.2E+04	533.2942	9.6E+04	45.0580	
	334.1993	1.3E+04	289.1415	1.0E+04	45.0578	20.332-20.513
	392.2407	1.0E+04	347.1825	2.0E+04	45.0582	20.404-20.597

	444.3084	5.5E+04	399.2508	1.3E+06	45.0576	26.383-26.659
SW 6	195.1127	4.3E+04	150.0554	1.2E+04	45.0573	3.449-3.522
	254.1859	7.1E+04	209.1281	1.8E+04	45.0578	3.449-3.522
	195.1127	5.5E+04	150.0554	1.5E+04	45.0573	3.449-3.522
	254.1859	9.0E+04	209.1281	2.3E+04	45.0578	3.449-3.522
SW 7	197.1292	2.6E+04	152.0714	1.6E+04	45.0578	3.427-3.511
	209.1287	1.2E+04	164.0709	1.6E+04	45.0578	3.427-3.511
	213.1595	1.9E+04	168.1016	1.4E+04	45.0579	3.427-3.511
	237.1595	6.5E+04	192.1022	3.5E+04	45.0573	3.427-3.511
	254.1861	9.4E+04	209.1287	1.2E+04	45.0574	3.427-3.511
	185.1283	1.7E+04	140.0702	1.5E+04	45.0581	3.451-3.487
	197.1282	3.1E+04	152.0707	1.6E+04	45.0575	3.451-3.487
	209.1277	1.4E+04	164.0698	1.8E+04	45.0579	3.451-3.487
	213.1586	2.4E+04	168.1006	1.6E+04	45.0580	3.451-3.487
	237.1586	8.5E+04	192.1013	3.7E+04	45.0573	3.451-3.487
	254.1852	1.2E+05	209.1277	1.4E+04	45.0575	3.451-3.487
	197.1284	3.1E+04	152.0709	1.6E+04	45.0575	3.451-3.511
	209.1280	1.4E+04	164.0700	1.9E+04	45.0580	3.451-3.511
	213.1588	2.3E+04	168.1009	1.6E+04	45.0579	3.451-3.511
	237.1589	8.2E+04	192.1016	3.8E+04	45.0573	3.451-3.511
	254.1855	1.2E+05	209.1280	1.4E+04	45.0575	3.451-3.511
	440.3734	1.4E+04	395.3153	1.1E+04	45.0581	30.051-30.208
	448.3626	1.4E+04	403.3053	1.1E+04	45.0573	30.761-30.942
SW 8	183.1130	1.3E+04	138.0557	1.5E+04	45.0573	2.482-2.603
	209.1292	1.2E+04	164.0715	1.3E+04	45.0577	3.445-3.493
	209.1292	1.1E+04	164.0715	1.2E+04	45.0577	3.445-3.493
	209.1291	1.2E+04	164.0713	1.4E+04	45.0578	3.445-3.517
SW 9	237.1595	5.6E+04	192.1021	5.2E+04	45.0574	3.452-3.488
	237.1594	5.4E+04	192.1021	5.3E+04	45.0573	3.452-3.512
	164.1432	1.1E+04	119.0858	1.3E+04	45.0574	13.906-14.087
	164.1432	1.3E+04	119.0859	1.7E+04	45.0573	13.894-14.219
SW 10	185.1290	1.8E+04	140.0716	1.5E+04	45.0574	3.449-3.485
	237.1595	7.4E+04	192.1019	3.8E+04	45.0576	3.449-3.485
	185.1289	1.8E+04	140.0708	2.2E+04	45.0581	3.449-3.510
	237.1595	7.3E+04	192.1019	3.9E+04	45.0576	3.449-3.510
	185.1289	2.0E+04	140.0708	2.4E+04	45.0581	3.449-3.510
	237.1595	7.8E+04	192.1019	4.1E+04	45.0576	3.449-3.510
	185.1289	1.6E+04	140.0712	1.6E+04	45.0577	3.449-3.497
	237.1595	6.4E+04	192.1019	3.3E+04	45.0576	3.449-3.497

	185.1289	1.8E+04	140.0708	2.1E+04	45.0581	3.449-3.510
	237.1595	7.0E+04	192.1019	3.7E+04	45.0576	3.449-3.510
	164.1431	1.1E+04	119.0856	1.6E+04	45.0575	14.012-14.145
WW 1	227.1400	1.6E+04	182.0824	8.9E+04	45.0576	2.511-2.643
	197.1283	1.3E+04	152.0706	3.9E+04	45.0577	4.351-4.616
	241.1550	1.5E+04	196.0973	3.8E+04	45.0577	4.351-4.616
	164.1427	1.9E+04	119.0851	1.6E+05	45.0576	11.317-11.63
	237.1595	1.9E+04	192.1020	1.1E+04	45.0575	11.461-11.762
	244.1688	8.2E+05	199.1106	4.9E+04	45.0582	11.907-12.039
	244.1684	1.2E+05	199.1104	5.8E+04	45.0580	12.003-12.268
	245.1706	2.3E+04	200.1132	1.1E+04	45.0574	12.003-12.268
	260.2001	9.2E+04	215.1421	2.3E+04	45.0580	13.639-13.783
	194.0814	1.4E+04	149.0233	1.3E+05	45.0581	13.734-14.866
	171.1487	2.6E+04	126.0912	1.1E+04	45.0575	15.420-15.648
	307.2379	2.8E+04	262.1801	1.8E+04	45.0578	15.420-15.648
	171.1487	2.9E+04	126.0912	1.0E+04	45.0575	15.420-15.624
	307.2379	3.1E+04	262.1801	2.0E+04	45.0578	15.420-15.624
	171.1489	1.4E+04	126.0911	1.5E+04	45.0578	15.516-15.793
	294.2062	4.4E+04	249.1482	1.4E+04	45.0580	15.913-16.238
	310.2167	1.6E+05	265.1587	6.5E+04	45.0580	16.731-17.2
	310.2165	1.7E+05	265.1585	7.1E+04	45.0580	17.116-17.284
	631.4374	1.1E+04	586.3800	2.5E+05	45.0574	19.919-20.557