## Title

NDMA Formation During Drinking Water Treatment: Veterinary Antibiotics as Precursors, the Effect of Natural Organic Matter and the Significance of Treatment Practices



## Author

Roback, Shannon

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# NDMA Formation During Drinking Water Treatment: Veterinary Antibiotics as Precursors, the Effect of Natural Organic Matter and the Significance of Treatment Practices

A dissertation submitted in partial satisfaction of the

requirements for the degree of Doctor of Environmental Science and Engineering

by

Shannon Louise Roback

2015

ABSTRACT OF THE DISSERTATION

NDMA Formation During Drinking Water Treatment: Veterinary Antibiotics as Precursors, the Effect of Natural Organic Matter and the Significance of Treatment Practices

by

Shannon Louise Roback

Doctor of Environment in Environmental Science and Engineering

University of California, Los Angeles, 2015

Professor Irwin H. Suffet, Chair

Nitrosodimethylamine (NDMA) is a nitrosated amine that has been associated with a $10^{-5}$ increase in lifetime cancer risk at the ng/L level. NDMA may be formed from a variety of anthropogenic amine precursors during drinking water treatment utilizing chloramines as a disinfectant. In this dissertation, ten veterinary antibiotics were tested for their ability to form NDMA. The antibiotics were tested at different pH, temperature, chlorine to ammonia weight ratio ($Cl_2/NH_3$) and time to determine the impact of these factors on formation. Molar conversions ranged from 0.04 to 4.9 percent, with antibiotics containing more than one dimethylamine (DMA) functional group forming significantly more NDMA. The highest formation for most of the compounds was seen near pH 8.4. The effect of $Cl_2/NH_3$ ratio, temperature, and hold time was somewhat varied for each chemical, suggesting that the effects of these parameters were compound-specific. This suggests that large-scale farming run-off may be

a new source NDMA precursors. NDMA formation is slowed by the presence of natural organic matter (NOM). It is not currently known which components of NOM are responsible for the reduction in NDMA formation. In this dissertation, water containing NOM was fractionated into different MW size groups or separated based on polarity. The high molecular weight NOM fractions (> 10 kDa), polar and charged components were shown to be the most effective in reducing the amount of NDMA formed. Some precursors have high sorption coefficients to NOM, which is the likely mechanism for reduction of NDMA formation from these compounds. Lastly, NDMA formation can be highly impacted by numerous factors relevant to drinking water treatment. In this dissertation, water samples and treatment plant data were collected from approximately 20 drinking water treatment plants in the U.S. and Canada over 2 years. Linear mixed effects models with random intercepts, which account for variability between treatment plants, were used to assess variable significance and create predictive equations. UV254 concentration in the plant influent, sucralose concentration, polyDADMAC concentration, pre-chlorination time, $Cl_2/NH_3$ ratio, use of GAC, water pH, and biofiltration were associated with NDMA concentration in the distribution system.

The dissertation of Shannon Louise Roback is approved.

Keith Stolzenbach

Michael K. Stenstrom

Curtis Eckhert

Irwin H. Suffet, Committee Chair

University of California, Los Angeles

2015

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ACKNOWLEDGEMENTS

Chapter II is an expansion on the work presented at the 248th American Chemical Society National Meeting in San Francisco, CA. Stuart Krasner of Metropolitan Water District of Southern CA and Irwin Suffet (PI, UCLA) are co-authors of this chapter. An earlier version of this work appears in the conference proceedings: S. Leavey, I. Suffet, S. Krasner, 2014. Veterinary Antibiotics as NDMA Precursors In: ACS Environmental Chemistry Division Proceedings, San Francisco, CA. The author would also like to acknowledge the generosity of the Metropolitan Water District of Southern CA for the use of their facilities, equipment, and training for this project. Without their help, this work would not have been possible.

Chapter III has not been published in any form, but Stuart Krasner and Irwin Suffet will be co-authors on any future publication of this work.

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VITA

EDUCATION

2011 **M.S., University of California, Los Angeles (UCLA)**
Environmental Health Science
**Graduate Certificate:** Leaders in Sustainability

2009 **B.S., California State University, Northridge (CSUN)**
Environmental and Occupational Health

PROFESSIONAL EXPERIENCE

2014- **Lecturer**
2015 California State University, Channel Islands, Camarillo, CA
Department of Environmental Science and Resource Management

2013- **Assistant Chemist**
2014 Metropolitan Water District of Southern California, La Verne, CA

2013 **Lecturer**
California State University, Northridge, Northridge, CA
Department of Environmental and Occupational Health

2011 **Teaching Assistant**
University of California, Los Angeles (UCLA), Los Angeles, CA

AWARDS

2014 UCLA, Dissertation Year Fellowship ($30K + tuition and fees)

2011 UCLA, Green Initiative Fund Grant award winner: "Tap It" sustainability project to reduce single use plastic water bottle use on the UCLA campus

PUBLICATIONS

2014 Chao Chen, **Shannon Leavey**, Stuart Krasner and Mel Suffet
"Applying a Polarity Rapid Assessment Method and Ultrafiltration to Characterize N-Nitrosodimethylamine Precursors in Wastewater Effluents" *Water Research*. 57:115-26.

2014 Minghuo Wu, Yichao Qian, Jessica M. Boyd, **Shannon Leavey**, Steve E. Hrudey, Stuart W. Krasner, and Xing-Fang Li
"Identification of Tobacco-Specific Nitrosamines as Disinfection Byproducts in Chloraminated Water" *Environmental Science and Technology.* 48 (3): 1828–1834.

2011 Michael Sullivan and **Shannon Leavey**
"Heavy Metals in Bottled Natural Spring Water" Journal of Environmental Health. 73(10):8-13. (Cover)

PRESENTATIONS

2014 **S. Leavey**, S. Krasner, M. Suffet
"Veterinary Antibiotics as a Source of NDMA Precursors" *248th National Meeting of the American Chemical Society*, San Francisco, CA.

2014 **S. Leavey**, S. Krasner, M. Suffet
"Modeling NDMA Formation in Distribution Systems" *American Water Works Association Water Quality Technology Conference,* New Orleans, LA.

2014 P. Piriou, C. Cazin, E. Fryde, **S. Leavey**, B. Raczko, M. Suffet, F. Zraick
"ETBE: Defining a Treatment Target and Ensuring Removal in Drinking Water Production by Conventional and Alternative Processes" *IWA World Water Congress & Exhibition,* Lisbon, Portugal.

2013 **S. Leavey**, M. Everett, P. Piriou and M. Suffet
"Development of a Rigorous Taste and Odor Method to Determine Odor Recognition Concentration in Drinking Water by Small Consumer Panels" *American Water Works Association Annual Conference and Exposition*, Denver, CO.

2013 M. Suffet, **S. Leavey**, M. Everret, P. Piriou
"Development of a Rigorous Taste and Odor Method to Determine the Odor and Flavor Objection and Rejection Thresholds of Drinking Water by Small Consumer Panels" *American Water Works Association Annual Conference and Exposition*, Denver, CO.

2013 C. Chen, **S. Leavey** and M. Suffet
"Development of an Easy and Selective Tool for Nitrosamine Precursor Identification in Water" *American Water Works Association Water Quality Technology Conference,* 2013, Long Beach, CA.

2013 **S. Leavey**, M. Everett, P. Piriou and M. Suffet
"Threshold, Recognition and Objection Odor Concentration as Tools to Set Water Treatment Goals as Exemplified by ETBE" *American Water Works Association Water Quality Technology Conference,* Long Beach, CA.

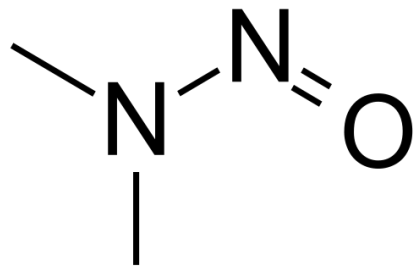
2013 S. Krasner, **S. Leavey**, M. Prescott, C. Guo
"Artificial Sweeteners as Emerging Indicators of Wastewater Discharges and NDMA Precursor Loading in Potable Source Waters" *American Water Works Association Water Quality Technology Conference,* Long Beach, CA.

# Chapter I: NDMA as a Disinfection Byproduct

NDMA as a Water Pollutant

Nitrosodimethylamine (NDMA) (Figure 1-1) is a nitrosamine consisting of a nitrosated dimethylamine molecule. NDMA may be produced during industrial processes as a byproduct. It is commonly formed during the production of unsymmetrical dimethylhydrazine, (UDMH) a component of rocket fuel (Brubaker et al. 1985; Brubaker, Bonilla, and Boparai 1989; Castegnaro et al. 1986; Lunn and Sansone 1994; Lunn et al. 1991). NDMA was first noted as a water contaminant after being detected in wells down gradient of a rocket engine testing facility in Sacramento, CA (DHS 2002; MacDonald 2002).

Figure 1-1: N-Nitrosodimethylamine Chemical Structure




After contamination of wells in Sacramento, the California Department of Health Services completed a survey of NDMA concentrations in drinking water in California (DHS 2002). NDMA was detected in high concentrations in plants utilizing a high proportion of treated wastewater and plants that used chloramines as a disinfectant (OCWD 2000; DHS 2002).

NDMA may also be present in some foods, such as beer and hot dogs (Lijinsky 1999). In some cases, the concentration in food may be higher than the concentrations found in drinking water.

However, NDMA may be avoided voluntarily be abstaining from certain foods, while avoiding drinking water is not possible.

Toxicity

The United States Environmental Protection Agency (USEPA) lists NDMA as a probable human carcinogen (DHS 2002). NDMA and other nitrosamines have been shown to be carcinogenic at the nanogram per liter level (Peto et al. 1991). USEPA's Integrated Risk Information System (IRIS) database classifies NDMA and 5 other nitrosamines as being associated with an increased lifetime cancer risk at these levels (DHS 2002). NDMA is highly genotoxic, inducing gene and chromosomal mutations and DNA damage (EPA 2006) (Cancer 1978) (Liteplo and Meek 2001). Nearly all of the nitrosamines that have been tested for carcinogenicity have proven to be carcinogenic (Brown 1998; Cancer 1978). Tumor formation has been seen primarily in the esophagus and liver, but also the in brain, lungs and urinary bladder (Brown 1998; Cancer 1978). Low dose exposure over long periods of time appears to be the most optimal condition for carcinogenicity (Brown 1998). USEPA's IRIS database estimates that a chronic exposure to drinking water contaminated with just 7 ng/L of NDMA confers a $10^{-5}$ lifetime cancer risk for the average adult (EPA 2003).

Formation

*Mechanism 1*

Chloramination of drinking water was shown to form NDMA first in a laboratory study and was later documented at drinking water and wastewater treatment plants utilizing chloramination (Child et al. 1996; Ash 1995; Jobb et al. 1994; Kimoto et al. 1980; Kimoto et al. 1981). Figure 1-2 shows one proposed mechanism in which the oxidation of UDMH results in the formation of NDMA. UDMH may be present in drinking water due to contamination or may be formed by the reaction of monochloramine and dimethylamine (Yagil and Anbar 1962). Mitch and Sedlak (Mitch and Sedlak 2002) and Choi and Valentine (Choi and Valentine 2002; Choi and Valentine 2002) were the first to demonstrate that NDMA can be formed via oxidation of UDMH by chloramines.

Figure 1-2 shows that the formation of NDMA from DMA in the presence of chloramines occurs via a two-step mechanism. DMA is converted to UDMH, which is then oxidized to form NDMA (Mitch and Sedlak 2002). Although present at lower concentrations than monochloramine during typical treatment plant operating conditions, dichloramine has been shown to be responsible for most of the formation of NDMA from organic amine precursors (Schreiber and Mitch 2006). A nucleophilic substitution reaction between dichloramine and unprotonated secondary amine precursors leads to the formation of a chlorinated UDMH which is then oxidized to form NDMA (Schreiber and Mitch 2006). The reaction resulting in the formation of

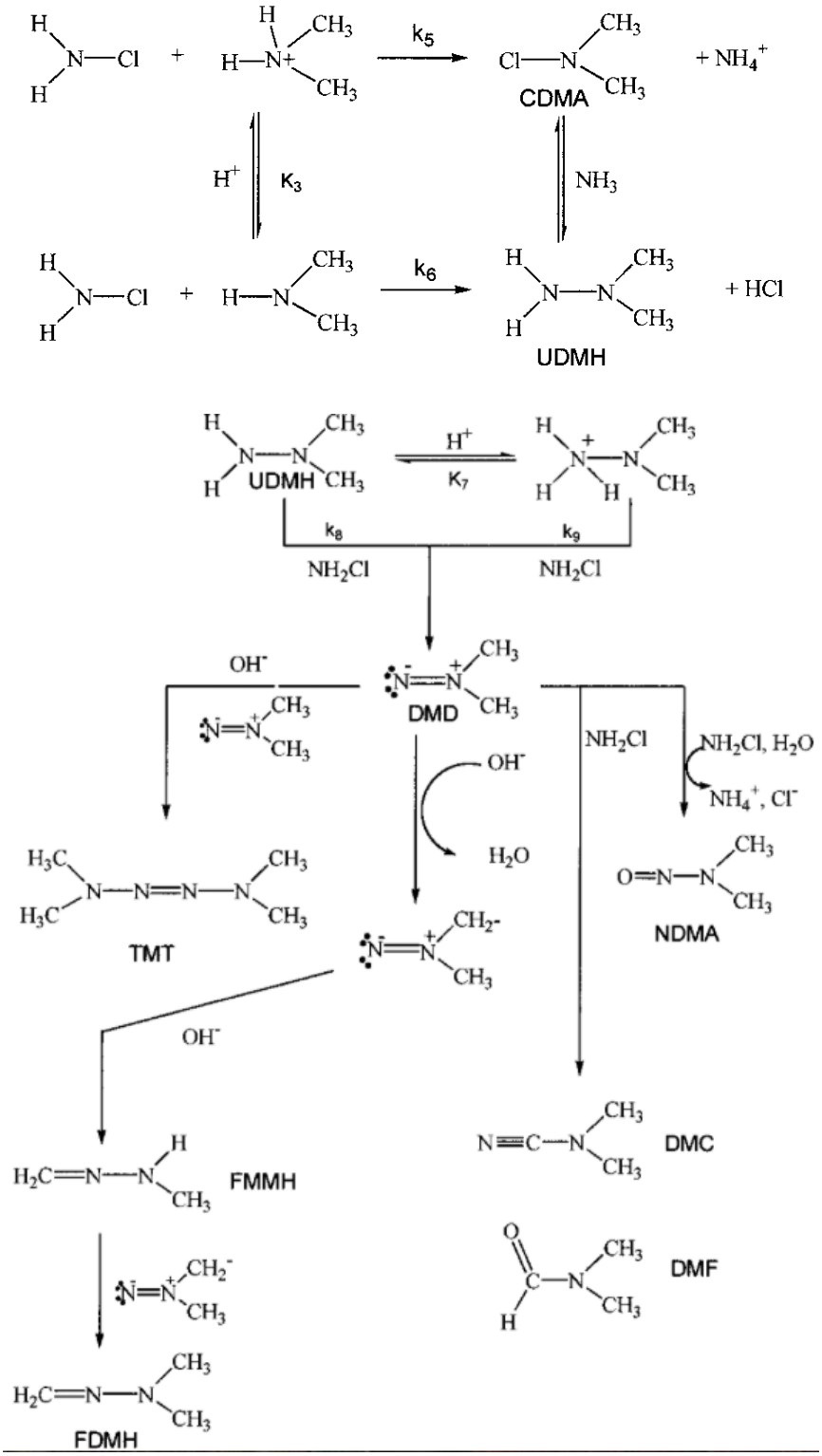
NDMA occurs slowly, over days (Mitch, Gerecke, and Sedlak 2003). For example, when water sources high in NDMA precursors were chloraminated in one study, NDMA formation did not plateau until day 5 (Mitch, Gerecke, and Sedlak 2003).

Using this mechanism, in addition to dimethylamine (DMA), NDMA may be formed from chemicals containing a DMA functional group. The release of the DMA group from tertiary amines is illustrated in Figure 1-3 using trimethylamine as an example. During chloramination, chlorination of trimethylamine forms dimethylamine and formaldehyde. This occurs via dehydrohalogenation and the subsequent hydrolysis of a chlorinated trimethylamine intermediate (Mitch and Schreiber 2008).

The release of the DMA group may be impacted by the nature of the adjoining functional groups and the stability of the leaving group (Selbes et al. 2013). Electron donating groups close to the DMA group may increase the rate of formation in the presence of dichloramine, while electron withdrawing groups may increase the rate of formation of NDMA in the presence of monochloramine (Selbes et al. 2013). This may make predicting NDMA formation difficult as determining concentrations of mono or dichloramine may not be easily achieved.

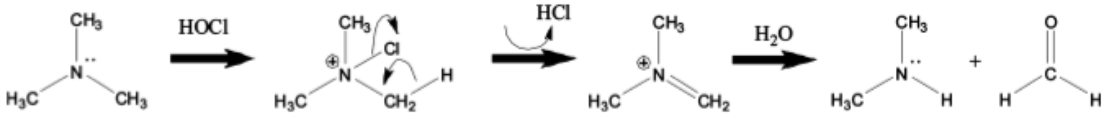
The stability of the leaving group may also impact NDMA formation. The higher the stability of the leaving group, the higher the NDMA yield (Selbes et al. 2013). Additionally, the structure of amines containing DMA groups may impact the release of the DMA group. Selbes et al. (2013) selected amines to test for their ability to form NDMA under chloramination. Some amines had very high molar conversion to NDMA (83.9%) while others had quite lower formation (0.2%)

Figure 1-2: First Proposed Mechanism for NDMA Formation via UDMH Intermediate (Mitch and Sedlak 2002)



(See Table 1-1) (Selbes et al. 2013). This suggests that the mechanism proposed in Figure 1-3 may be more likely to occur with higher efficiency in certain cases.

Figure 1-3: Creation of Dimethylamine from Tertiary Amines (Mitch and Schreiber 2008)




*Mechanism 2*

A second mechanism for the formation of NDMA from tertiary amines has also been proposed. DMA has relatively low molar conversion to NDMA (>3 %), therefore, using mechanism 1, it is hard to understand how certain precursors may have molar conversions of up to 90% (assuming this mechanism functions by release of DMA that is then converted to NDMA). Mechanism 2 is initiated by nucleophilic substitution by mono or dichloramine on the DMA moiety (Le Roux et al. 2012) (Liu et al. 2014). In the second step, an elimination reaction of hydrogen chloride forms an intermediate that reacts with oxygen. After this, an N-O bond forms and the N-N bond cleaves which produces a nitrosating agent. In the 3rd step, an NO+ cation is generated which reacts with the amine and forms NDMA (see Figure 1-4). The formation of a stable carbocation is an important aspect of this mechanism, which may not proceed as easily without this step. Therefore different chemical structures impacting the carbocation resonance are influential on

the ability of the precursor to form NDMA. This mechanism would explain how higher yielding precursors form NDMA as it does not involve the release of DMA as a critical step.

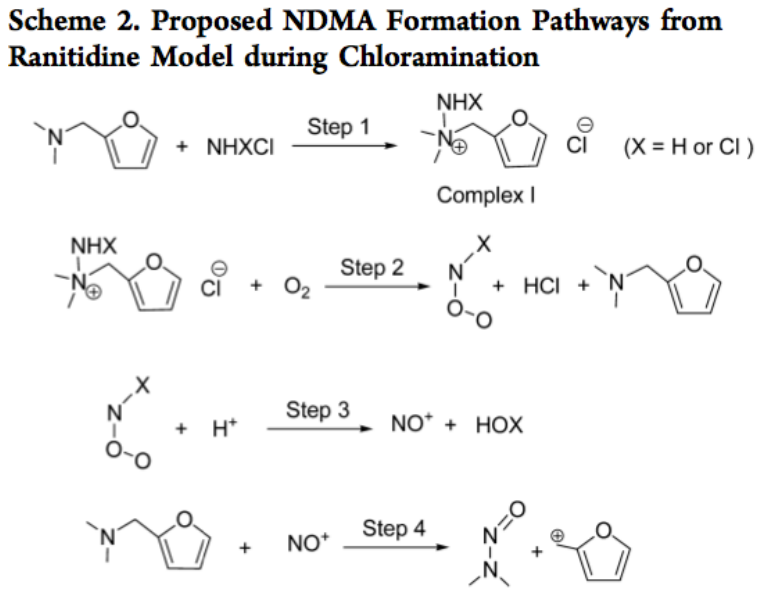
Table 1-1: Structure of Amines' Impact on NDMA Formation (Selbes et al. 2013)

| Compound | This study[a] | Studies reported in DDW | |
|---|---|---|---|
| | Molar yield (%[b]) (EB[c]) | Yield (%[b]) | Reference[d] |
| DMA | 1.2 (0.12) | 3.0 | Lee et al., 2007 |
| | | 0.082 | Mitch et al., 2009 |
| | | 1.2 | Le Roux et al., 2011b |
| | | 2.3 | Le Roux et al., 2012a |
| TMA | 1.9 (0.16) | 1.2 | Lee et al., 2007 |
| | | 0.017 | Mitch et al., 2009 |
| DMEA | 0.5 (0.09) | – | – |
| DMBA | 0.3 (0.05) | – | – |
| DMiPA | 83.9 (0.67) | – | – |
| DMtBA | 6.2 (0.03) | – | – |
| DMAAcCN | 2.4 (0.28) | – | – |
| DMEtOH | 0.3 (0.14) | 0.5 | Lee et al., 2007 |
| DMEDA | 0.8 (0.08) | – | – |
| DMEtSH | 0.8 (0.01) | – | – |
| DMAN | 0.2 (0.03) | 1.2 | Lee et al., 2007 |
| 4-DMAP | 0.06 (0.02) | – | – |
| 2-DMAP | 0.09 (0.01) | 0.37 | Le Roux et al., 2012a |
| 2-Cl-DMAN | 0.02 (0.02) | – | – |
| DMAPhOH | 1.0 (0.05) | 1.0 | Le Roux et al., 2012a |
| DMPhA | 0.4 (0.06) | – | – |
| DMBzA | 83.8 (0.99) | 19.63 | Mitch et al., 2009 |
| RNTD | 80.5 (2.85) | 80.2 | Le Roux et al., 2011a |
| | | 89.9 | Shen and Andrews, 2011a |
| | | 82.7 | Shen and Andrews, 2011b |
| DMAFuOH | 81.8 (1.58) | 74.9 | Le Roux et al., 2012a |
| DMPMA | 25.0 (1.97) | – | – |
| DMTMA | 77.6 (1.99) | – | – |

a Experimental conditions include compound dose of 200 nM, 100 mg/L chloramine (as $Cl_2$), contact time of 5 days, pH 7.5 adjusted with 10 mM phosphate buffer.

Liu et al. (2014) provide computational information on activation free energies of various tertiary amine structures for the release of NDMA and formation of the carbocation (Liu et al. 2014). The wide range of activation free energies confirms that tertiary amines may have differing abilities to form NDMA, according to this mechanism, based on their structure.

Figure 1-4: Mechanism 2 for the Formation of NDMA via Nucelophilic Substitution (Liu et al. 2014)




*Effect of pH, Temperature and Catalysts on NDMA Formation*

Previous research has suggested that NDMA formation increases with increasing pH and temperature (Krasner 2012). NDMA formation was shown to be most efficient at a pH between 8 and 9 (Mitch and Sedlak 2001). Assuming mechanism 1, this may be due to the fact that conversion of DMA to UDMH is more favorable at pH close to 11 and the conversion of UDMH to NDMA is favorable at low pH near 7. A pH between 8 and 9 does not highly limit the

formation in either of the two steps. For example, if the reaction occurred near pH 7, the first step in the mechanism will not progress as efficiently and if it occurred at pH 11, the second step would be hindered. Bromide may act as a catalyst for NDMA formation during chloramination (Le Roux, Gallard, and Croué 2012), however this effect when bromide is spiked into authentic waters is only seen at very high (> 500 ug/L) concentrations (Shah et al. 2012).

*Ozone*

Unlike NDMA yields from chloramines, most organic amine precursors form very little NDMA upon ozonation (Yang et al. 2009). However a small number of amines do form significant amounts of NDMA upon ozonation. Amines with sulfamide or hydrazine functional groups may have molar conversions to NDMA exceeding 50 % (Schmidt and Brauch 2008) (Kosaka et al. 2009). NDMA formation from ozone occurs more rapidly than it does from chloramines with formation occurring in less than one hour (Gunten et al. 2010). In Germany, NDMA formation exceeded 10 ng/L in one water treatment plant due to the ozonation of a degradation product of tolylfluanide, a fungicide (Schmidt and Brauch 2008). The degradation product, N,N-dimethylsulfamide (DMS), had a molar conversion rate to NDMA of 30-50% (Schmidt and Brauch 2008). Schmidt and Brauch also found that UDMH could be oxidized by ozone to form NDMA and had a very high molar conversion rate (80%). Several semicarbazide anti-yellowing agents present in drinking water treatments in Japan were also responsible for the formation of NDMA concentrations above 10 ng/L during ozonation (Kosaka et al. 2009). The molar conversion rates of the two anti-yellowing agents studied, 4,4′-hexamethylenebis (1,1-

dimethylsemicarbazide) (HDMS) and 1,1,1′,1′-tetramethyl-4,4′-(methylene-di-phenylene) disemicarbazide (TMDS) were 10 and 27 percent, respectively (Kosaka et al. 2009).

## NDMA Precursors

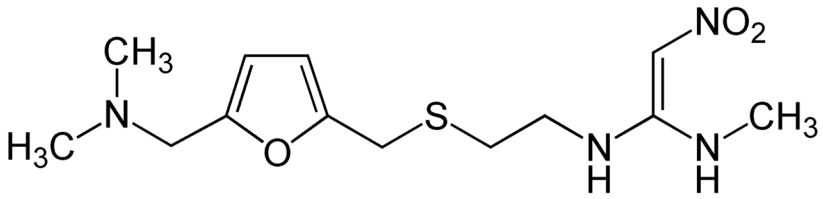
### *Chemical characteristics*

While dimethylamine was one of the first precursors identified that yielded NDMA upon chloramination, certain chemical characteristics have since been identified that render a molecule a likely NDMA precursor. In addition to DMA, amines containing a DMA functional groups may be NDMA precursors (Weissmahr and Sedlak 2000).

Studies have shown that most NDMA precursors are secondary, tertiary or quaternary amines containing a DMA functional group (Kemper, Walse, and Mitch 2010) (Mitch and Sedlak 2004). Nitrosamines formed from primary amines may degrade rapidly (Ridd 1961), while nitrosamines formed from secondary amines are more stable (Krasner et al. 2013). Tertiary amines will release a secondary amine upon chlorination, which is the mechanism by which nitrosamines are formed from most tertiary amines (Mitch and Schreiber 2008). In Shen and Andrews (2011) tertiary amines with ß-aryl functional groups were shown to have high conversion to NDMA, some exceeding 80% molar conversion (Shen and Andrews 2011). The human pharmaceutical, ranitidine, is in this group with molar conversion near 90% (Shen and Andrews 2011). Ranitidine also has a strong electron donating group adjacent to the first carbon atom attached to the nitrogen atom of the DMA group which increases the stability of the carbocation and yields a

low activation free energy and thus high NDMA formation (Liu et al. 2014). The molar conversion to NDMA for most tertiary and secondary amines is near 2 % (Mitch and Sedlak 2004) and the molar conversion of DMA to NDMA is similar (under 3 percent) (Choi and Valentine 2002). Quaternary amines are the lowest forming of the group (Kemper, Walse, and Mitch 2010).

Figure 1-5: Ranitidine Chemical Structure




Chen et al. (2014) found that NDMA precursors were more likely to have a positive charge, be non-polar and be of very low (less than 1 kDa) or high (greater than 10 kDa) molecular weight (Chen et al. 2014). Other studies have found that nitrosamine precursors tend to be hydrophilic (Pehlivanoglu-Mantas and Sedlak 2008; Dotson, Westerhoff, and Krasner 2009) and of low molecular weight (Krauss et al. 2010) (Pehlivanoglu-Mantas and Sedlak 2008).

*Sources*

Table 1-3 shows some of the pharmaceuticals, personal care products, herbicides and pesticides that may be present in wastewater treatment plants and have been shown to form NDMA (Shen and Andrews 2011) (Chen and Young 2008) (Kemper, Walse, and Mitch 2010). Precursors are

mostly anthropogenic chemicals and most have a DMA functional group. Many known precursors are human or animal pharmaceuticals that may contaminate drinking water sources.

1. Wastewater Treatment Plant Effluent

Wastewater treatment plant effluent has been identified as one of the most significant sources of NDMA precursors producing from 300- 1300 ng/L of NDMA upon chloramination (Mitch and Sedlak 2004). Eutrophic waters not impacted by wastewater formed only 58 ng/L in a similar study (Gerecke and Sedlak 2003). The most obvious precursor described, DMA, has typically accounted for only 12% of the precursors in wastewater effluent (Mitch and Sedlak 2004).

2. Natural Organic Matter

Natural organic matter (NOM) can be a precursor for NDMA if nitrogen in the NOM reacts with inorganic nitrogen in monochloramine (Mitch and Schreiber 2008). The more nitrogen rich fractions of NOM have higher NDMA formation (Lee, Westerhoff, and Croué 2007). In Dotson (2009), hydrophobic acids were shown to have no reactivity to form NDMA (Dotson, Westerhoff, and Krasner 2009). TOC and UV254 and dissolved organic nitrogen concentration have also not been found to correlate to NDMA concentrations (Chen and Westerhoff 2010). The NDMA formation from different MW fractions of NOM in another study is attributed to sorbed trace organic chemicals (Krauss et al. 2010). Krauss et al. 2010 found that 50% of all NDMA precursors were associated with colloids or macromolecules in one wastewater influent. (Krauss et al. 2010). Therefore, the reason for NOM appearing to be an NDMA precursor in

some studies may be due to the fact that certain NOM matrices may be contaminated with NDMA precursors.

3. Drinking Water Treatment Chemicals

In addition to wastewater effluent, certain drinking water treatment processes or techniques may also add NDMA precursors to drinking water. Figure 1-6 shows that certain cationic polymers used in drinking water treatment that contain nitrogen may be NDMA precursors, especially polyDADMAC and polyamine (Najm and Trussell 2001) (Kohut and Andrews 2003) (Bolto 2005) (Park et al. 2009).

Figure 1-6: Degradation of (A) Polyamine and (B) PolyDADMAC and Subsequent Formation of NDMA (Park et al. 2009)

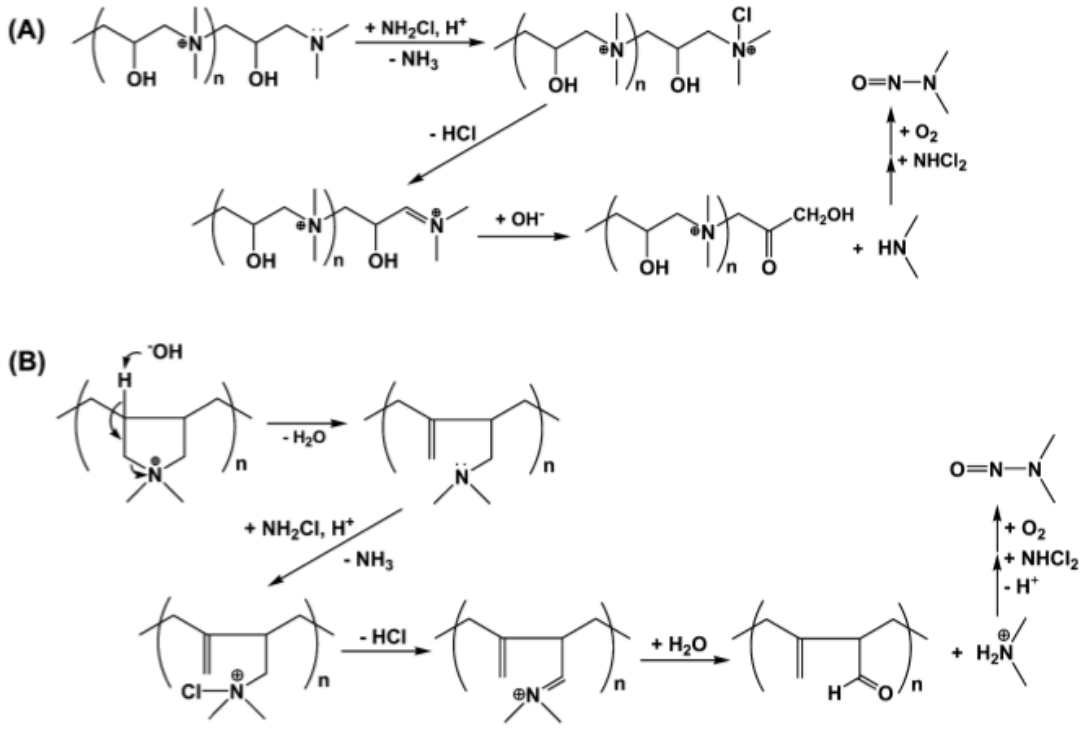


Table 1-2 shows that anion exchange resins used during water treatment to remove nitrate, arsenate, and perchlorate have also been shown to be a source of NDMA precursors (Kemper et al. 2009) (Kimoto et al. 1980).

Table 1-2: NDMA Formation on Mixed Anion (Dowex 21K) and Cation (Dowex 50W- X8) Exchange Resin Column (Kimoto et al. 1980)

| Experiment | Influent | Influent† (l) | NDMA in effluent (ppb) |
|---|---|---|---|
| 1 | Tap water | 5 | 1.26‡ |
| | | 4 | 1.77‡ |
| | | 6 | 2.03‡ |

Human and Veterinary Antibiotics

*Use*

Most antibiotics currently available can be used to treat both humans and other animals.

The majority of antibiotics produced in the United States are used on animals farmed for human consumption. In 2011, the U.S. Food and Drug Administration reported that 29.9 million pounds were used on farmed animals, or 80.5% of the total antibiotics consumed in the U.S. (FDA 2011) (Services 2012). Antibiotics are frequently used in the treatment of disease and as a component of animal feed to serve as growth promoters (Cohen 1998). The usage of antibiotics in animal feed increased by almost 8 percent from 2009 to 2011 with an additional 2.2 million pounds of antibiotics being used on farmed animals in 2011 (FDA 2009, 2011). During this time period the

amount of antibiotics sold for human use decreased by 1 percent (Services 2012; Department of Health and Human Services and Food and Drug Administration 2010).

Table 1-3: Some Known Anthropogenic Precursors of NDMA

| Chemical | Use | Molar Conversion % in DI water |
|---|---|---|
| Amitriptyline | pharmaceutical | > 1 (Shen and Andrews 2011) |
| Azithromycin | pharmaceutical | > 1 (Shen and Andrews 2011) |
| Carbinoxamine | pharmaceutical | ~1 (Shen and Andrews 2011) |
| Chlorpheniramine | pharmaceutical | ~7 (Shen and Andrews 2011) |
| Clarithromycin | pharmaceutical | > 1 (Shen and Andrews 2011) |
| DEET | insecticide | > 1 (Shen and Andrews 2011) |
| Diltiazem | pharmaceutical | ~ 3 (Shen and Andrews 2011) |
| Diphenhydramine | pharmaceutical | > 1 (Shen and Andrews 2011) |
| Doxylamine | pharmaceutical | ~10 (Shen and Andrews 2011) |
| Erythromycin | pharmaceutical | > 1 (Shen and Andrews 2011) |
| Escitalopram | pharmaceutical | > 1 (Shen and Andrews 2011) |
| Lidocaine | pharmaceutical | > 1 (Shen and Andrews 2011) |
| Metformin | pharmaceutical | > 1 (Shen and Andrews 2011) |
| Nizatidine | pharmaceutical | 4.8 (Shen and Andrews 2011) |
| Ranitidine | pharmaceutical | 89.9 (Shen and Andrews 2011) |
| Roxithromycin | pharmaceutical | > 1 (Shen and Andrews 2011) |
| Sumatriptan | pharmaceutical | ~ 8 (Shen and Andrews 2011) |
| Tetracycline | pharmaceutical | 1.2 (Shen and Andrews 2011) |
| Tramadol | pharmaceutical | > 1 (Shen and Andrews 2011) |
| Venlafaxine | pharmaceutical | ~ 1 (Shen and Andrews 2011) |
| Methadone | pharmaceutical | 23-70 (Hanigan et al. 2015) |
| HDMS | anti-yellowing agent | 10 (Kosaka et al. 2009) |
| TMDS | anti-yellowing agent | 27 (Kosaka et al. 2009) |
| N,N-dimethylsulfide (DMS) | degradation product of fungicide | 30-50 (Schmidt and Brauch 2008) |
| DMA | raw material for industrial chemicals | > 3 (Choi and Valentine 2002) |

Of the 29.9 million pounds of antibiotics being applied in animal agriculture, 61% of those antibiotics have been deemed by The United States Food and Drug Administration (FDA) as important in human medical human therapy (FDA 2011). Close to 93% percent of these antibiotics are used in feed and water with less than 8 percent being used in an injection, intramammary, oral or topical solution. For non-medically important antibiotics, 99% are used in animal feed (FDA 2011). Antibiotics used to increased the rate of weight gain account for 70% of the medically important antibiotics used, and 71% of non-medically important antibiotics used (FDA 2011). Ninety-seven percent of medically important antibiotics were available to farmers over the counter without a prescription (FDA 2011). The increasing amount of antibiotics being used in animal agriculture operations has raised concerns about the increase of antibiotic resistant organisms, which can pose risks to humans. The excess health care costs of antibiotic resistant infections in the U.S. is estimated to be $20 billion per year with societal costs reaching $35 billion per year (Roberts et al. 2009).

Figure 1-7 shows that some veterinary antibiotics have dimethylamine functional groups, and therefore may be NDMA precursors. The majority of antibiotics applied in animal agriculture in the U.S. are tetracyclines which account for 42% of the antibiotics used in total and 68% of the medically important antibiotics used (FDA 2011). The next most common are ionophores (30%), penicillins (7%) and macrolides (3%) (FDA 2011). Many tetracycline and macrolide antibiotics have DMA functional groups, indicating they could be converted to NDMA under chloramination conditions. Antibiotics are also used as growth promoters or for therapeutic indications in Canada, Australia, New Zealand and Europe (Sarmah, Meyer, and Boxall 2006). However European Parliament banned antibiotics used as growth promoters by Regulation No

1831/2003 in 2006 (Castanon 2007). In China, Japan and Russia the use of antibiotics in animal agriculture is restricted to antibiotics not used for human medical therapy (Sarmah, Meyer, and Boxall 2006).

*Environmental Occurrence*

Veterinary antibiotics used in large-scale farming operations can contaminate water sources primarily through the disposal of unused or expired compounds, via overland flow run off, in unsaturated zone transport on fields which agricultural waste has been applied, and via leaky waste-storage structures. Poor absorption in the guts of farm animals may result in up to 95% of veterinary antibiotics being excreted as the parent compound (Elmund et al. 1971) (Magnussen et al. 1991) (Beconi-Barker et al. 1996). Additionally, some metabolites of antibiotics such as sulfonamides may be capable of being transformed back to the parent compound in the environment (Sarmah, Meyer, and Boxall 2006). As a result, occurrence of veterinary antibiotics in the environment especially near large-scale agricultural operations should be further evaluated. Antibiotics used in animal agriculture have been detected in groundwater, surface water or water treatment plant effluent in the United States, Canada, the United Kingdom, Germany, Italy, Switzerland, and Australia (Table 1-4). The stability of tetracycline in animal slurry solutions even during changes in temperature and aeration through repeated stirring may result in a large amount of the antibiotic being transferred to the environment via manure application (Winckler and Grafe 2001).

*Removal During Drinking Water Treatment*

Figure 1-7 shows that in drinking water treatment plant studies, pharmaceuticals and personal care products (PPCPs) including some antibiotics have been poorly removed during coagulation, flocculation and sedimentation with alum and iron salts and during lime/soda ash softening (Westerhoff et al. 2005) (Adams et al. 2002). However, Figure 1-9 and 1-10 show the use of powdered activated carbon and oxidation processes including the use of chlorine and ozone may be capable of reducing antibiotics concentrations (Westerhoff et al. 2005; Adams et al. 2002).

Figure 1-7: Structure of Select Veterinary Antibiotics

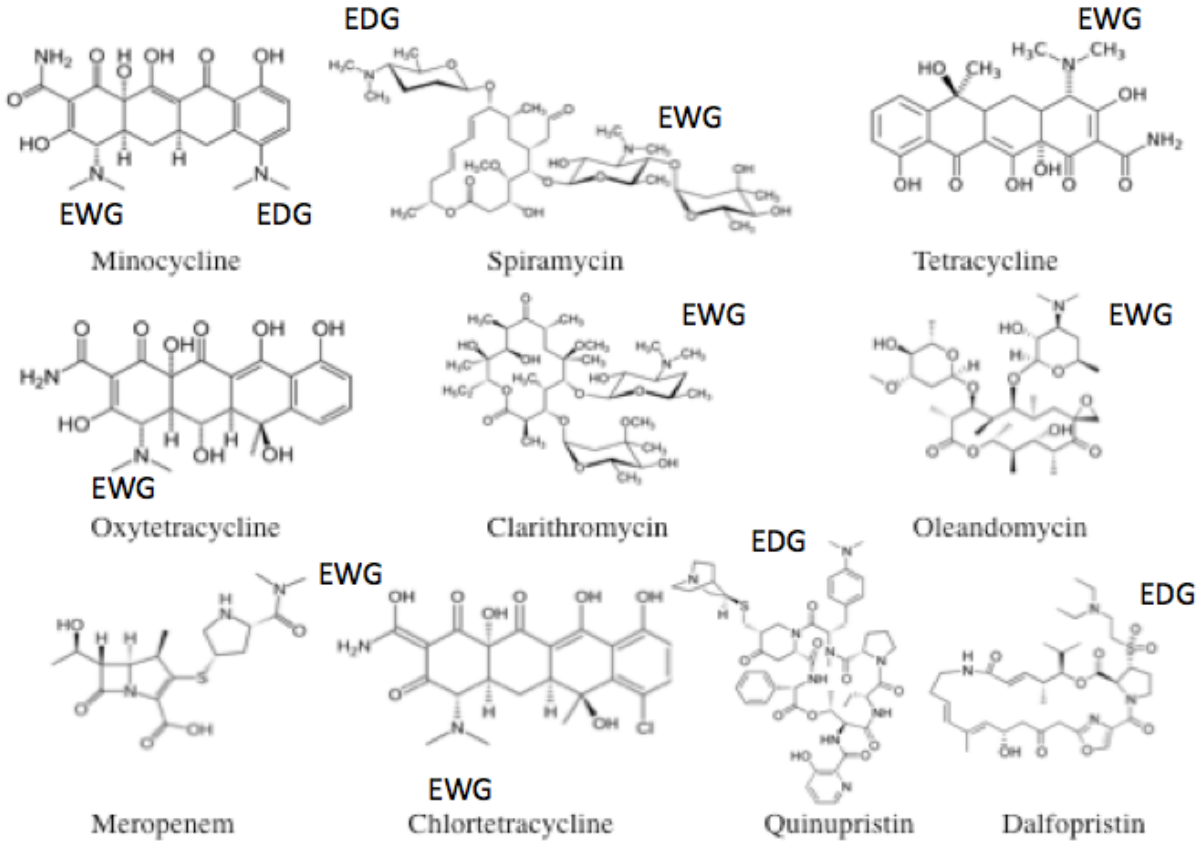


Table 1-4: Occurrence of Veterinary Antibiotics in the Aquatic Environment

| Antibiotic (ng/L) | Wastewater Effluent | Surface Water | Ground Water | Country | Reference |
|---|---|---|---|---|---|
| | 328 | 65 | | | (Giger et al. 2003) |
| | | 600 | | | (Göbel et al. 2007) |
| | 350 | 380 | | Switzerland | (Göbel et al. 2007) |
| | 240 | 260 | | | (Hirsch et al. 1999) |
| | | 37 | | | (Christian et al. 2003) |
| | 38 | | | Germany | (Alexy et al. 2006) |
| Clarithromycin | | 20.3 | | Italy | (Calamari et al. 2003) |
| Spiramycin | | 74.2 | | Italy | (Calamari et al. 2003) |
| | 20 | 1 | | Germany | (Färber and Färber 2002) |
| | | 5 | | | (Arikan, Rice, and Codling 2008) |
| | 300 | 1200 | | | (Karthikeyan and Meyer 2006) |
| | | 53 | | | (Haggard and Bartsch 2009) |
| | | 110 | | | (Kolpin et al. 2002) |
| | | | 400 | USA | (Krapac et al. 2001) |
| | 977 | | | Canada | (Miao et al. 2004) |
| Tetracycline | 30 | 35 | | Australia | (Watkinson, Murby, and Costanzo 2007) |
| | | 340 | | | (Kolpin et al. 2002) |
| | | 47 | 388 | | (Arikan, Rice, and Codling 2008) |
| | | 20 | | USA | (Haggard and Bartsch 2009) |
| | 20 | | | Australia | (Watkinson, Murby, and Costanzo 2007) |
| Oxytetracycline | | 32000 | | UK | (Kay, Blackwell, and Boxall 2005) |
| Tetracycline + Oxytetracycline | | 2000 | | USA | (Campagnolo et al. 2002) |

Figure 1-11 shows that differences in removal efficiency exist even among compounds of similar structure. For example in one study of tetracycline compounds, coagulation removed 22 percent of chlortetraycline, but 58 percent of minocycline, while use of granular activated carbon removed up to 95 percent of tetracycline, but only 50-70 of minocycline (Choi, Kim, and Kim 2008).

NDMA Formation Potential Tests

Since NDMA may be formed by the reaction of precursor chemicals with monochloramine or dichloramine, tests may be set up to elicit the load of NDMA precursors in a given water. This is done by chloraminating a water containing precursors and then measuring the resultant NDMA. Tests may be completed by chloraminating a real water which may already contain precursors, or by spiking known precursors into deionized water or water from another source.

Formation potential tests are typically designed to generate the highest possible value for NDMA. The inputs used in formation potential tests for this dissertation include a pH value of 8.4, a water temperature of 25° C, a chlorine to ammonia weight ratio of 3:1 and a hold time of 3 days (Krasner et al. 2007). Chlorine was spiked after an ammonia addition to avoid free chlorine contact time, which may degrade precursors (Shah et al. 2012). The sample was held in the dark in order to avoid sunlight photolysis of NDMA (Chen, Lee, et al. 2010). Although NDMA formation may be higher in samples held for longer than 3 days, 3 days was chosen for these

experiments as it is the average water distribution system hold time for many water conveyance systems.

Table 1-5a/b: Degradation of Antibiotics by Wastewater Bacteria Present Typically in Activated Sludge; a.(Al-Ahmad, Daschner, and Kummerer 1999) and b.(Alexy et al. 2006)

| Test Compound | Supplied By | Test Concentration (μg/ml) | Biodegradation After 28 Days (%) | Biodegradation After 40 Days (%) |
|---|---|---|---|---|
| Cefotiam dihydrochloride | Takeda Pharma GmbH | 4.8 | 7 | 10 |
| Ciprofloxacin | Bayer MG, Lever Kusen | 3.5 | 0 | 0 |
| Meropenem | Zeneca-Grünenthal, GmbH Stolberg | 2.5 | 7 | 7 |
| Penicillin G | Zeneca-Grünenthal, GmbH Stolberg | 3.0 | 27 | 36 |
| Sulfamethoxazole | Sigma Aldrich Chemie GmbH, Steinheim | 3.8 | 0 | 0 |

| | | Concentration | Biodegradation in high concentration (ThOD) | | |
|---|---|---|---|---|---|
| Substance | Source | Low [μg/l] | High [mg/l] | 14 days [%][a] | 28 days [%][a] |
| 1. Amoxicillin | Sigma Aldrich Chemie GmbH, Steinheim | 5.14 | 3.27 | 3 | 5 |
| 2. Benzylpenicillin sodium salt | Sigma Aldrich Chemie GmbH, Steinheim | 5.00 | 3.01 | 21 | 27 |
| 3. Ceftriaxone disodium | Hoffmann-La Roche AG, Grenzach-Wyhlen | 5.00 | 5.32 | 1 | 3 |
| 4. Cefuroxime sodium salt | Sigma Aldrich Chemie GmbH, Steinheim | 10.00 | 4.80 | −3 | −1 |
| 5. Chlortetracycline hydrochloride | Sigma Aldrich Chemie GmbH, Steinheim | 3.00 | 3.65 | −1 | 1 |
| 6. Clarithromycin | IDC, Abbott Laboratories Ldt., Queensborough, England | 3.00 | 2.43 | −3 | 0 |
| 7. Clindamycin | RosenPharma GmbH, Blieskastel | 3.00 | 3.07 | −2 | 3 |
| 8. Erythromycin | Fluka Chemie AG, Sigma-Aldrich Laborchemikalien GmbH, Steinheim | 3.00 | 2.46 | −3 | −3 |
| 9. Gentamicin sulfate | Sigma Aldrich Chemie GmbH, Steinheim | 3.00 | 3.05 | −3 | −3 |
| 10. Imipenem | MSD Sharp & Dohme GmbH, Haar | 3.50 | 3.47 | −2 | 1 |
| 11. Metronidazole | Sigma Aldrich Chemie GmbH, Steinheim | 5.95 | 5.95 | 0 | 1 |
| 12. Monensin sodium salt | Fluka Chemie AG, Sigma-Aldrich Laborchemikalien GmbH, Steinheim | 10.00 | 2.35 | 4 | 1 |
| 13. Nystatin | Calbiochem, Darmstadt | 3.00 | 2.56 | −1 | 4 |
| 14. Ofloxacin | Sigma Aldrich Chemie GmbH, Steinheim | 3.30 | 3.05 | 0 | −1 |
| 15. Sulfamethoxazole | Sigma Aldrich Chemie GmbH, Steinheim | 35.00 | 3.76 | 2 | 4 |
| 16. Tetracycline | Sigma Aldrich Chemie GmbH, Steinheim | 3.00 | 3.09 | −4 | 2 |
| 17. Trimethoprim | Sigma Aldrich Chemie GmbH, Steinheim | 4.60 | 3.25 | 2 | 4 |

Figure 1-8: PPCP Removal Using Alum, Iron and Water softening (Westerhoff et al. 2005)

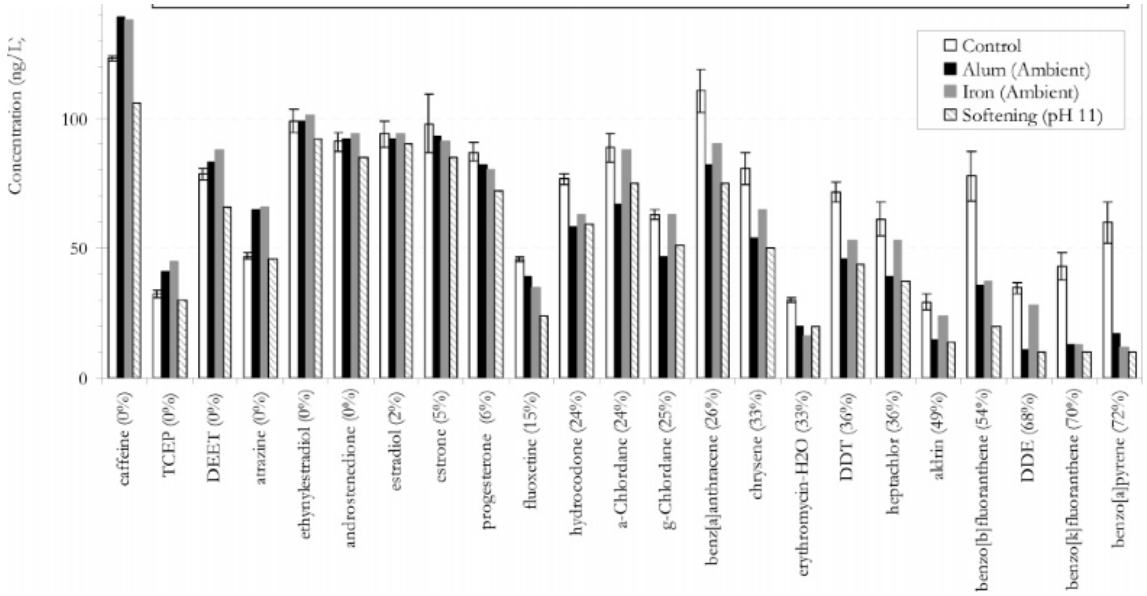



Figure 1-9: PPCP Removal Using PAC (Westerhoff et al. 2005)

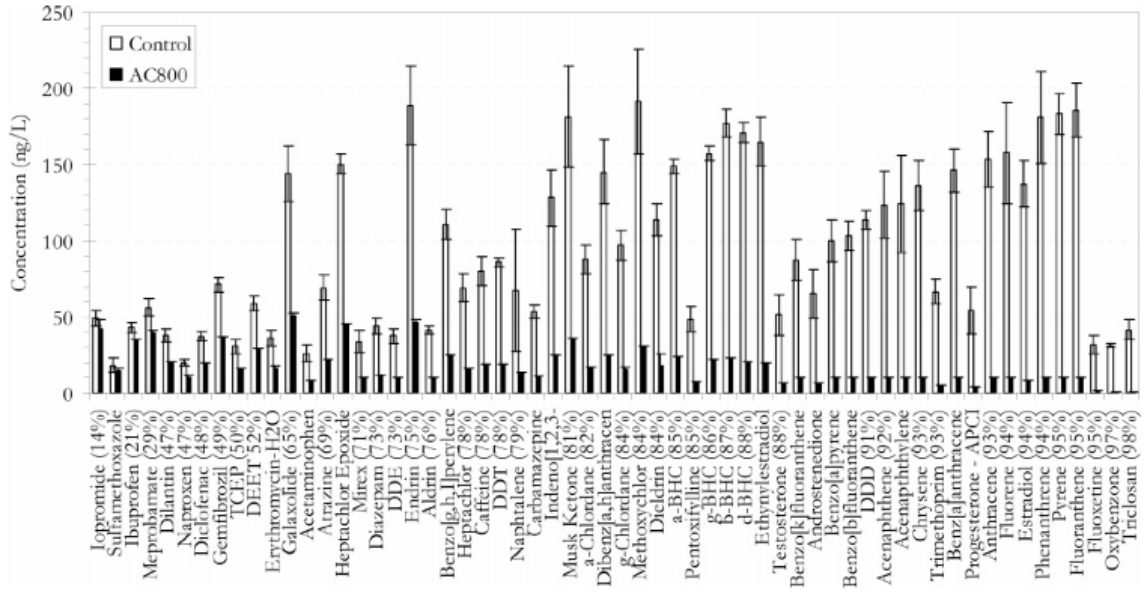


Figure 1-10: Reduction in Antibiotic Concentrations by Ozone (Adams et al. 2002)

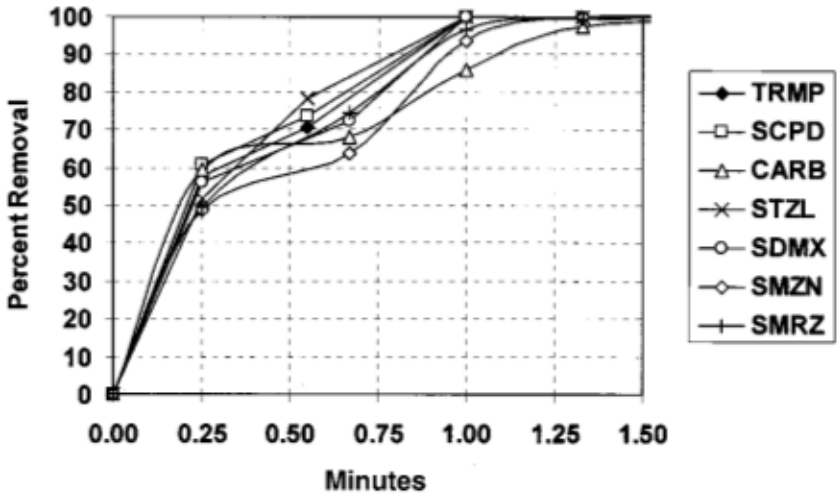
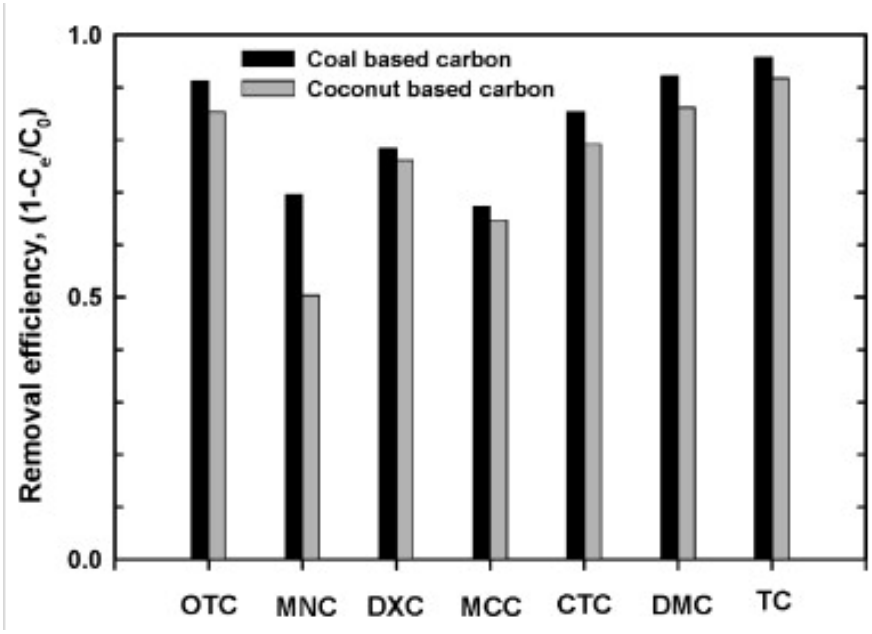



Figure 1-11: Removal of Antibiotics by Granular Activated Carbon (Choi, Kim, and Kim 2008)



Natural Organic Matter (NOM)

NOM, measured as total organic carbon in mgC/L, is naturally occurring decomposed plant and animal matter that is present at varying levels in all natural waters. NOM has not been shown to be an efficient NDMA precursor in the existing literature unless it is very nitrogen rich (Krasner et al. 2013), but it has been shown to slow the formation of NDMA from other precursors during chloramination (Shen and Andrews 2011). NOM has a complex chemical structure and it is not currently known what functional groups of NOM are reducing the rate of the formation of NDMA from precursor chemicals.

NOM may consist of high and low molecular weight components, as well as polar and non-polar and positively or negatively charged centers. NOM also consists of humic and fulvic acids which have slightly different chemical composition. Humic acids contain polar and non-polar components and are typically anionic and of low to moderate molecular weight (Hong and Elimelech 1997). Fulvic acids are the lowest molecular weight portion of humic substances. They may also be polar or non-polar, but tend to be more aliphatic and contain more negatively charged components than humic acids due to the larger amount of acidic groups present (Tombácz 1999).

Sorption of Antibiotics to NOM

Sorption of antibiotics by NOM can occur. Different physico-chemical properties of veterinary antibiotics impact their ability to sorb to soils or sediments and determine their mobility in soil

water systems. Tetracyclines were found by Li (2010) to strongly sorb to swine manure compost and soils where swine manure compost was present. In lab soil/compost column tests at 25°C, tetracyclines were shown to be 50% degraded between 20 and 41 days (Li et al. 2010). In another study, tetracyclines were shown to be 50% degraded at 37- 77 days, while clarithromycin was shown to have a much shorter time to degradation at 1.1-1.9 days (Chenxi, Spongberg, and Witter 2008). Sorption of antibiotics to clay sorbents can be pH dependent and may be reduced in the presence of dissolved organic matter, which may increase mobility (Kulshrestha, Giese, and Aga 2004; Aga, Goldfish, and Kulshrestha 2003). Work by Loke et al. 2002, suggests that $K_{ow}$ is not an adequate estimator of an antibiotic's sorption coefficient (Loke, Tjørnelund, and Halling-Sørensen 2002). This is because matrix differences and differences in pH greatly impact many antibiotics' sorption ability (Loke, Tjørnelund, and Halling-Sørensen 2002).

Tetracyclines and clarithromcyin have been shown to have high sorption coefficients to dissolved organic matter (Sithole and Guy 1987) (Sibley and Pedersen 2007). However, mobilization to greater depths in soil for tetracyclines is less likely. In a study by Gonsalves and Tucker, oxytetracycline residues were not found below 20 cm in a Florida sandy soil even after repeated applications of oxytetracycline where soil was drenched (Gonsalves and Tucker 1977). The sorption of these compounds to dissolved organic matter may both increase their mobility and decrease their ability to be biodegraded.

Table 1-4 shows that veterinary antibiotics have frequently been found in wastewater treatment plant effluent as well as drinking water treatment plant influent (Ternes 1998) (Golet et al. 2001; Alexy et al. 2006; Miao et al. 2004; McArdell et al. 2003) (Stackelberg et al. 2004) (Giger et al.

2003). Antibiotic removal during wastewater treatment is largely dependent on the ability of the individual antibiotic to be biodegraded and its sorption coefficient with respect to activated sludge. Table 1-5 shows tests using wastewater bacteria support the idea that many antibiotics are not likely biodegraded during secondary wastewater treatment (Al-Ahmad, Daschner, and Kümmerer 1999; Kümmerer, Al-Ahmad, and Mersch-Sundermann 2000; Alexy, Kümpel, and Kümmerer 2004). However, antibiotics with higher sorption coefficients, such as tetracyclines may be substantially removed during the activated sludge process (adsorption coefficient for activated sluge= 8400 +/- 500 mL/g) (Kim et al. 2005). Compounds such as clarithromycin, with lower sorption values for activated sludge (adsorption coefficient for activate sludge= 262 +/- 93), were not as easily removed (Göbel et al. 2007). In one wastewater treatment plant, certain antibiotics were not removed by microfiltration or reverse osmosis, including oleandomycin (Watkinson, Murby, and Costanzo 2007).

The organic matter in wastewater effluent could become a mode of transportation for sorbed antibiotics (Ternes 1998). In a study of antibiotics present downstream from a wastewater treatment plant, the concentration of antibiotics or degradation products remained relatively static up to 3 kilometers away from the plant. This indicates that the stream served as a transport mechanism and may be an inadequate method for removing compounds (Haggard and Bartsch 2009).

The sorption of pharmaceuticals by NOM is a mechanism that would lead to less formation when NOM is in the water. Certain pharmaceuticals, such as tetracycline, have strong sorption to NOM. Tetracycline sorption to humic acids may occur due to the hydrogen bonding of polar

amide and carbonyl functional groups on tetracycline to polar phenol groups in humic substances (Sithole and Guy 1987). Shen et al. 2011 suggest that the reduction in NDMA formation from precursors due to NOM occurs as matrix components inhibit precursors from reacting with chloramines (Shen and Andrews 2011). Therefore, tetracycline may be highly sorbed to the NOM, which decreases its availability to react with chloramines and form NDMA. NOM does not just have amide and carbonyl functional groups and so different parts of the NOM's complex chemical structure may be more or less effective at sorbing pharmacueticals. Additionally, different pharmaceuticals may sorb to NOM more or less effectively. Therefore different NOM components should be tested for their ability to slow NDMA formation from different precursors.

Removal of NDMA During Drinking Water Treatment

Once NDMA has been formed it is difficult and expensive to remove from drinking water. NDMA is photolyzed in the 175- 275 nm UV range (Sharpless and Linden 2003). UV treatment at high doses may remove NDMA to ng/L levels, however utilizing this high dose may be cost prohibitive for many treatment plants. Additionally, NDMA may be reformed in the distribution system if precursors are not removed as treatment plants typically provide a residual disinfectant (Plumlee et al. 2008). Removal of NDMA by granular activated carbon (GAC), has been shown to be relatively ineffective, as the GAC has little adsorptive capacity for NDMA (Fleming et al. 1996). NDMA is capable of being biodegraded, however attempts to isolate the responsible bacteria have failed (Tate and Alexander 1975) (Kaplan and Kaplan 1985) (Gunnison et al. 2000) (Sharp, Wood, and Alvarez-Cohen 2005).

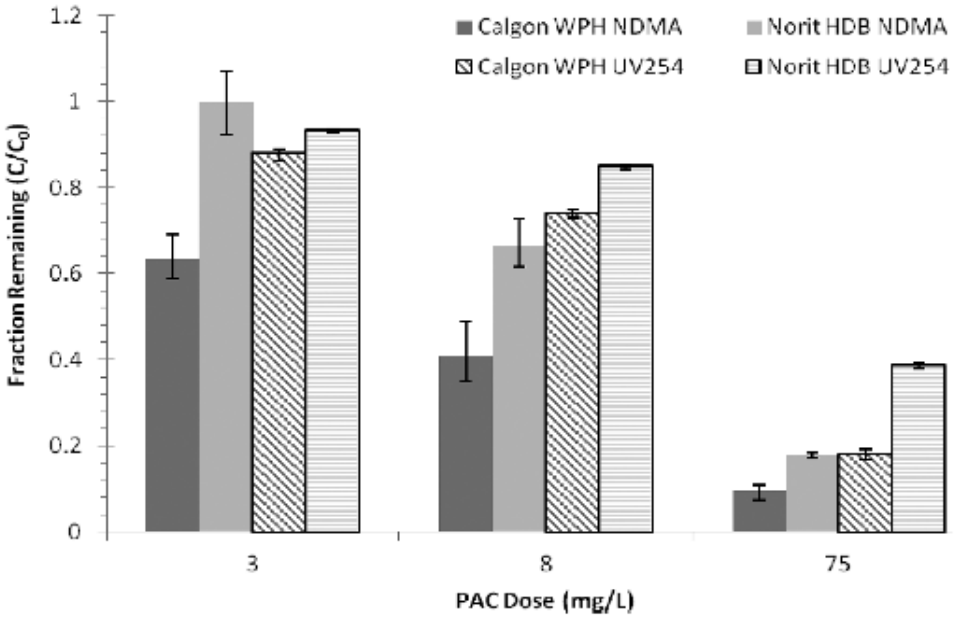
Destruction of Precursors

Therefore, the best way to reduce NDMA formation is to remove NDMA precursors before chloramination rather than attempting to remove the NDMA once it is formed. NDMA precursors are varied and diverse and may be amenable to different treatment techniques based on their chemical structure. In order to evaluate the effectiveness of treatment techniques, NDMA precursors can be measured using an NDMA formation potential (FP) test. NDMA precursor removal may be measured by the reduction in formation potential of NDMA before and after various treatment techniques.

While effective at removing bulk organic matter, both alum coagulation and soda lime softening have shown little to no removal of NDMA FP (Krasner 2008) (Mitch 2009). Alternatively, bench-scale studies have shown that the use of activated carbon, while not effective at removing NDMA, may be effective at removing NDMA precursors. Figure 1-12 shows that some types of powdered activated carbon (PAC) reduced NDMA FP by almost 40% at a dose of 3 mg/L, while higher doses resulted in reductions of almost 90% (Hanigan et al. 2012). Pilot-scale and full-scale treatment plant studies have also shown granular activated carbon (GAC) to be effective in reducing NDMA FP by 60-80% (Hanigan et al. 2012). While GAC may be especially effective at removing precursors in deionized water, it may become less effective when those precursors are in a surface water matrix due to sorption of precursors, such as antibiotics, on to NOM (Hanigan et al. 2012).

One of the most effective methods of NDMA precursor removal is oxidation. Chlorine and ozone in particular have been shown to be very effective at reducing NDMA FP (Wilczak et al. 2003) (Lee et al. 2007) (Chen and Valentine 2008) (Charrois and Hrudey 2007). However, similar to GAC, ozone has been shown to be less effective at removing precursors in surface water matrices and may also form NDMA from select precursors (Pisarenko et al. 2012) (Gunten et al. 2010) (Schmidt and Brauch 2008). Removal of precursors during chlorination has been shown to be highly impacted by pH and temperature (Lee and von Gunten 2010) (Krasner 2008). Precursors are destroyed most effectively by free chlorine between pH 8 and 9. Destruction of precursors is increased during free chlorination with increasing temperature (Krasner et al. 2013).

Figure 1-12: NDMA FP Removal by PAC (Hanigan et al. 2012)



Additionally, chlorine dioxide, permanganate, ferrate, hydrogen peroxide and UV have been shown to be capable of reducing precursors (Krasner et al. 2013). Removal of precursors by ozone has shown to be very effective with removal up to 50% in some cases where ozone is applied in doses used for disinfection (Shah et al. 2012). In the same study, at doses used for disinfection, chlorine had similar removal to ozone. Chlorine dioxide and UV were relatively ineffective. When the dose was increased, as it would be during advanced oxidation, UV removed precursors by close to 30% (Shah et al. 2012).

Additionally, NDMA formation may be affected by the manner in which chloramines are applied and certain water quality characteristics. The presence of bromide ion has been shown to increase NDMA formation (Chen, Yang, et al. 2010) (Luh and Mariñas 2012). Chlorine to ammonia nitrogen ratio has also been shown to influence the amount of NDMA formed (Schreiber and Mitch 2005).

Modeling Disinfection Byproduct Formation

Table 1-6 shows the models that have been completed for chlorine disinfection byproducts. Trihalomethanes (THMs) are regulated chlorine disinfection byproducts. Models for trihalomethanes range from models that vary known influential factors in formation to

Table 1-6: Chlorine Disinfection Byproduct Models

| Study | Outcome | Type |
|---|---|---|
| Kavanaugh et al. (Kavanaugh et al. 1980) | THM | Experimental |
| Morrow et al. (Morrow and Minear 1987) | THM | Observational |
| Reiches et al. (Reiches and Wilkins Iii 1983) | THM | Observational |
| Urano et al. (Urano, Wada, and Takemasa 1983) | THM | Experimental |
| Golfinopoulos et al. (Golfinopoulos and Arhonditsis 2002) | THM | Observational |
| Amy et al. (Amy, Minear, and Cooper 1987) | THM | Experimental |
| Moore et al. (Moore, Tuthill, and Polakoff 1979) | Chloroform | Observational |

see the resultant impact on THM concentrations (experimental models) (Kavanaugh et al. 1980) (Urano, Wada, and Takemasa 1983) to models that collect treatment plant data to determine which factors are most associated with increased THM concentrations (observational models) (Golfinopoulos and Arhonditsis 2002).

There has been one experimental study completed which models NDMA formation as a factor of monochloramine concentration at fixed dichloramine precursor concentrations (Kim and Clevenger 2007). However, there are currently no models for predicting NDMA concentration using other variables that have been shown to impact formation. Additionally, there are no models using real treatment plant data to determine which factors are primarily responsible for higher or lower yields of NDMA in situ.

In Summary

NDMA is a strong carcinogen that may be found in drinking water. It is produced when DMA-containing precursors are oxidized. This usually occurs due to chloramines or, in select cases, ozone. Precursors are varied and diverse and consist of many anthropogenic chemicals such as pharmaceuticals, personal care products, herbicides, pesticides and industrial chemicals. NDMA precursors are typically secondary or tertiary amines with a dimethylamine functional group. NDMA formation may be impacted by various water quality characteristics, such as pH, temperature and the presence of certain water contaminants. It can also be impacted by the nature of the precursor, such as the presence of EDGs or EWGs adjacent to the DMA functional group and the structure of the compound. Precursors may be destroyed via various pre-oxidation techniques, such as free chlorine contact time and oxidation with ozone. Veterinary antibiotics are prevalent in the environment and may be structurally capable of producing NDMA upon oxidation. These antibiotics have both EDG and EWG groups adjacent to the DMA group and this may impact their formation efficiency. Natural organic matter may slow NDMA formation, but it is unknown what constituents of the NOM are responsible for this effect. It is hypothesized that water matrix components may decrease the initial contact of precursors with chloramines. Some precursors have strong sorption to NOM and this may be the reason for decreased NDMA yields in the presence of NOM. Certain statistical models have been developed to estimate other disinfection byproduct yields, but none have been made to estimate NDMA yields at drinking water treatment plants. Therefore, bench-scale tests and some pilot plant testing have provided most of the information about the impact of water treatment plant

operations on NDMA formation. No models have been constructed using data from a large number of real treatment plants.

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# Chapter II: Veterinary Antibiotics Used in Animal Agriculture as a Source of NDMA Precursors

Abstract

The formation of carcinogenic N-nitrosodimethylamine (NDMA) during chloramination at drinking water treatment plants has raised concerns as more plants have switched from chlorine to chloramine disinfection. In this study, a new source of NDMA precursors has been elucidated. Veterinary antibiotics are used in large quantities at animal agricultural operations. They may contaminate drinking water sources and may not be removed during wastewater and drinking water treatment. Ten antibiotics used in animal agriculture were shown to produce NDMA or N-nitrosodiethylamine (NDEA) during chloramination. Molar conversions ranged from 0.04 to 4.9 percent, with antibiotics containing more than one dimethylamine (DMA) functional group forming significantly more NDMA. The highest formation for most of the compounds was seen near pH 8.4, in a range of pH 6 to 11 that was investigated. The antacid ranitidine, a known NDMA precursor, was included for comparison and the same effect of pH was seen. The effect of chlorine-to-ammonia ratio ($Cl_2/NH_3$), temperature, and hold time was somewhat varied for each chemical, suggesting that the effects of these parameters were compound-specific. These analyses suggest that veterinary antibiotics may form NDMA in finished drinking water.

## Introduction

N-Nitrosodimethylamine (NDMA) is a disinfection byproduct that can be formed during drinking water treatment. It is preferentially formed by chloramines (Schreiber and Mitch 2006). The use of chloramines during drinking water treatment has increased in recent years as regulation of chlorine disinfection byproducts has resulted in many treatment plants switching to

the use of alternative disinfectants (Seidel et al. 2005). Precursors of NDMA are varied and diverse; however, they are typically secondary, tertiary or quaternary amines (Selbes et al. 2013; Krasner et al. 2013). Known sources of precursors include certain human pharmaceuticals and personal care products (PPCPs), certain pesticides and herbicides, soluble microbial products, certain polymers used during water treatment, and wastewater treatment plant effluent (Krasner et al. 2013) (Shen and Andrews 2011).

The U.S. Environmental Protection Agency's (USEPA) Integrated Risk Information System (IRIS) database classifies NDMA and five other nitrosamines as carcinogenic with low ng/L levels being associated with a $10^{-6}$ lifetime cancer risk. NDMA and four other nitrosamines are on the USEPA's Contaminant Candidate List 3 and will be considered for regulation as part of USEPA's six year review of the Disinfection Byproduct Rule in 2015 (USEPA 2014) (USEPA 2009). California currently has a notification level for NDMA and two other nitrosamines at 10 ng/L each and a Public Health Goal at 3 ng/L (CDPH 2009; OEHHA 2006). Other nitrosamines can be formed during chloramination; however, NDMA was the most frequently detected nitrosamine in drinking water during the USEPA's Unregulated Contaminant Monitoring Rule 2 monitoring program (USEPA 2012).

In previous studies, NDMA precursors were found in wastewater-impacted drinking water supplies (Guo and Krasner 2009). Certain PPCPs in the wastewater discharges were believed to be an important source of the precursors (Shen and Andrews 2011). More recently, NDMA precursors were found to increase in concentration during runoff events in certain watersheds, where the wastewater impact was diluted out (Krasner 2015). This suggests that other sources of

NDMA precursors could be in these watersheds. One possible source could be veterinary antibiotics from animal agriculture operations.

Veterinary Antibiotics

The majority of all antibiotics distributed in the United States are used on animals farmed for human consumption. In 2011, the U.S. Food and Drug Administration reported that 29.9 million pounds were used on farmed animals or 80.5 percent of the total antibiotics consumed in the U.S. (FDA 2011) (Services 2012). Antibiotics are frequently used in the treatment of disease and as a component of animal feed to serve as growth promoters (Cohen 1998). The usage of antibiotics in animal feed increased by almost 8 percent from 2009 to 2011 (FDA 2009, 2011). During this time period, the amount of antibiotics sold for human use decreased by 1 percent (Services 2012; Department of Health and Human Services and Food and Drug Administration 2010).

Of the antibiotics applied in animal agriculture, 61 percent have been deemed as medically important for humans (FDA 2011). The majority of antibiotics applied in animal agriculture in the U.S. are tetracyclines, which accounted for 42 percent of the antibiotics used in total (FDA 2011). The next most common are ionophores (30 percent), penicillins (7 percent), and macrolides (3 percent) (FDA 2011).

Environmental Fate of Veterinary Antibiotics

Veterinary antibiotics used in large-scale farming operations can contaminate water sources through the disposal of unused or expired compounds, via overland flow run off, in unsaturated zone transport on fields in which agricultural waste has been applied, and via leaky waste-storage structures (Sarmah, Meyer, and Boxall 2006). Poor absorption in the guts of farm animals may result in up to 95 percent of a veterinary antibiotic being excreted as the parent compound (Elmund et al. 1971) (Magnussen et al. 1991) (Beconi-Barker et al. 1996). Additionally, metabolites of the antibiotic may be capable of being transformed back to the parent compound in the environment (Sarmah, Meyer, and Boxall 2006). As a result, the occurrence of veterinary antibiotics in the environment, especially near large-scale agricultural operations, is likely.

Antibiotics used in animal agriculture have been detected in surface water or wastewater treatment plant effluents and in one groundwater in North America, Europe, and Australia. The stability of tetracycline in animal slurry solutions, even during changes in temperature and aeration through repeated stirring, may result in a large amount of the antibiotic being transferred to the environment via manure application (Winckler and Grafe 2001). Different physico-chemical properties of veterinary antibiotics impact their ability to sorb to soils or sediments and determine their mobility in soil/water systems. Sorption of antibiotics to clay sorbents can be pH-dependent and may be reduced in the presence of dissolved organic matter, which may increase mobility (Kulshrestha, Giese, and Aga 2004; Aga, Goldfish, and Kulshrestha 2003). The

sorption of these compounds to dissolved organic matter may both increase their mobility and decrease their ability to be biodegraded.

Fate of Veterinary Antibiotics in Water Treatment Plants and the Environment

Veterinary antibiotics have frequently been found in wastewater treatment plant effluents, as well as drinking water treatment plant influents (Ternes 1998) (Golet et al. 2001; Alexy et al. 2006; Miao et al. 2004; McArdell et al. 2003) (Stackelberg et al. 2004) (Giger et al. 2003). Antibiotic removal during wastewater treatment is largely dependent on the ability of the individual antibiotic to be biodegraded and to be sorbed by activated sludge. Tests using wastewater bacteria support the idea that many antibiotics are not likely biodegraded during secondary wastewater treatment (Al-Ahmad, Daschner, and Kümmerer 1999; Kümmerer, Al-Ahmad, and Mersch-Sundermann 2000; Alexy, Kümpel, and Kümmerer 2004). However, antibiotics with higher sorption coefficients, such as tetracyclines, may be substantially removed during the activated sludge process (Kim et al. 2005). Additionally, organic matter in wastewater effluent may become a mode of transportation for sorbed antibiotics (Ternes 1998). In a study of antibiotics present downstream from a wastewater treatment plant, the concentration of antibiotics or degradation products remained relatively static up to 3 kilometers away from the plant, indicating that the stream served as a transport mechanism and would be an inadequate method for removing compounds (Haggard and Bartsch 2009).

In drinking water treatment plant studies, PPCPs, including some antibiotics, have been shown to be poorly removed during coagulation or during lime softening (Westerhoff et al. 2005) (Adams

et al. 2002). However, the use of powdered or granular activated carbon or oxidation processes, including the use of chlorine or ozone, may be capable of reducing antibiotic concentrations (Westerhoff et al. 2005; Adams et al. 2002).

The objective of this study was to evaluate the contribution of veterinary antibiotics to NDMA precursor loadings in watersheds. The reactivity of these antibiotics to form NDMA was assessed. Veterinary antibiotics were chosen for study because they were commonly used and/or had structural characteristics that would shed light on their reactivity. Although wastewater discharges in watersheds have been shown to be a source of NDMA precursors, to our knowledge, there have been no previous papers linking antibiotics used in large-scale agricultural operations or agricultural run-off to being a source of NDMA precursors in drinking water supplies. As such, we have investigated the conversion of veterinary antibiotics to NDMA. As some are also human antibiotics, some of these had been studied before (Shen and Andrews 2011) (Tian et al. 2014) (Bi et al. 2013). The antibiotics spiramycin, oleandomycin, chlortetracycline, meropenem, quinupristin and dalfopristin had not been tested for their ability to form NDMA. The antibiotics that had been studied previously (tetracycline, oxytetracycline, minocycline, clarithromycin) were included for comparison. In addition, a PPCP with high reactivity to form NDMA, the antacid ranitidine (Shen and Andrews 2011), was included in order to compare pH effects during NDMA formation to the antibiotics.

## Experimental

### Materials

The antibiotics: tetracycline, oxytetracycline, chlortetracycline, minocycline, spiramycin, clarithromycin, oleandomycin, meropenem, quinupristin, dalfopristin, and ranitidine were tested for their ability to form NDMA during chloramination. All compounds were chosen due to the fact that they had at least one dimethylamine or diethylamine functional group. All of the chemicals were analytical grade (>97% purity), except dalfopristin and quinupristin, which were 92.1 and 83.6 % pure, respectively. Tetracycline, oxytetracycline, chlortetracycline, spiramycin, clarithromycin, merenopenem, and ranitidine were purchased from Sigma Aldrich, CA. Quinupristin and dalfopristin were purchased from Molcan Corporation, Ontario, Canada, and oleandomycin was purchased from Santa Cruz Biotechnology, Inc., TX. NDMA analytical and internal standards were purchased from Sigma Aldrich, CA. Experiments were conducted using Milli-Q water produced from an Ultra Pure Water System (MilliPore Corp., U.S.A.).

### NDMA Formation Potential (FP) Tests

In order to determine the amount of NDMA that may be formed by the reaction of chloramines with each of the veterinary antibiotics, NDMA FP tests (Krasner et al. 2007) were conducted. Each of the antibiotics was diluted in Milli-Q water and then spiked with a mixture of chlorine and ammonia. Initial tests were conducted at pH 8.4, at 25ºC, with a 3:1 chlorine-to-ammonia-

nitrogen ($Cl_2$/N) weight ratio. At full-scale drinking water treatment plants, the $Cl_2$/N weight ratio is in the range of 3:1 to 5:1. A typical distribution system pH for U.S. drinking water plants is approximately 8. A summer time temperature, which should increase FP, was chosen. A chlorine dose of 8 mg/L as $Cl_2$ was used, where the ammonia was added first. This was to avoid any free chlorine contact time, as chlorine can destroy NDMA precursors (Shah et al. 2012). The sample was held for 3 days in a dark water bath. This represents a typical time in a distribution system. The test was conducted in the dark to avoid sunlight photolysis of the NDMA (Chen et al. 2010).

All of the antibiotics, except chlortetracycline, dalfopristin, and quinupristin, were tested in triplicate. Concentrations of antibiotics tested were chosen in order to yield NDMA values within the range of the analytical method (see Table 2-1). Additionally, $pK_a$ values of the antibiotics were used to choose pH values to study in FP testing for each antibiotic that maximized the amount of protonated or deprotonated species. The chosen pH range also represents values that are commonly seen during drinking water treatment. Approximately 0.5 mM of phosphate, borate, and carbonate buffer were used for pH 6 and 7, pH 8 and 9, and pH 10 and 11, respectively. Water temperature, hold time, and $Cl_2$/N ratio were also varied to discern the effect of the different test parameters on NDMA formation. In addition to 25ºC, water temperatures of 5ºC (winter time temperature) and 15ºC (intermediate value) were evaluated. In addition to 3 days, hold times of 1 and 7 days were evaluated, which represent the typical range of detention times in a distribution system. In addition to a $Cl_2$/N weight ratio of 3:1, a ratio of 5:1 and 6.3:1 were evaluated. The range of $Cl_2$/N weight ratios at full-scale plants is typically 3:1 to 5:1, where there is primarily only monochloramine at a 3:1 ratio and there is some

dichloramine at a 5:1 ratio (White 2005). At a $Cl_2$/N weight ratio of 6.3:1, which is past the maximum point on the breakpoint curve, there is substantially more dichloramine (White 2005).

Table 2-1: Concentrations of Antibiotics Tested

| Antibiotic | Concentration (nM) |
|---|---|
| Spiramycin | 12.5 |
| Oleandomycin | 300 |
| Clarithromycin | 300 |
| Minocycline | 10 |
| Tetracycline | 50 |
| Oxytetracycline | 50 |
| Chlortetracycline | 50 |
| Meropenem | 100 |
| Quinupristin | 150 |
| Dalfopristin | 150 |

NDMA Analysis

Samples were analyzed for NDMA following solid-phase extraction onto a bead resin (Ambersorb) using gas chromatography/tandem mass spectrometry (GC/MS/MS) with chemical ionization (Cheng et al. 2006). The method uses an NDMA-d6 internal standard that is added before the extraction step, and the minimum reporting level was 2 ng/L.

Ultraviolet Absorbance

Ultraviolet absorbance was measured for all of the antibiotics to determine the effect of time and pH on antibiotic degradation in Milli-Q water using a UV-1700 (Shimadzu, Japan).

Results

Nitrosamine formation was measured using the FP test for all 10 veterinary antibiotics. All of the antibiotics have a dimethylamine (DMA) functional group, except dalfopristin, which has a diethylamine (DEA) functional group. At pH 8.4, at 25ºC, and after 3 days, average molar conversions to NDMA for 9 antibiotics ranged from 0.04 to 4.9 percent (Table 2-2). One antibiotic, dalfopristin, was converted to N-nitrosodiethylamine (NDEA) with a 0.4 percent molar yield. Two of the macrolide antibiotics, clarithromycin and oleandomycin, had lower NDMA yields (0.04 percent) than the tetracyclines (0.9-1.7 percent), whereas spiramycin and minocycline were notable exceptions at 3.4 and 4.9 percent yields, respectively. Minocycline and spiramycin each have two DMA groups, which may be the reason for the higher yield of NDMA from these two antibiotics.

Table 2-2: Molar Conversion of Veterinary Antibiotics to NDMA*

| **Antibiotic** | **Molar Conversion (Percent)** |
|---|---|
| Minocycline | 4.9 ± 0.9 |
| Spiramycin | 3.4 ± 0.2 |
| Tetracycline | 1.7 ± 0.1 |
| Oxytetracycline | 1.4 ± 0.02 |
| Quinupristin | 0.13 |
| Meropenem | 0.11 ± 0.02 |
| Chlortetracycline | 0.9 |
| Clarithromycin | 0.04 ± 0.003 |
| Oleandomycin | 0.04 ± 0.01 |

*Antibiotics were chloraminated at pH 8.4 at 25ºC for 3 days with a 3:1 $Cl_2$/N weight ratio

One proposed mechanism for the formation of NDMA from tertiary amines involves the release of DMA from the tertiary amine by the electrophilic transfer of chlorine to the nitrogen in the DMA group, followed by the creation of a carbonyl via the removal of chlorine before the resulting release of the DMA group (Mitch and Schreiber 2008). However, the molar conversion rate to NDMA from DMA is low (<3%) (Choi and Valentine 2002). According to the first mechanism, the formation of NDMA from DMA-containing compounds may be impacted by the type of chloramine present, the nature of the adjoining functional groups, and the stability of the leaving group (Selbes et al. 2013). Compounds with electron withdrawing groups (EWGs) react preferentially with monochloramine and compounds with electron donating groups (EDGs) react preferentially with dichloramine (Selbes et al. 2013). At a pH value of 8.4 and with a $Cl_2$/N weight ratio of 3:1, monochloramine will be the primary chloramine formed (Chapin 1931; White 2005).

A second mechanism for the formation of NDMA from tertiary amines has also been proposed. DMA has a relatively low molar conversion to NDMA, therefore using mechanism one, it is hard to understand how certain precursors may have molar conversions of up to 90% (assuming this mechanism functions by release of DMA that is then converted to NDMA). Mechanism 2 is initiated by nucleophilic substitution by mono or dichloramine on the DMA moiety (Le Roux, Gallard, Croué, et al. 2012) (Liu et al. 2014). In the second step, an elimination reaction of hydrogen chloride forms an intermediate, which reacts with oxygen. After this, an N-O bond forms and the N-N bond cleaves, which produces a nitrosating agent. In the third step, a $NO^+$ cation is generated, which reacts with the amine and forms NDMA. The formation of a stable carbocation is an important aspect of this mechanism, which may not proceed as easily without

this step. Therefore, different chemical structures impacting the carbocation resonance are influential on the ability of the precursor to form NDMA. This mechanism would explain how higher yielding precursors form NDMA as it does not involve the release of DMA as a critical step.

Liu et al. (2014) provide computational information on activation free energies of various tertiary amine structures for the release of NDMA and formation of the carbocation (Liu et al. 2014). The wide range of activation free energies confirms that tertiary amines may have differing abilities to form NDMA, according to this mechanism, based on their structure.

In Selbes (2013), selected amines were tested for their ability to form NDMA during chloramination (Selbes et al. 2013). 2-Dimethyl-isopropylamine (DMiPA) had high molar conversion (83.9 percent) to NDMA, whereas dimethylaniline (DMAN) had low molar conversion (0.2 percent) (Selbes et al. 2013). According to the first mechanism, the two highest NDMA-forming veterinary antibiotics, minocycline and spiramycin, both have a structure similar to DMiPA adjoining the DMA group that allows for creation of a carbonyl precursor after the electrophilic transfer of the chlorine from monochloramine to the nitrogen in the DMA group. Spiramycin has two DMA groups that are adjoining a group similar to DMiPA and are thus capable of completing this reaction. The minocycline has one DMA group connected to a structure similar to DMiPA, whereas the second group is attached to a structure similar to DMAN, which has a relatively low NDMA molar yield. However, the high molar yield of minocycline suggests that this second DMA group was still fairly reactive. If we consider the second mechanism to explain why minocycline or spiramycin may form greater amounts of

NDMA, it is clear that one of the DMA groups on minocycline will form a somewhat stable carbocation, whereas the second one has an activation free energy according to Liu et al. of about 55, making it unlikely to react according to the second mechanism (Liu et al. 2014). Therefore, for minocycline, one DMA group may be forming NDMA according to the second mechanism and one may be forming according to the first. Spiramycin has two DMA groups that have a structure similar to the amine corresponding to an activation free energy of 24.9, according to Liu et al., which suggests that the nucleophilic mechanism with a comparable substrate to spiramycin should occur (slowly) at room temperature. Therefore, the second mechanism may proceed for this compound; however, it is not so favored that the first mechanism could be ruled out.

Tetracycline and oxytetracycline have lower molar yields and one DMA group attached to a structure similar to DMiPA. The much lower yields of tetracycline and oxytetracycline underscore the importance of the reactivity of the second DMA group on minocycline. The stability of the leaving group may account for the difference in the molar conversions of tetracycline, oxytetracycline, and chlortetracycline. As the formation reaction proceeds, the leaving group of the tetracycline and oxytetracycline will become an unsaturated ketone, which is a fairly stable leaving group. Unsaturated ketones contain a carbon-carbon double or triple bond (Woodward 1941). However, chlortetracycline will have a ketone leaving group that is less stable. The stability of the leaving group is associated with higher molar conversion to NDMA and this may account for the lower conversion of chlortetracycline (0.9 percent) to NDMA than either tetracyline or oxytetracycline (1.4-1.7 percent). If we consider the tetracycline compounds as proceeding according to the second mechanism, the DMA group on the tetracycline and

oxytetracycline is attached to a structure that will form a somewhat stable carbocation (the same structure as is on the first DMA group on minocycline). However, chlortetracycline will form a secondary carbocation during this reaction, which is less stable. If the transformation of chlortetracycline can be attributed to mechanism two, this is likely the reason for the smaller molar yield compared to the other tetracycline compounds.

Quinupristin has one DMA group attached to a structure similar to DMAN, which may account for its low molar yield (0.13 percent). It also does not form a very stable carbocation via mechanism two, which makes the formation of NDMA less favorable according to either mechanism and this is reflected in its low molar yield. Meropenem will not be capable of producing a carbonyl after the release of chlorine from the imine, which is formed via the electrophilic transfer of chlorine to the nitrogen in the DMA group, resulting in a lower yield (0.11 percent). Meropenem will also form a carbocation on a carbonyl carbon according to the second mechanism, which is not very stable. Meropenem, therefore, according to either mechanism is unlikely to form very much NDMA and this is reflected in its molar yield. Lastly, clarithromycin and oleandomycin may have lower yields (0.04 percent) due to the fact that they are less soluble than the other antibiotics tested or due to the fact that the DMA group is attached to a structure that does not react as easily as the structures found in the other veterinary antibiotics. According to the second mechanism, the DMA groups on clarithromycin and oleandomycin should react similarly to the DMA groups on spiramycin. Therefore, the mechanism could proceed, albeit slowly, at room temperature. However, these compounds only have one DMA group, as opposed to spiramycin, which has two.

In Shen and Andrews (2011), tetracycline and clarithromycin were tested for their ability to form NDMA. The molar conversions were comparable to those determined in this study, 1.2 percent for tetracycline and < 1 percent for clarithromycin (Shen and Andrews 2011). These yields were derived using a $Cl_2$/N mass ratio of 4.2:1, a pH of 7, and a temperature of 21°C. (Shen and Andrews 2011). Minocycline was found to be an NDMA precursor in Le Roux (2011) with a molar conversion percent of 8.4 (Le Roux, Gallard, and Croué 2011). This yield was produced at a pH of 8.5 with a $Cl_2$/N molar ratio of at least 1:1.2 at 20°C, and the sample was held for 5 days (Le Roux, Gallard, and Croué 2011).

pH Tests

The $pK_a$ of each of the antibiotics was used to determine chemical speciation. Spiramycin, oleandomycin, and clarithromycin had similar $pK_a$s and yielded 2 chemical species. Tetracycline and oxytetracycline yield 4 chemical species and minocycline yielded 5. Tests were conducted to determine if the speciation of the antibiotic affected its ability to form NDMA. FP tests were conducted using a 3:1 $Cl_2$/N weight ratio at 25°C and were held for 3 days. Results are shown in Figure 2-1. The most notable trend was that all of the compounds, except oleandomycin, had the highest formation at pH 8.4, regardless of speciation. However, compound stability at different pH levels must be considered. Thus, UV absorbance was measured for each of the UV-absorbing antibiotics over a series of days at different pH levels (data for day 3 shown in Table 2-3 for two of the UV-absorbing antibiotics; data for other days and for the other UV-adsorbing antibiotics not shown). Antibiotics varied in their degradation rates. Tetracycline compounds had rapid pH-dependent hydrolysis reactions that yield

transformation products (Loftin et al. 2008). The transformation products of these compounds also contain DMA functional groups. Therefore, these compounds may form NDMA despite having different UV absorbance from the parent compound. The stability of some NDMA precursors, such as ranitidine, has been shown to be unimportant in the transformation to NDMA (Le Roux, Gallard, Croué, et al. 2012). However, in this study, the NDMA results correspond well with degradation of the parent compounds seen in UV tests. Although the kinetics of NDMA formation are not necessarily linked to the reactivity or stability of the parent compound (Le Roux, Gallard, Croué, et al. 2012), at least in the case of some precursors, the UV tests in this study suggest there may be an effect.

Chlortetracycline had a more rapid degradation and it was shown to form the least amount of NDMA in the tetracycline group (Loftin et al. 2008). Spiramycin had very slow degradation due to hydrolysis (Calza et al. 2010) and the spiramycin UV results reflected this. The UV results for the tetracycline group correspond to the likely transformation of chlortetraycline, tetracycline, and oxytetracycline, with degradation of the UV absorbance for chlortetracycline exceeding the other two. Meropenem degraded over 3 days at high pH (pH = 10) whereas spiramycin stability was not affected by pH. Therefore, the low formation of NDMA from spiramycin at pH levels other than 8.4 could not be attributed to degradation of the compound at high or low pH. Meropenem had only 35 percent of the compound present at high pH, but the molar conversion at high pH was only 10 percent of that at pH 8.4. So stability alone did not fully account for the lower conversion at high pH. Although deprotonated amines are expected to form NDMA more readily than protonated amines, this hypothesis was not supported by our experiments or in other studies of NDMA formation (Selbes et al. 2013).

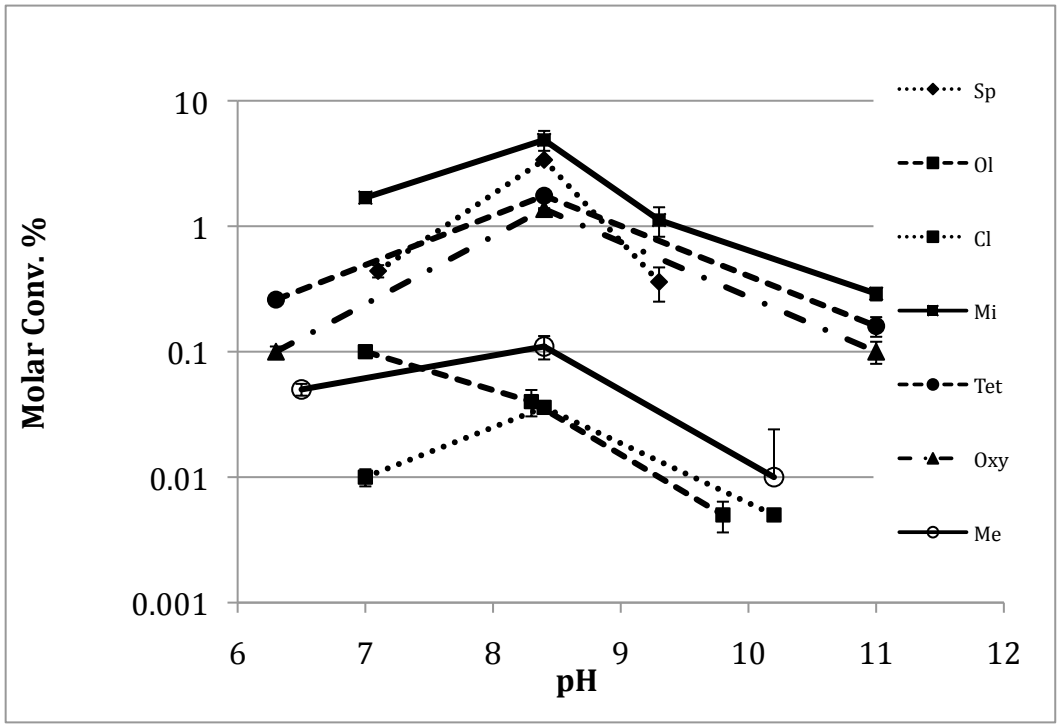
Another factor to consider is that the speciation of chloramines is pH-dependent (more monochloramine at high pH, more dichloramine at low pH). Dichloramine concentration peaks near pH 4 and decreases after that, whereas monochloramine concentration peaks near pH 8. Dichloramine is not present at appreciable amounts at or above pH 8. Because dichloramine has been determined to be the chloramine species responsible for the majority of NDMA formation from organic amines (Schreiber and Mitch 2006), this suggests that differences in the formation of NDMA from most of the antibiotics at different pH levels may be due to something other than chloramine speciation.

$Cl_2$/N Ratio Tests

$Cl_2$/N ratio has been shown to impact the amount of NDMA that may be formed from precursors (Schreiber and Mitch 2005, 2007; Krasner 2012). This may be due to the fact that varying amounts of monochloramine and dichloramine are formed at each $Cl_2$/N ratio, assuming pH is held constant. Dichloramine has been shown to be capable of producing more NDMA than monochloramine (Shah et al. 2012; Schreiber and Mitch 2006). Three $Cl_2$/N weight ratios (3:1, 5:1, and 6.3:1) were evaluated. The tests were conducted at pH 8.4 at 25°C and were held for 3 days. The four antibiotics with the highest formation were used in these tests. Three of the four antibiotics had the highest formation at a $Cl_2$/N weight ratio of 3:1, with only spiramycin having a higher formation at a weight ratio of 5:1. None of the antibiotics had high formation at a ratio of 6.3:1. Although this ratio was chosen to maximize dichloramine concentration, the high pH of the test may have resulted in dichloramine quickly dissipating. Dichloramine is formed much

more favorably near pH 4 and drops significantly at or above pH 8 (Palin 1949). Therefore, the impact of dichloramine in this test may not be evident.

Figure 2-1: Impact of pH on Molar Conversion of Veterinary Antibiotics to NDMA*



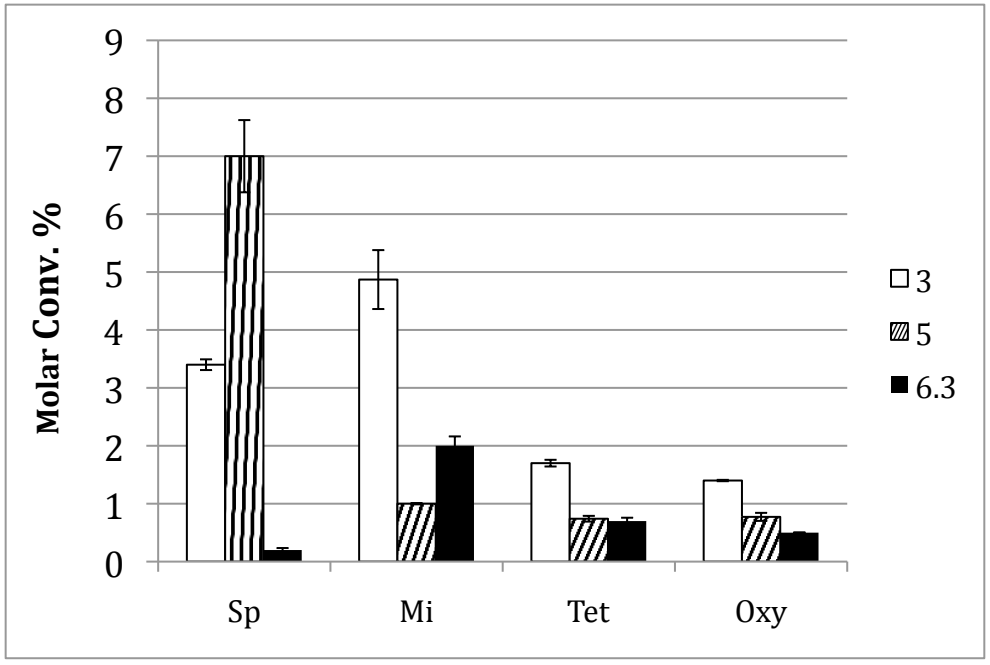

*Spiramycin (Sp), Oleandomycin (Ol), Clarithromycin (Cl), Minocycine (Mi), Tetracycline (Tet), Oxytetracycline (Oxy), Meropenem (Me). Tests were conducted at 25°C with a 3:1 $Cl_2$/N ratio and held for 3 days.

Table 2-3: Stability of Meropenem and Spiramycin at Different pH Levels*

| Antibiotic | pH | Molar Conversion Percent | Percent left at day 3 |
|---|---|---|---|
| Spiramycin | 7.1 | 0.4± 0 | 99% |
| | 8.4 | 3.4± 0.2 | 100% |
| | 9.3 | 0.4± 0.1 | 100% |
| Meropenem | 6.5 | 0.05± 0 | 66% |
| | 8.4 | 0.11± 0 | 91% |
| | 10.2 | 0.01± 0 | 35% |

*Antibiotics were chloraminated at 25°C with a 3:1 $Cl_2$/N ratio and held for 3 days.

Figure 2-2: Impact of $Cl_2$/N on Molar Conversion of Selected Veterinary Antibiotics to NDMA*




*Spiramycin (Sp), Minocycline (Mi), Tetracycline (Tet), Oxytetracycline (Oxy). Antibiotics were chloraminated at 25ºC for 3 days.

Temperature Tests

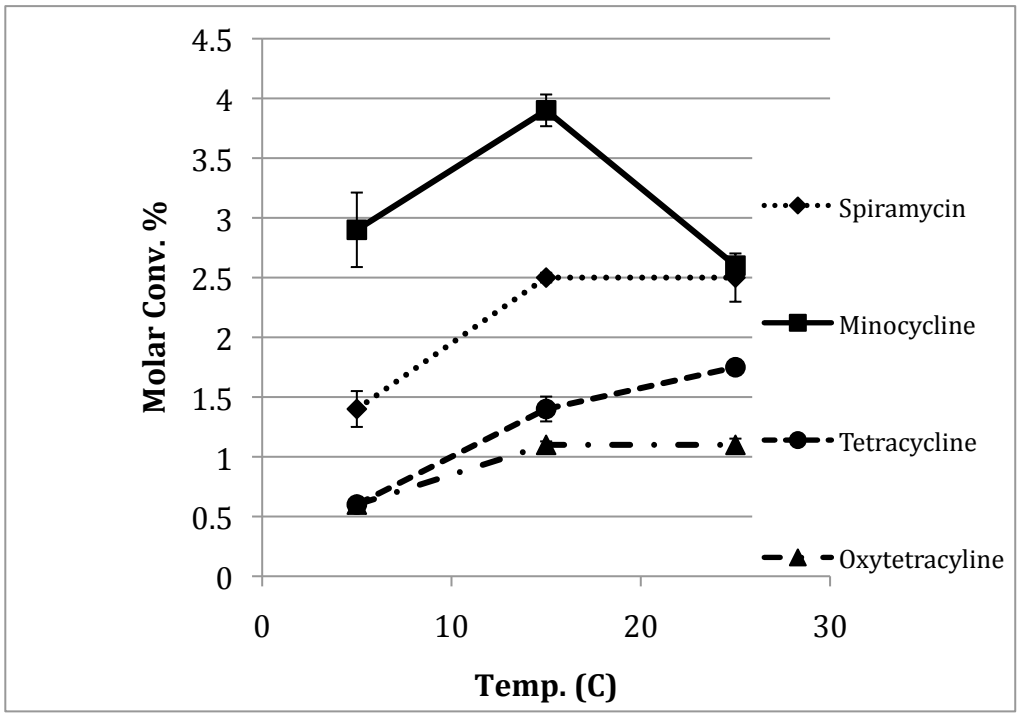
Previous studies have shown that NDMA formation increases with temperature (Krasner 2012). In order to determine the effect of temperature on the molar conversion of selected veterinary antibiotics to NDMA, FP tests were conducted at 5, 15, and 25°C. The tests were conducted at pH 8.4, with a $Cl_2$/N weight ratio of 3:1, and were held for 3 days. The molar conversion rate increased in going from 5°C to 15°C, and typically plateaued or continued to increase at 25°C for the four antibiotics tested (minocycline, spiramycin, tetracycline, and oxytetracycline). Minocycline was the only antibiotic with the highest formation at 15°C and lower formation at 25°C, which may indicate that minocycline was unstable at higher temperatures. Future tests should be conducted to confirm this hypothesis. This suggests that temperature effects are compound specific, although it is likely that lower temperatures slow the formation of NDMA from any antibiotic. Dichloramine may be more persistent as the temperature decreases (Wei and Morris 1974). However, this did not seem to increase the formation of NDMA from the antibiotics at 5°C.

Hold Time Tests

The conversion of precursor chemicals to NDMA occurs slowly over a matter of days (Mitch et al. 2003). Shen and Andrews found that the conversion to NDMA from three pharmaceuticals began to plateau between 10 and 45 hr (Shen and Andrews 2011). Three hold times were chosen for this study based on common drinking water distribution system detention times. The tests were conducted at pH 8.4, with a $Cl_2$/N weight ratio of 3:1 at 25°C. The formation of NDMA

began to plateau after day 3 or continued to increase somewhat. Spiramycin had the greatest increase from day 1 to day 3.

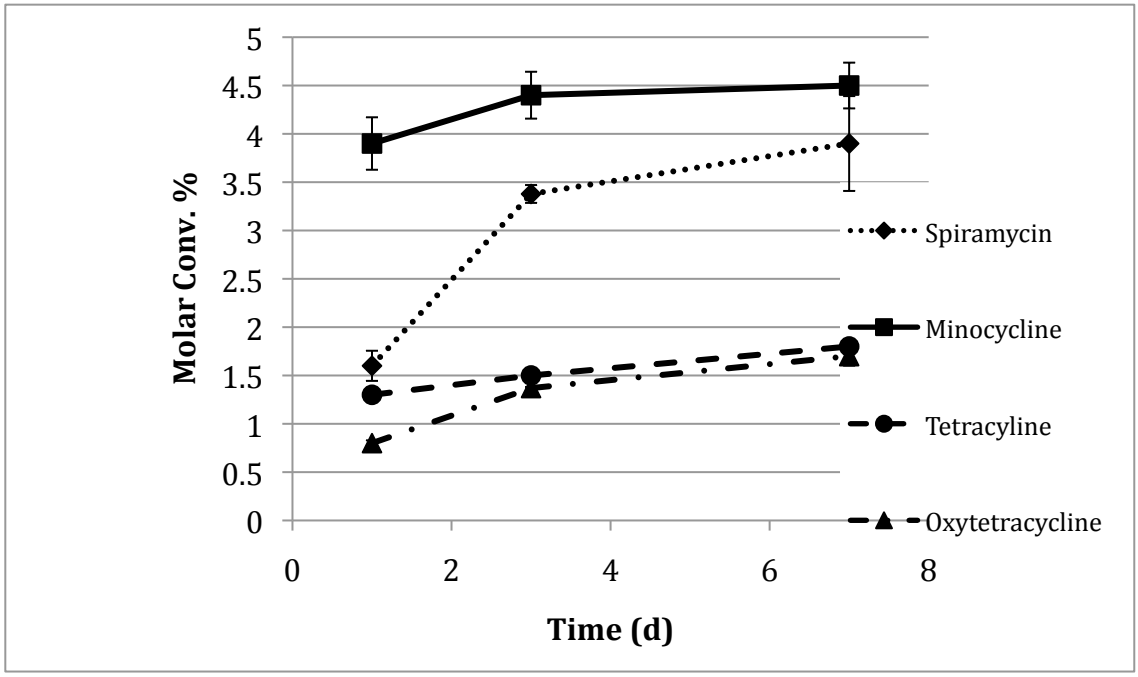
Figure 2-3: The Impact of Temperature on the Molar Conversion of Selected Veterinary Antibiotics to NDMA




*Antibiotics were chloraminated at pH 8.4 with a 3:1 $Cl_2$/N weight ratio and held for 3 days.

The UV absorbance for spiramycin remained at 100 percent through day 7 in Milli-Q water. Eighty-one percent of tetracycline was remaining at day 6. Minocycline and oxytetracycline had 87 and close to 90 percent remaining at day 3 and 74 and 59 percent remaining at days 6 and 7, respectively. For some antibiotics, the percent increase in molar conversion from day 3 to day 6 or 7 may have plateaued in part because the chemical was degrading over this time period.

Figure 2-4: The Impact of Hold Time on the Molar Conversion of Selected Antibiotics to NDMA*




*Antibiotics were chloraminated at pH 8.4 with a 3:1 $Cl_2$/N weight ratio at 25°C.

Compounds Containing DMA Moieties and pH

The higher amount of dichloramine present at lower pH levels and the stability of some of the antibiotics at lower pH suggest that the formation of NDMA from some of the compounds should be maximized in the lower pH range. However, for all but one of the veterinary antibiotics, the highest formation occurred at pH 8.4. To determine if other pharmaceuticals with a DMA moiety had the highest formation near pH 8.4, ranitidine was tested at pH 7, 8.4, and 9. The highest conversion to NDMA from ranitidine in these tests also occurred at pH 8.4.

However, whereas the impact of pH was highly significant for the veterinary antibiotics (Figure 2-1), the impact of pH for ranitidine was not as significant (molar conversion ~60 percent at pH 7 or 9, 80 percent at pH 8). Nonetheless, this suggests that for pharmaceuticals with DMA-containing groups, the highest formation may tend to occur near pH 8.4 (at least for tests conducted with a 3:1 $Cl_2$/N weight ratio at 25°C). This may be due to the original NDMA formation mechanism proposed by Mitch and colleagues (Mitch and Sedlak 2001). That work suggested that the conversion of DMA to NDMA occurred via a two-step pathway in which DMA was converted to an unsymmetrical dimethylhydrazine intermediate before conversion to NDMA. In the first step, the conversion is favorable at high pH near 11, and in the second step the conversion is favorable at low pH near 7. A conversion of DMA-containing chemicals to NDMA near pH 8.4 may not greatly inhibit either the first or second step and allow the reaction to more easily proceed. Indeed, the conversion of DMA to NDMA has been shown to have a higher yield between pH 8 and 9, including in research on a revised formation mechanism (Schreiber and Mitch 2006) (Le Roux, Gallard, and Croué 2011). This work also suggests that this trend may hold true not only for DMA, but also for compounds containing DMA moieties.

Formation of NDMA from Veterinary Antibiotics in Real World Scenarios

In general, molar conversions to NDMA from these veterinary antibiotics were low, but similar to other anthropogenic chemicals. Using the highest concentrations that heretofore have been measured in aquatic environments and assuming chloramination conditions given in the first round of testing, NDMA yields from these antibiotics could be assumed to range from 0 to 72 ng/L in finished water. Treatment plants may have the ability to reduce antibiotic

concentrations, so future work is needed to determine the impact of these veterinary antibiotics on NDMA formation at impacted drinking water treatment plants. Determination of the concentration of these veterinary antibiotics in impacted watersheds, along with the molar conversions determined in this research, will allow for this impact to be more fully understood.

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# Chapter III: Understanding the Mechanism by Which Natural Organic Matter Decreases the Rate of NDMA Formation in Drinking Water

Abstract

N-Nitrosodimethylamine (NDMA) has been shown to be a disinfection byproduct in chloraminated water. NDMA has been shown to be formed from certain chemicals containing dimethylamine (DMA) functional groups. NDMA formation from chemicals with DMA functional groups has been shown to be slowed by the presence of natural organic matter (NOM). In this study, NOM fractionated by size or polarity was evaluated to help define the mechanism of how NOM decreases NDMA formation. NOM was fractionated by size with ultrafiltration membranes or polarity with solid-phase extraction cartridges. The NOM fractions were tested for their ability to slow the formation of NDMA from two DMA-containing precursor chemicals, tetracycline and spiramycin.

The high molecular weight NOM fractions (> 10 kDa) were shown to be the most effective in reducing the amount of NDMA formed from the precursor chemicals. The 5-10 kDa fraction also reduced formation. The most likely mechanism is that higher molecular weight fractions of NOM may reduce the formation of NDMA by providing a larger structure to bind NDMA precursors, as well as prevent initial contact with chloramines. The filtrate of a C-18 non-polar cartridge was also effective at reducing NDMA formation from tetracycline. The non-polar cartridge will remove primarily non-polar NOM components, leaving more polar components. Therefore, it is likely that polar NOM components are responsible for the reduction in NDMA formation. A possible mechanism for the reduction of NDMA formation from tetracycline is sorption due to the hydrogen bonding of polar amide and carbonyl functional groups on

tetracycline to polar phenol functional groups in the humic acid in the more polar NOM effluent from the C-18 sorption column.

## Introduction

In order to comply with the U.S. Environmental Protection Agency's (USEPA's) Disinfection Byproduct Rule, many water treatment plants have switched from using chlorine to chloramines, as a secondary disinfectant (Seidel et al. 2005). Chlorine reacts with NOM present in the water to form disinfection byproducts such as trihalomethanes (THMs) and haloacetic acids (HAAs) (Rook 1974) (Stevens, Moore, and Miltner 1989), some of which are carcinogenic. However, as chloramines have gained popularity, drinking water treatment plants are faced with new disinfection byproduct issues caused by chloramination, such as the formation of N-nitrosodimethylamine (NDMA) (Krasner et al. 2013).

## NDMA

NDMA is preferentially formed by chloramines (Mitch, Gerecke, and Sedlak 2003) (Schreiber and Mitch 2006), but may also be formed by ozone in the presence of ozone-reactive precursors (Choi and Valentine 2002; Mitch and Sedlak 2001; Kosaka et al. 2009; Schmidt and Brauch 2008). Precursors of NDMA are secondary, tertiary or quaternary amines and include certain pharmaceuticals and personal care products, herbicides, polyDADMAC (polymer used during drinking water treatment), and wastewater treatment plant effluent (Shen and Andrews 2011) (Krasner et al. 2013).

NDMA is classified by the USEPA's Integrated Risk Information System (IRIS) as a possible human carcinogen with low ng/L levels being associated with an increased lifetime cancer risk (IRIS 1993). During the USEPA's Unregulated Contaminant Monitoring Rule 2 (UCMR 2), NDMA was detected in the effluent of 34% of the chloramine plants tested (Russell et al. 2012). Other nitrosamines may be formed as disinfection byproducts, but NDMA was the most frequently detected nitrosamine during UCMR2, accounting for 95% of the nitrosamine detections (USEPA 2012).

The USEPA currently does not regulate NDMA, however NDMA and 4 other nitrosamines are on the Contaminant Candidate 3 List (CCL3). These nitrosamines will be evaluated for regulation in 2015 as part of the USEPA's 6-year review of the Disinfection Byproduct Rule (USEPA 2014) (USEPA 2009). There is currently a notification level in California of 10 ng/L each for NDMA and 2 other nitrosamines and a Public Health Goal of 3 ng/L (CDPH 2009; OEHHA 2006).

Natural Organic Matter and NDMA Precursors

NOM naturally occurs from the decomposition of plant matter, which is present at varying levels in all natural waters (Thurman 2012). Some research has suggested that NDMA may be formed from the polar and basic fractions of NOM (Chen and Valentine 2007). However, in other research, hydrophobic acids were shown to have no reactivity to form NDMA (Dotson, Westerhoff, and Krasner 2009). NDMA formation from different molecular weight (MW)

fractions of NOM was attributed to sorbed trace organic NDMA precursor molecules (Krauss et al. 2010). Krauss et al. (2010) found that 50% of all NDMA precursors were associated with colloids or macromolecules in one wastewater influent (Krauss et al. 2010). Therefore, the reason for NOM appearing to be an NDMA precursor in some studies may be due to the fact that certain NOM matrices may be contaminated with NDMA precursors.

Shen and Andrews determined that the presence of NOM slowed the formation of NDMA from three dimethylamine (DMA)-containing NDMA precursors during chloramination (Shen and Andrews 2011). Water from one river and one lake was spiked with ranitidine, chlorpheniramine or doxylamine and chloraminated under standard conditions to determine NDMA formation potential (FP). Both natural waters slowed the formation of NDMA from these precursors. The TOC of the river water was 6.2 mg/L versus 2.3 mg/L in the lake water and the UV254 absorbance was 0.143 $cm^{-1}$ versus 0.024 $cm^{-1}$ for the river and lake water, respectively. This resulted in a SUVA of 2.32 Lm/mg for the river water and 1.08 Lm/mg for the lake water. The river water was shown to slow the formation of NDMA from the precursor chemicals more effectively. The authors hypothesize that the reduced reaction time was the result of water matrix components inhibiting initial contact of the precursors with chloramines (Shen and Andrews 2011).

NOM has a complex chemical structure and it is not currently known what polarity and size characteristics of the NOM were causing a reduction in the rate of the formation of NDMA from precursor chemicals. NOM consist of a heterogeneous mixture of high and low MW components, of polar or non-polar character, with positively or negatively charged parts. NOM

consists of humic and fulvic acids, which are of a slightly different chemical composition, and non-humic substances (Reckhow, Singer, and Malcolm 1990). Humic acids contain polar and non-polar components, are typically anionic and of high MW (Hong and Elimelech 1997). Fulvic acids are the lowest MW portion of humic substances. They may also be polar or non-polar, but tend to be more aliphatic and contain more negatively charged components than humic acids due to the larger amount of acidic groups present (Tombácz 1999). In a critical review of literature on the structure of NOM, Sutton and Sposito (2005) describe NOM as a structure containing diverse, relatively low molecular weight components held together by hydrophobic interactions and hydrogen bonds. Within this structure, molecules may be strongly bound to the NOM via hydrogen bonding.

Various methods have been used to fractionate NOM and examine its multiple components. One method of separating NOM is to use macroreticular resins during which pH is adjusted to <3 and then eluted through an XAD-8 resin. After being desorbed from the XAD-8 resin, a hydrophobic fraction is produced (Thurman and Malcolm 1981). Additionally, there is a Polarity Rapid Assessment Method (PRAM), which uses solid-phase extraction (SPE) cartridges to obtain filtrates containing a majority of specific NOM components (i.e., anionic, polar or non-polar constituents), which is then analyzed to determine polarity and is conducted at ambient pH (Rosario-Ortiz, Snyder, and Suffet 2007). The structure of NOM can be impacted by both the ionic strength and pH of the solution (Kunal and Schnitzer 1980). Therefore, the PRAM technique can be adjusted to evaluate environmental waters as they would interact in the environment. Additionally, ultrafilters of different size ranges can be used to separate MW size fractions of NOM (Revchuk and Suffet 2009).

Tetracycline and spiramycin are human and veterinary antibiotics that are used in large quantities in large-scale animal agriculture operations (FDA 2011). Both have been found in environmental waters and both have been shown to be precursors of NDMA (Leavey, Krasner, and Suffet 2014). They each contain a DMA functional group, which may be nitrosated to form NDMA during chloramination. Spiramycin contains two DMA groups. One or both of these antibiotics were tested for their ability to form NDMA in different NOM water fractions to discern the effect of the various NOM size and polarity fractions on NDMA formation rate. Additionally, NOM concentration was varied to determine the effect of the concentration of NOM paired with the MW of the NOM components.

## Experimental

### Materials

Experiments were conducted using Milli-Q water produced from an Ultra Pure Water System (MilliPore Corp., U.S.A.). NOM reverse osmosis (RO) isolate was purchased from the International Humic Substances Society (IHSS) (Denver, CO). The sample was collected from a drinking water reservoir in Vallsjøen, Skarnes, Norway. This is a pristine sample location and was chosen in order to reduce the risk of occurrence of any NDMA precursors isolated in the NOM sample. The IHSS RO isolate may contain a high amount of NaCl, so a cation exchange resin was used to desalt the sample. 5 meq of HCl was passed through a column with cation exchange resin to saturate it with $H^+$. The column was then rinsed until there was no $Cl^-$

residual, which was checked using $AgNO_3$. The NOM water solution at pH 8 was then passed through the column and the sample that eluted was used in these experiments. The ultrafiltration procedure of Revchuk and Suffet (Revchuk and Suffet 2009) was completed using Millipore Ultracell regenerated cellulose filters (Billerica, MA). The filters were soaked in Milli-Q water for 15 minutes, 3 times, and then stored overnight in 5% NaCl solution before use, in accordance with the manufacturer's instructions. Extract-Clean SPE cartridges used in the polarity fractionation procedure were purchased from Grace Alltech (Columbia, MD). Tetracycline, spiramycin, and NDMA analytical and internal standards were purchased from Sigma Aldrich (CA).

Methods

In the first set of experiments, the NOM was diluted to 10 mg/L, yielding a TOC concentration of 5.9 mg/L, an ultraviolet absorbance at 254 nm (UV254) of 0.270 abs/cm, and a specific UV absorbance (SUVA) of 4.6 L/mg-m. This high of a value of SUVA indicates that the NOM was very high in humic substances. The raw NOM water was then either filtered using an ultrafiltration procedure or run through an SPE cartridge using the PRAM procedure. In the second set, the NOM was diluted to a TOC concentration of 3.4 mg/L and then filtered using the ultrafiltration procedure only.

Ultrafiltration

Ultrafiltration was performed using a Millipore solvent-resistant stirred cell (XFUF 076 01). After membrane preparation and storage in 5% NaCl solution overnight, filters were flushed using 100 mL of Milli-Q water under 55 psi of $N_2$ to wash off any remaining glycerine, which is used as a membrane preservative (Revchuk and Suffet 2009). 200 mL of the raw NOM water was then filtered under 55 psi of $N_2$. The last 10% of the NOM water was not filtered and was discarded to reduce breakthrough of the material (Chen et al. 2014). 10 kDa, 5 kDa, and 1 kDa regenerated cellulose MW size exclusion filters were used to separate the NOM water into <10 kDa, <5 kDa, and <1 kDa fractions and to calculate the <1 kDa, 1-5 kDa , 5-10 kDa, and >10 kDa fractions.

Polarity Fractionation

PRAM used SPE cartridges to fractionate the NOM water mixture (Rosario-Ortiz et al. 2004). This study uses a method similar to the PRAM procedure to separate the NOM water into fractions, however it does not use analytical data to characterize polarity as the PRAM method does. A C-18 SPE cartridge was used to adsorb non-polar NOM constituents, yielding an NOM effluent fraction that contained predominantly polar and charged NOM constituents. SPE cartridges contained 100 mg of sorbent and had a total volume of 1.5 mL with an average pore size of 60 Å. C-18 cartridges were wet with 10 mL of methanol and then rinsed with 200 mL of Milli-Q water. All cartridge filtrates collected during the filter clean up were analyzed for TOC and UV254 to ensure that no cartridge materials were leached out during sample collection.

Cartridges were rinsed until TOC measurements were under 0.3 mg/L. NOM water was then pumped through the cartridges using a syringe pump (KD Scientific, Holliston, MA) at a flow of 1.2 mL/min and the filtrate was collected (Rosario-Ortiz et al. 2004).

NDMA FP Tests

Each NOM fraction was spiked with tetracycline or spiramycin to yield a 22.2 or 12.4 µg/L concentration, respectively. The sample was then spiked with 8 mg/L as $Cl_2$ of chlorine and 1.6 mg/L as N of ammonia corresponding to a 5:1 chlorine to ammonia weight ratio (the maximum on the breakpoint curve). Ammonia was spiked first in order to avoid destruction of precursors by free chlorine (Shah et al. 2012). The samples were held in a 25°C water bath for 24 hours. The sample was buffered at pH 8 using a borate buffer at 0.043 M in the sample. At the end of 24 hours, the samples were quenched with sodium sulfite to end any reactions with chloramines. The samples were then extracted onto a bead resin (Ambersorb) and analyzed for NDMA using gas chromatography/tandem mass spectrometry (GC/MS/MS) with chemical ionization (Cheng et al. 2006). This method uses an internal standard that was added before the extraction step and the minimum reporting level was 2 ng/L. Quality control (QC) samples included matrix spikes, matrix spike duplicates, laboratory fortified blanks, method blanks, external calibration curves, internal standards, and re-injections. The error in NDMA analysis using this analytical method is typically <15% (Leavey, Krasner, and Suffet 2014).

## Results and Discussion

### Initial Kinetic Curve

Figure 3-1 shows the kinetic curves created for tetracycline in both NOM-fortified and Milli-Q (DI) water with borate buffer. In our study, with a NOM concentration yielding a TOC value of 5.9 mg/L, the NOM fortified water not only slowed down the formation of NDMA, it reduced the overall formation within the window of time studied. At the longest hold time of 72 hours, NDMA formation in the NOM-spiked water only reached 17% of the NDMA concentration in the buffered Milli-Q water (Figure 3-1). Differences between this study and that of Shen and Andrews (2011) may reflect testing in different NOM matrices, where the one in this study was very high in humic substances.

### MW Fractions

Both of the low-MW fractions (<5 kDa and <1 kDa) yielded NDMA concentrations within the analytical error of the concentration of NDMA formed from tetracycline in Milli-Q water, suggesting that the lower MW fulvic acids and non-humic substances were not primarily responsible for the reduction in NDMA formation. The <10 kDa fraction did reduce the formation of NDMA from tetracyline, however not as much as the raw NOM water, where the <10 KDa fraction formed slightly more than double the amount of NDMA than the raw NOM water. This suggests that the high-MW components of NOM (>5 kDa), especially those above

10 kDa, were most responsible for the reduction in NDMA formation. The proportion of TOC in each fraction is shown in Figure 3-2. The NOM water in this study was high in humic substances (based on SUVA), as it had a large fraction of high-MW components. As the percentage of bulk TOC that was moderate or high-MW NOM came down, the formation of NDMA rose.

Figure 3-1: NDMA Formation from Tetracycline in the Presence of NOM at pH 8 with Ionic Strength of 0.04 M

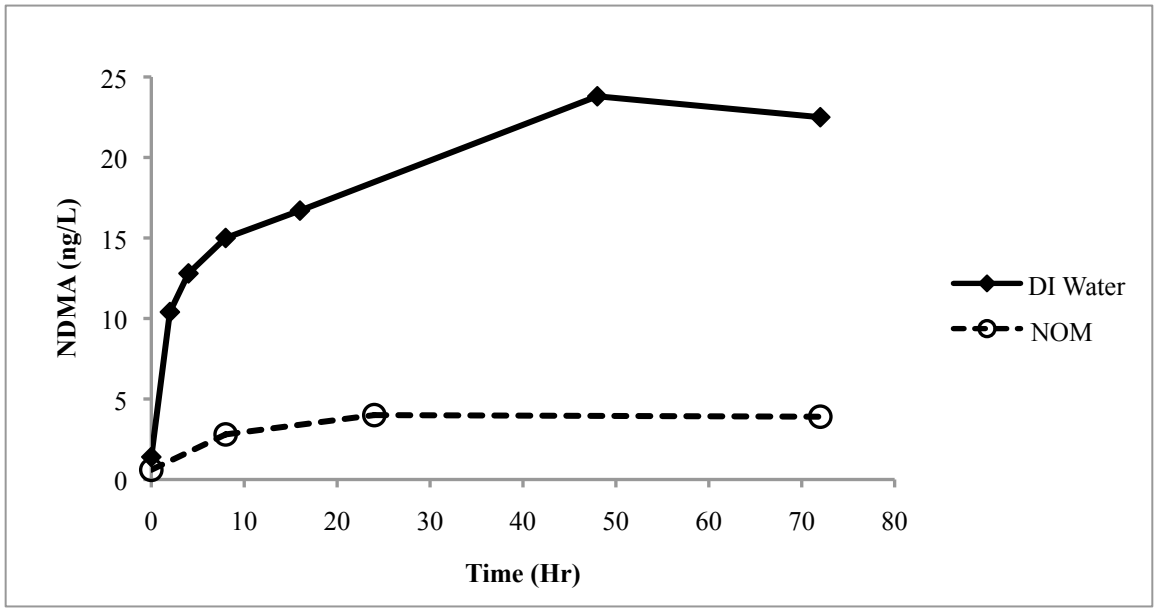
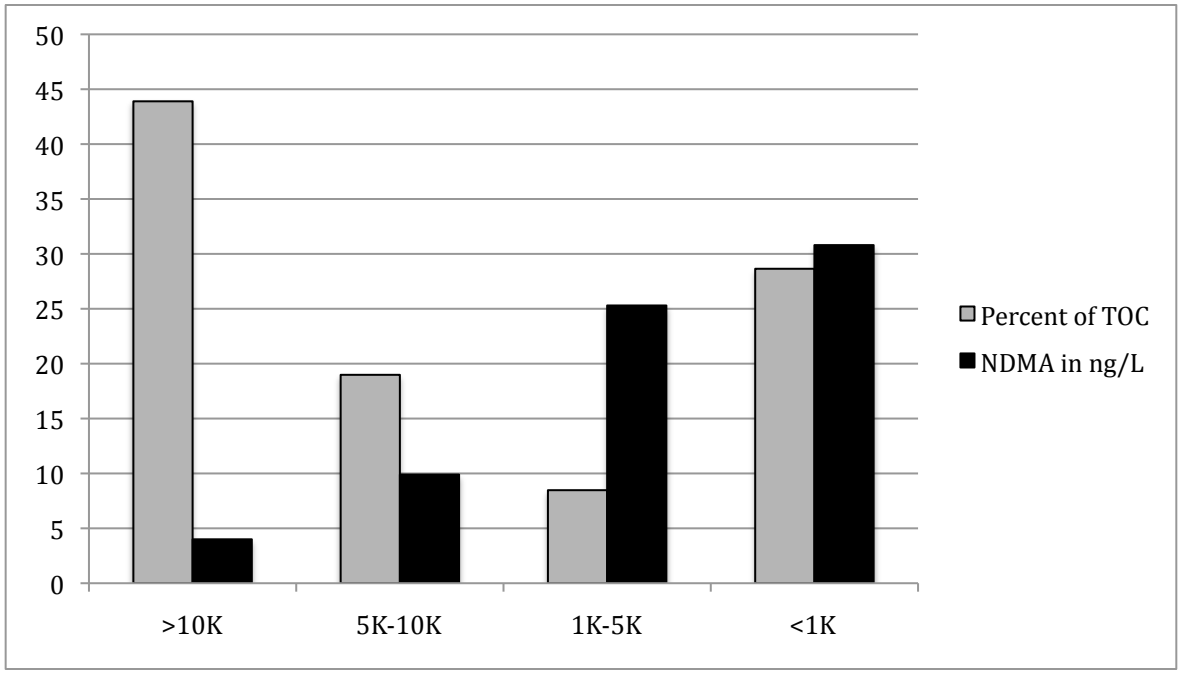


Figure 3-2: Percent of TOC in Each MW Size Range (Daltons) versus NDMA Formation from Tetracycline at 24 Hours




Round 2 Testing: MW Fractions

Additional tests were completed to confirm the effect of high-MW NOM on NDMA formation at a lower NOM concentration. Samples were spiked with either tetracycline or spiramycin. Results were comparable to the first round for tetracycline. When the NOM was diluted to a TOC concentration of 3.4 mg/L the observed effects of high-MW NOM were still evident. The <10 KDa fraction significantly reduced NDMA formation at 24 hours, whereas the <5 KDa fraction was similar to NDMA formation in Milli-Q water. Spiramycin followed the same trend as tetracycline. Formation of NDMA from spiramycin was reduced by 88% in the <10 KDa

fraction, whereas the < 5 KDa fraction had similar formation of NDMA from spiramycin as in Milli-Q water.

The reduction in NDMA formation rate shown in Shen and Andrews (2011) was much more evident in a river water matrix (TOC = 6.2 mg/L) than a lake water matrix (TOC = 2.3 mg/L). The moderately high TOC level in the bulk NOM sample in this study (TOC = 5.9 mg/L) and the low TOC level of the low-MW fractions (<5 KDa) of the NOM water (TOC = 2.2 mg/L) might suggest that TOC concentration may be a predictor of NOM's effect on NDMA formation. However, the NOM fractions above 5 KDa were most responsible for the reduction in NDMA formation, accounting for about 60% of the total TOC of the water. The smaller MW fractions, while still accounting for ~40% of the TOC, were essentially not effective at reducing NDMA formation. This suggests that TOC alone is not the best indicator of a NOM enriched water's ability to slow NDMA formation, but MW components above 5 KDa is a key factor. Note, many natural waters high in TOC often tend to be high in humic substances and high in MW (Volk et al. 2000).

One would expect the lower MW components characterized in part as fulvic acids to have more active free polar functional groups to interact with polar tetracycline. However, the data show that the most likely mechanism is that higher MW fractions of NOM may reduce formation of NDMA by providing a larger structure to bind NDMA precursors, as well as prevent initial contact with chloramines. The chloramine demand for all fractions was similar.

Polarity Fractions

Figure 3-3: Effect of NOM Polarity and Charge on NDMA Formation using NOM water at pH 8 with ionic strength of 0.04 M

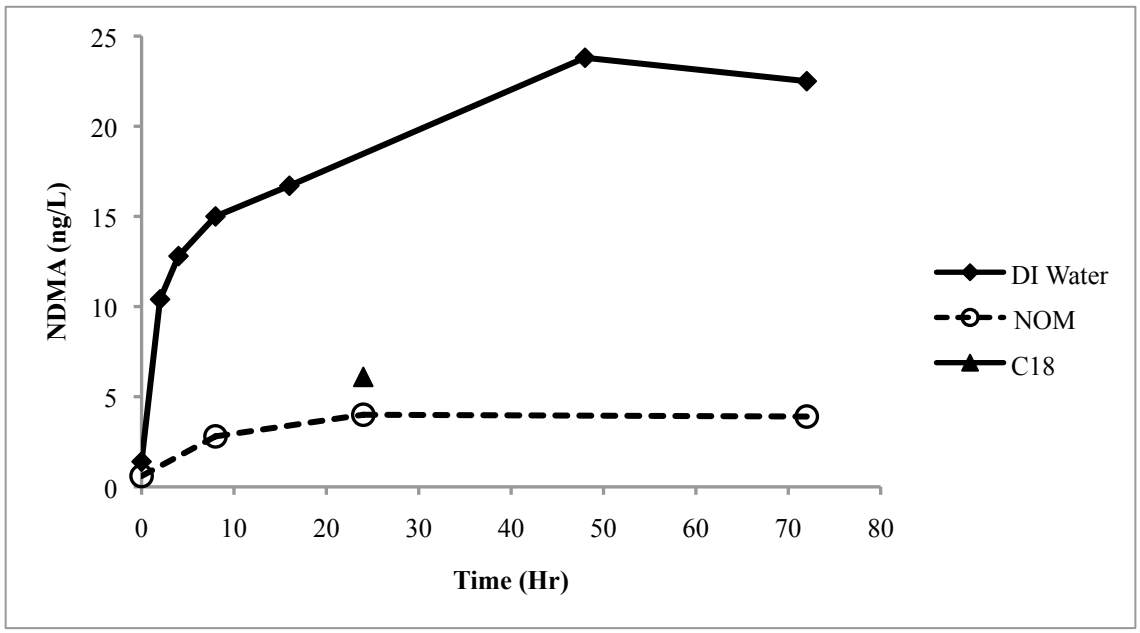
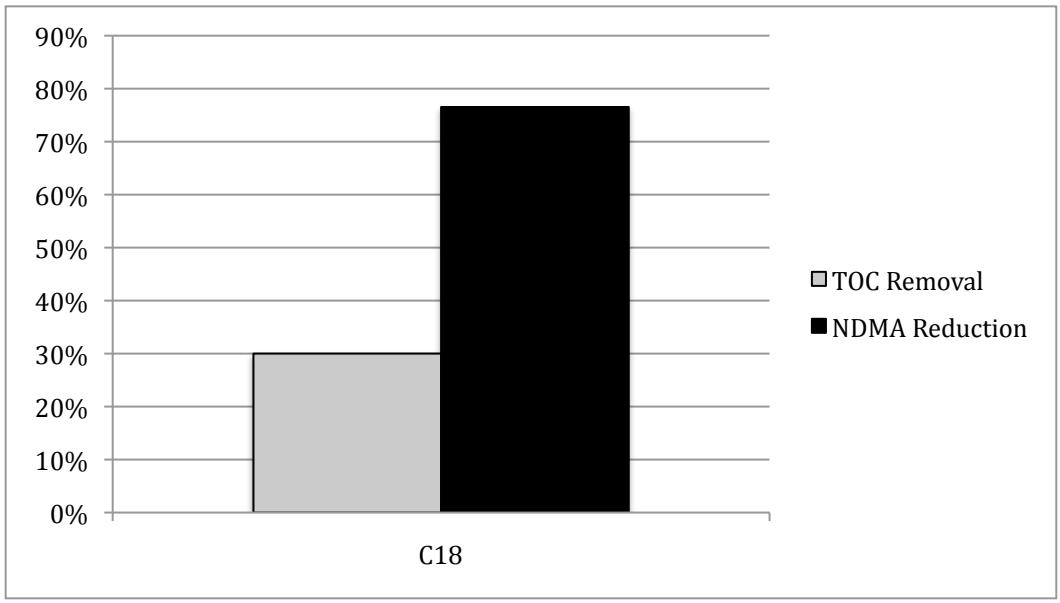



Figure 3-3 shows that the C-18 filtrate sufficiently reduced NDMA formation at 24 hours from tetracycline, the only antibiotic tested with this fraction. The removal was within the experimental error of the removal in raw NOM, suggesting that this was as effective as the raw NOM. The C-18 cartridge primarily removes non-polar components, leaving polar constituents and charged components of all sizes of NOM. Figure 3-4 shows that about 30% of the TOC was removed by the C-18 cartridge. Tetracycline may have high sorption to polar and charged NOM which may be occurring due to the hydrogen bonding of polar amide and carbonyl functional

groups on tetracycline to polar phenol groups in NOM (Sithole and Guy 1987). Indeed it is, in part, hydrogen bonding which is responsible for the association of various different components of NOM. Hydrogen bonding is also responsible for the large molecular size of NOM (Piccolo 2001). Miano et al. (1992) also showed that the pesticide glyphosate could bind to NOM via hydrogen bonding (Miano et al. 1992). Shen and Andrews (2011) suggested that the reduction in NDMA formation from precursors due to the presence of NOM occurs as matrix components inhibited precursors from reacting with chloramines. Therefore, the mechanism appears to be that the tetracycline in the somewhat more polar fraction of NOM may be sorbed to the NOM, which decreases its availability to react with chloramines and form NDMA.

Figure 3-4: TOC Removal and NDMA FP Reduction at 24 Hours by the C-18 SPE Cartridge



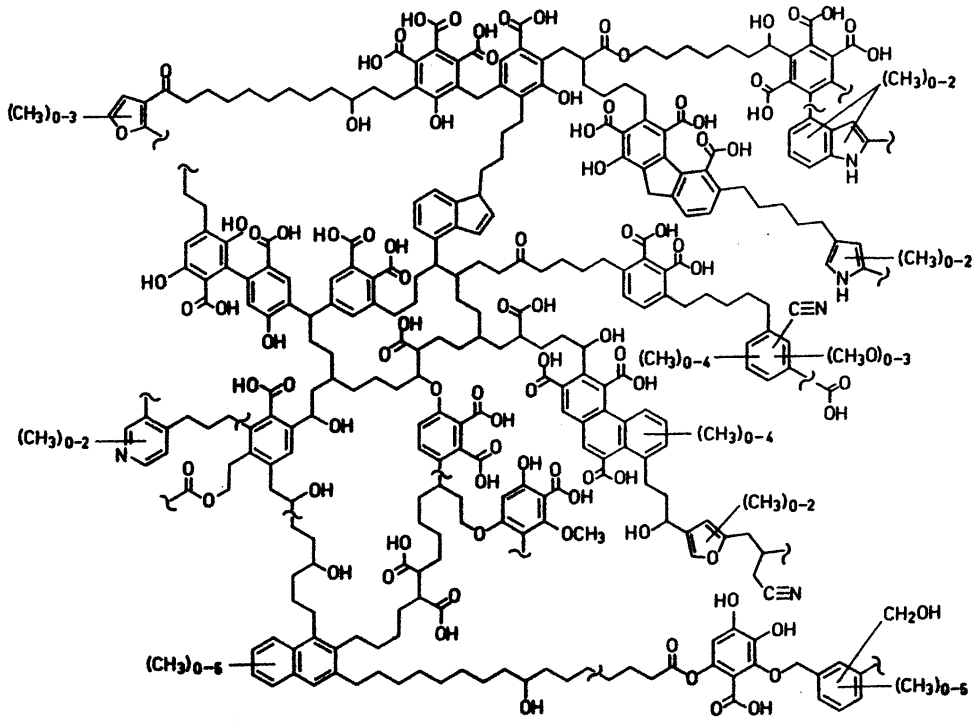

Chloramine demand may be increased in waters high in organic matter, however the total chlorine residuals present after the NDMA FP tests were complete were still relatively high (> 6

mg/L as $Cl_2$). This suggests that there was an adequate amount of chloramines present to complete the reaction and, therefore, the reason for the reduction of NDMA may be the unavailability of sorbed tetracycline. A ratio of average chloramine exposure for each sample to TOC value of each sample suggests that there is more chloramine available in the low TOC samples. However, the rate of NDMA formation for each sample did not correspond directly to low chloramine demand. Thus, Shen and Andrews (2011) suggestion that the reduction in NDMA formation from precursors due to NOM occurs as matrix components inhibit precursors from reacting with chloramines does appear to concur.

In the NOM fraction, a neutral phenol at pH 8 will readily form hydrogen bonds with tetracycline and it will be harder for the sorbed tetracycline to react with chloramines to form NDMA. The $pK_a$ of phenol is 10 and at pH 8 would still be in the PhOH form, which will make it capable of hydrogen bonding. NOM has a high proportion of phenolic groups (Schnitzer 1976), which makes hydrogen bonding likely at this pH level. Figure 3-5 represents one of the many proposed general structures of NOM molecules. Phenolic OH and alcoholic OH make up the largest portion of functional groups in NOM (Schnitzer 1976) (Chen et al. 2002).

Previous literature has shown that NDMA precursors tend to be polar (Dotson, Westerhoff, and Krasner 2009) and may contain a positive charge (Chen et al. 2014). This suggests that the mechanism for sorption proposed above may be relevant to other NDMA precursors.

Figure 3-5: Proposed Structure of Humic Acid (Schulten and Schnitzer 1993)



Conclusions and Recommendations

NOM is a complex mixture of compounds containing polar, non-polar, low cationic content and high anionic content, and large and small MW components.

- In this study, different NOM components were shown to exert different effects on the formation of NDMA from precursor chemicals. This was seen for two antibiotics that were previously shown to be NDMA precursors.
- For both precursors, high-MW NOM (>10 kDa) was shown to significantly reduce NDMA formation. NOM from 5 kDa to 10 kDa also reduced formation, although not as much as the >10 kDA fraction. The increased sorption abilities of high-MW NOM is the

likely reason for this reduction, as antibiotic sorption results in less antibiotic available to react with chloramines to form NDMA. The most likely mechanism is that higher MW fractions of NOM may reduce the formation of NDMA by providing a larger structure to bind NDMA precursors, as well as prevent initial contact with chloramines.

- The polar components were also shown to significantly reduce the formation of NDMA from tetracycline (spiramycin was not tested). This may be due to the fact that the polar amide and carbonyl functional groups on tetracycline sorb to polar phenol groups in the polar fraction of NOM.

Further research is needed to determine if the effects seen here hold true for other NDMA precursors. NDMA has a wide variety of precursors, including other pharmaceuticals, other anthropogenic chemicals, etc. Sorption of organic compounds to NOM in this study has been shown to be impacted by various properties of both the NDMA precursor compounds and the NOM. NDMA precursors of different chemical structure should be tested for their ability to form NDMA in the presence of total source water NOM and different NOM components.

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# Chapter IV: NDMA Formation in Water Treatment Plants: A Multivariate Analysis of Factors Influencing Formation

Abstract

The formation of the carcinogen N-Nitrosodimethylamine (NDMA) during drinking water treatment has raised concerns in the drinking water industry. Many bench-scale laboratory tests and pilot plant studies have been completed to try to determine which factors during water treatment increase or decrease the amount of NDMA formed in drinking water. This study uses data from over 20 drinking water treatment plants in the United States and Canada to determine which factors are most highly correlated with the NDMA concentration in delivered water using a mixed effects model with a random intercept. This type of model has not been used previously with trihalomethane (THM) models due to the fact that those studies did not sample such a large number and range of plants.

UV254 absorbance in the plant influent and pre-chlorination time used by a plant are highly correlated with NDMA concentration in finished water as well as the percentage change between NDMA formation in the plant influent and finished water. Other water quality parameters including sucralose concentration in the plant influent, polyDADMAC concentration added, aqueous pH, and chlorine to ammonia weight ratio used in the plant are also correlated with NDMA concentration in the distribution system. Lastly, NDMA precursor loading was correlated with the use of polyDADMAC (where precursors were added) and the use of ozone and GAC treatment (where precursors were removed.)

## Introduction

In 2006, the United States Environmental Protection Agency (USEPA) issued rules regarding toxic chemicals formed during disinfection of drinking water (EPA 2006). The agency regulated total THMs and haloacetic acids (HAAs), which are formed during the reaction of chlorine with natural organic matter. In order to comply with USEPA's new rules, many treatment plants switched to alternative disinfectants. The use of chloramine instead of chlorine significantly decreased the levels of THMs and HAAs in their water supply (Seidel et al. 2005). While using chloramines as a disinfectant is effective at reducing the formation of THMs and HAAs, others disinfection byproducts can be created.

Nitrosodimethylamine (NDMA) is a disinfection byproduct that is formed during drinking water treatment with chloramines. It is preferentially formed by the reaction of chloramine with secondary or tertiary amines (Schreiber and Mitch 2006). It may also be formed during ozonation reactions (Schmidt and Brauch 2008) (Kosaka et al. 2009). NDMA is one member of a group of N-nitrosamines that may be formed as disinfection byproducts (Choi and Valentine 2002; Mitch and Sedlak 2001; Kosaka et al. 2009; Schmidt and Brauch 2008) (Krasner et al. 2013). In the United States Environmental Protection Agency's (USEPA) Unregulated Contaminant Monitoring from 2008 to 2010, NDMA was the most commonly detected nitrosamine in drinking water treatment plant effluent, accounting for 95% of the nitrosamine detections (USEPA 2012). According to USEPA's Integrated Risk Information System (IRIS), NDMA is considered carcinogenic at low ng/L levels. California currently has a 3 ng/L Public Health Goal for NDMA and a 10 ng/L notification level (CDPH 2009; OEHHA 2006). NDMA

and four other nitrosamines are currently on USEPA's Contaminant Candidate List 3 and will be considered for regulation as part of USEPA's six year review in 2015 (USEPA 2014) (USEPA 2009).

Once NDMA has been formed it is difficult and expensive to remove from drinking water. NDMA is photolyzed in the 175 - 275 nm UV range (Sharpless and Linden 2003). UV treatment at high doses may remove NDMA to ng/L levels, however utilizing this high dose may be cost-prohibitive for many treatment plants (Plumlee et al. 2008). Removal of NDMA by granular activated carbon (GAC) has been shown to be relatively ineffective, as the GAC has little adsorptive capacity for NDMA (Fleming et al. 1996). NDMA is capable of being biodegraded; however attempts to isolate the responsible bacteria have failed (Tate and Alexander 1975) (Kaplan and Kaplan 1985) (Gunnison et al. 2000) (Sharp, Wood, and Alvarez-Cohen 2005).

Therefore, in order to reduce NDMA formation, treatment plants may be better served by focusing on the removal of NDMA precursors before chloramination instead of removing the NDMA once it is formed. NDMA precursors are varied and diverse and may be amenable to different treatment techniques based on their chemical structure. In order to evaluate the effectiveness of treatment techniques, NDMA precursors can be measured using an NDMA formation potential (FP) test. NDMA FP tests are completed by chloraminating water containing precursors and measuring the amount of NDMA formed over a certain period of time. NDMA precursor removal is then quantified as the reduction in formation potential of NDMA before and after various treatment techniques. This method is employed due to the uncertainty about the type of precursors present. NDMA precursors are varied and diverse (Shen and Andrews 2011).

Thus trying to measure the many unknown precursor present is less effective than measuring the amount of NDMA formed in a particular water.

While effective at removing bulk organic matter, both alum coagulation and soda lime softening have shown little to no removal of NDMA FP (Krasner 2008) (Mitch 2009). Alternatively, bench-scale studies have shown that the use of activated carbon, while not effective at removing NDMA, may be effective at removing NDMA precursors. Pilot-scale and full-scale treatment plant studies have also shown granular activated carbon (GAC) to be effective in reducing NDMA FP by 60-80% (Hanigan et al. 2012). While GAC may be especially effective at removing some precursors in deionized water, it may become less effective when those precursors are in a surface water matrix (Hanigan et al. 2012).

One of the most effective methods of NDMA precursor removal is oxidation. Chlorine and ozone in particular have been shown to be very effective at reducing NDMA FP (Wilczak et al. 2003) (Lee et al. 2007) (Chen and Valentine 2008) (Charrois and Hrudey 2007). However, similar to GAC, ozone has been shown to be less effective at removing precursors in surface water matrices and may also form NDMA from select precursors (Pisarenko et al. 2012) (Gunten et al. 2010) (Schmidt and Brauch 2008).

Additionally, NDMA formation may be affected by the manner in which chloramines are applied and certain water quality characteristics. In the application of chloramines, chlorine to ammonia nitrogen ratio has been shown to influence the amount of NDMA formed (Schreiber and Mitch 2005).

NDMA FP may also be increased by certain water treatment techniques. PolyDADMAC used as a coagulant aid has been shown to be a source of NDMA precursors (Child et al. 1996). However, different factors such as the presence of dichloramine, polymer degradation and DMA release from polymers, can greatly impact how effective certain water treatment polymers are as NDMA precursors (Park et al. 2015) (Park et al. 2009).

Model equations for chlorine disinfection byproducts have been used to develop an understanding of the relationship between different factors that impact disinfection byproduct formation and actual formation. For example, there have been two main study designs used to assess the factors that impact THM formation, a chlorine disinfection byproduct. Experimental study designs vary known factors in formation to see the resultant impact on THM concentrations (Kavanaugh et al. 1980) (Urano, Wada, and Takemasa 1983). Observational studies use data that has already been generated, typically in treatment plants, to determine which factors are most associated with increased THM concentrations (Golfinopoulos and Arhonditsis 2002). Both of these types of approaches use linear regression to correlate the factors to the outcome variable, in this case, THM concentrations.

The evidence for the trends in NDMA formation previously described is based on bench-scale studies with fewer pilot plant and full treatment plant tests. It is clear that the water matrix may impact formation of NDMA from known precursors (Shen and Andrews 2011). Thus, it is important to discern the effect of these factors in real world scenarios. The objective of this study is to use data collected from over 20 water treatment plants in the United States and

Canada to evaluate which water quality conditions and treatment techniques are most significant in the formation of NDMA in "real" systems. This data will be used to develop equations relating parameters to NDMA formation and indicate which parameters are most important in minimizing NDMA formation. Additionally, this information will be used to determine if certain treatment processes are adding or removing NDMA precursors.

## Experimental

### Materials

NDMA analytical and internal standards were purchased from Sigma Aldrich, CA. Experiments were conducted using Milli-Q water produced from an Ultra Pure Water System (MilliPore Corp., U.S.A.).

### Methods

#### NDMA

NDMA analysis was performed at the Metropolitan Water District of Southern California (MWD). Samples were analyzed for NDMA following solid phase extraction onto a bead resin (Ambersorb) using gas chromatography/tandem mass spectrometry (GC/MS/MS) with chemical ionization (Cheng et al. 2006). The method detection limit was 2 ng/L.

Study Design

Using an observational study design, samples were collected from treatment plants over 2 years. In year one, plants were sampled quarterly and in year 2 select plants were sampled. There were 20 plants sampled in year 1. Nineteen of those plants were also sampled in year 2. In year one, most of the plants were sampled 3-4 times and in year 2 most of the plants were sampled 2-3 times. Participating utilities completed a survey detailing treatment processes, including the temperature and pH of the collected water. Additional water quality measurements such as total organic carbon (TOC) concentration, ultraviolet absorbance (UV254) and ammonia concentration were completed at MWD. Water was collected at the plant influent, before and after various treatment processes, at the plant effluent and in the distribution system at the average and maximum detention time. The complete list of variables considered in the study is included in Table 4-1. These variables were chosen because previous studies had shown an association between NDMA concentration and the variable or because they were a commonly measured water quality indicator. The pre-chlorination time variable had a very wide distribution of times, so the log value was taken in order to obtain a more normal distribution. Plants sampled after chloramine addition were quenched using sodium sulfite to prevent the additional formation of NDMA during transportation of the samples.

The plant effluent and distribution system samples were measured for NDMA, while the samples taken before and after treatment processes were measured for NDMA FP. Before and after treatment samples were not measured for NDMA due to the fact that chloramines had not been applied in the treatment train at this point and therefore no NDMA had likely been formed. By

measuring NDMA FP before and after treatment, an estimate about the reduction of NDMA precursors due to the treatment process is possible. Formation potential tests were set up at 25° C, using a 3:1 chlorine to ammonia weight ratio, at pH 8 and held for 3 days.

Table 4-1: Variables Considered in the Study

| |
|---|
| Quarter |
| TOC (mgC/L in Plant Influent) |
| UV254 (abs/cm in Plant Influent) |
| NH3 (mg/L in Plant Influent) |
| Sucralose (µg/L in Plant Influent) |
| PolyDADMAC dose (mg/L as percent active ingredient) |
| O3 (yes/no) |
| Prechlorination time (minutes) |
| Log Prechlorination time (minutes) |
| GAC (yes/no) |
| Water temp. in the Distribution System (DS) |
| Water temp. at NH2Cl point |
| pH in the DS |
| pH at NH2Cl point |
| Cl2:NH3 weight ratio |
| PAC (y/n) |
| Time in the DS at sampling point (maximum hold time) |
| Biofilter (y/n) |
| Month of collection |
| Season of collection |
| NDMA FP in the Plant Influent |

Statistical Approach

Linear mixed effects models with random intercepts to account for the correlations induced by repeated measurements within the treatment plants are used to assess the effects of various treatment factors on NDMA and NDMA FP. This type of model has not been used previously with THM models due to the fact that those studies did not sample such a large number and range of plants. By using a random intercept, the model accounts for the fact that certain plants will tend to form large amounts of NDMA and some will tend to form low concentrations. This model makes the estimate more conservative to account for this variability between plants. Three different models were created and an additional analysis was performed on specific treatment techniques. In Models 1, 2 and 3 all of the variables listed in Table 1 were used as predictors.

In each model, individual predictors were examined and then a backwards stepwise procedure was used to create an optimal multi-predictor model. Data from year one and year two were included in the final models. However, since a greater number of samples in year two were from plants that had shown more potential for reducing NDMA precursors, there was the potential for bias. While including plant-level random effects should adjust for much of this, several sensitivity checks were also performed. First, baseline values of NDMA and the key predictors between plants that were and were not sampled in the second year were tested to determine if they were different. The baseline NDMA values were not significantly different in year 1 and year 2 nor were the key predictors. Second, a mixed model was used to test for differences in, NDMA values between the two years using year as a predictor in determining differences

between NDMA values. NDMA values and NDMA percent change values did not fluctuate greatly between year one and year two (p=0.43, 0.37).

Finally, the models were rerun using only year 1 data. The basic pattern of effects remained the same, although actual significance levels changed due to the reduction in sample size.

Model 1: Final NDMA Concentration Model

Model 1 assesses which factors most impact the amount of NDMA formed during drinking water treatment as measured by the concentration in the distribution system at maximum detention time. The p-values were used to determine the significance of the correlation and beta coefficients were used to determine the magnitude and direction of the effect, and were derived for each of the considered factors.

Model 2: Final NDMA Influent Adjusted Model

Model 2 assesses which factors most impact the final NDMA concentration in the distribution system, but it includes the NDMA FP in the plant influent as one of the variables. In this way we are accounting for the fact that some plants will have a high amount of precursors coming into the plant. By using this as a variable, we can see which factors are still significant when the amount of NDMA FP coming into the plant is accounted for.

## Model 3 Percent Reduction Model

Model 3 assesses which factors most impact the change between the amount of NDMA that could be potentially formed at the plant influent (as measured by NDMA formation potential in the plant influent) and the amount of final NDMA formed in the distribution system at maximum detention time. This model was created to determine which treatment or water quality factors were most correlated with a decrease in NDMA formation. Percent change and raw change scores were calculated, but percent change was used to account for the fact that certain plants started with very low NDMA FP in the plant influent.

## Treatment Effects Analysis

Finally, changes in NDMA FP immediately before and after application of particular processes such as the application of PolyDADMAC (a known NDMA precursor), ozone oxidation, and the use of GAC were measured to obtain direct measurements of treatment effects (Treatment Effects Analysis). Due to the high number of possible factors involved in obtaining a final NDMA concentration, the effects of individual treatments may be obscured. By assessing the impact of these processes on NDMA precursors alone, a better understanding of their effect is gained. Additionally, the treatment schemes of the plants samples in this study were not randomly assigned, therefore there may be a bias introduced at certain plants that are designed to deal with particular water quality challenges. Therefore, the before and after treatment data has a stronger implication as to whether or not the individual process is effective.

Results and Discussion

Model 1 (Final NDMA Concentration Model)

The variables that remained in the model after applying the backwards stepwise procedure using alpha=0.05 as the measure of significance are presented in Table 4-2.

Table 4-2: Model 1 (Final NDMA Concentration Model)

| Predictor | P-value | Beta Coef. |
|---|---|---|
| UV254 conc. | 0.00 | 35.80 |
| Sucralose conc. | 0.04 | 1.03 |
| PolyDADMAC conc. | 0.01 | -2.60 |
| Prechlorination time (log) | 0.00 | -7.50 |
| GAC use* | 0.03 | 4.40 |
| pH at chloramine injection point | 0.02 | -2.60 |
| $Cl_2$/N ratio | 0.02 | -1.00 |
| Biofilter use* | 0.00 | -10.40 |

*denotes categorical variable

Increases in UV254 absorbance and sucralose concentration in the plant influent were associated with increases in NDMA formation in the distribution system (p-values <.0001 and .04 respectively). Sucralose, a non-degradable sugar substitute, has been used as an indicator of wastewater discharge in surface waters due to its low percent of false positives and ubiquity in water with sewage discharges (Oppenheimer et al. 2011). Wastewater effluent is a common

source of NDMA precursors (Krasner et al. 2013), therefore it would be expected to have a higher sucralose value, denoting a higher amount of wastewater discharge, would be correlated with an increased NDMA concentration.

In Model 1, use of GAC filtration was also associated with an increase in NDMA formation ($p = .03$), which is unexpected as the use of GAC has been shown to remove precursors in bench-scale tests. However, GAC use was also associated (correlation coefficient= 0.46) with UV254 absorbance. Since UV254 was highly correlated with NDMA FP in the plant influent (correlation coefficient=0.73) the relationship between use of GAC and high NDMA may be due to the fact that GAC is used at plants with worse influent water quality, which results higher NDMA values in the distribution system.

A higher pH at the point of chloramination was associated with a decrease in NDMA formation ($p =0 .02$). NDMA formation has been shown to be affected by pH in various studies, where the optimal pH for formation is between 8 and 9 (Schreiber and Mitch 2006) (Le Roux, Gallard, and Croué 2011). A longer pre-chlorination time was associated with a decrease in the amount of NDMA formed in the distribution system ($p < .001$) and was the second most significant treatment technique in the model.

Use of a biofilter is the variable most significantly associated with a decrease in NDMA concentration. Biofiltration, or use of a filter with biological activity has been shown to both reduce NDMA formation and increase formation in different cases (Krasner 2015). In general,

plants sampled in this study had a lower NDMA concentration in the distribution system when using a biofilter.

A lower chlorine to ammonia ratio used during chloramination procedures was shown to be correlated with a slightly lower amount of total NDMA formed ($p = 0.02$). This suggests that higher chlorine to ammonia ratios would form more NDMA. Dichloramine tends to be more effective at forming NDMA than monochloramine (Shah et al. 2012; Schreiber and Mitch 2006) and dichloramine formation is optimized at a chlorine to ammonia ratio near 6.3:1. Therefore, plants operating at these higher ratios would be expected to form more NDMA, given that the pH was suitable to dichloramine formation.

Lastly, higher polyDADMAC concentration was associated with a slightly lower NDMA concentration in the distribution system ($p = 0.01$). PolyDADMAC has been shown to be a potential source of NDMA precursors, however the effectiveness as a precursor is dependant upon many factors. Figure 4-1 illustrates the range of polyDADMAC concentrations versus the amount of NDMA formed in the distribution system. In some cases, NDMA formation was very low despite a high dose of polyDADMAC. Additionally, Figure 4-2 shows the change scores of NDMA FP tests of water taken before and after the addition of polyDADMAC, which illustrates that this treatment was effective at adding precursors in some cases, but not in others.

Figure 4-1: PolyDADMAC Dose, UV254 Absorbance, Pre-chlorination Time (log), and Biofilter Use v. NDMA Concentration in the Distribution System at Maximum Detention Time

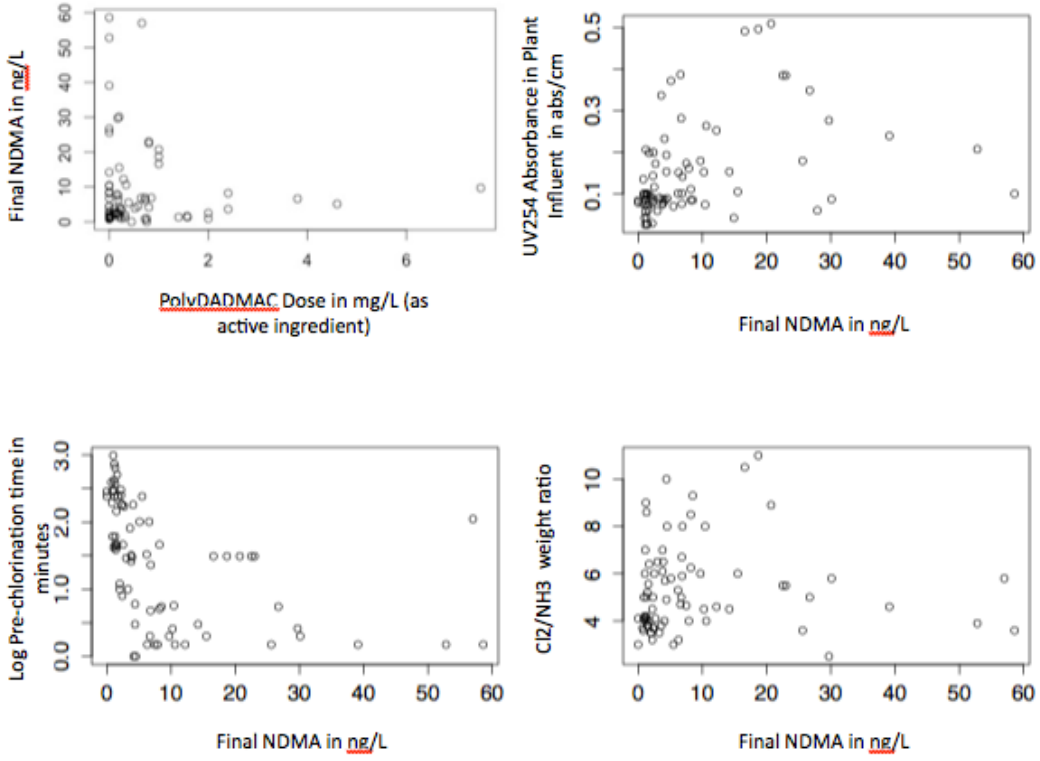


Figure 4-2: Change Score of NDMA FP Before and After Polymer Addition at Real Treatment Plants

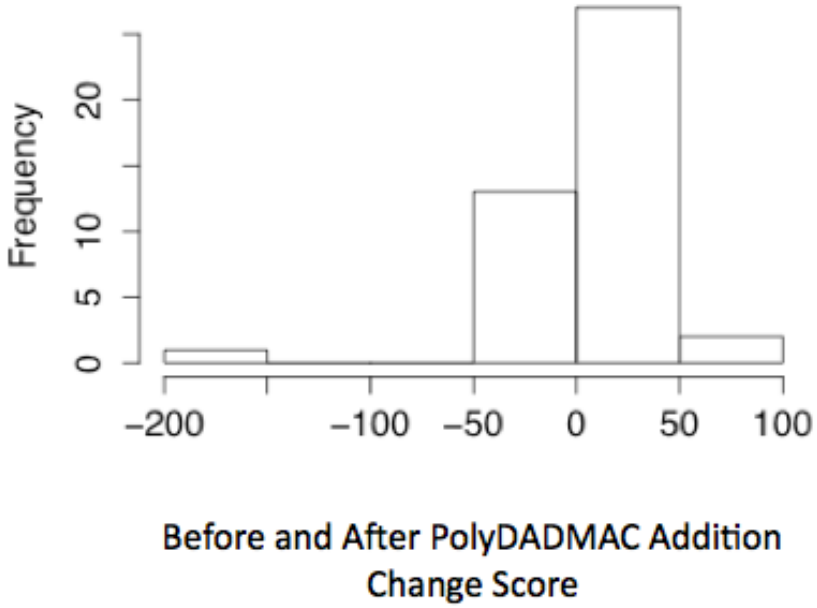

Figure 4-3: Model 1 (Final NDMA Concentration Model) Predictive Equation

$NDMA_{DS}$= 35.8(UV254 $conc._{PI}$) + 1(Suc $conc._{PI}$) - 2.6(PolyDADMAC conc.) - 7.5(logPre-chlorination time in minutes) +4.4 (GAC use=1, no GAC use=0) - 2.6($pH_{NH2Cl}$) - 1($Cl_2$/N ratio) - 10.4(Biofilter use=1, no Biofilter use=0) +38.8

Please note that UV254 absorbance and sucralose concentration are measured at the plant influent.

Based on the p-values, the most significant factors in predicting NDMA concentration in the distribution system at maximum detention time are UV254 absorbance in the plant influent, pre-chlorination time and the use of a biofilter. Where an increase in UV254 was associated with an increase in NDMA, an increase in pre-chlorination time was associated with a decrease in NDMA and use of a biolfilter was associated with a decrease in NDMA.

Model 2 (Final NDMA Influent Adjusted)

Model 2 was also fit using a backwards stepwise regression. Predictors with the lowest p-values were eliminated sequentially until the only remaining variables had p-values <0.05. The variables that remained in the model after applying the backwards stepwise procedure using alpha=0.05 as the measure of significance are presented in Table 4-3.

Table 4-3 shows that the NDMA formation potential at the plant influent is one of the most significant predictors of final NDMA formation. However, this measurement may not be useful

to plants attempting to predict NDMA formation due to the fact that many plants do not complete formation potential tests. When NDMA FP is added to the model it is indeed highly significant (p=0.02). After addition, of NDMA FP to the model, the sucralose concentration, polyDADMAC concentration, use of GAC, pH at the point of chloramine addition and $Cl_2$/N ratio are no longer significant predictors. However, use of ozone during water treatment and the length of time between the end of the treatment plant (where chloramines are typically spiked) and the point where the NDMA sample is collected became significant.

Table 4-3: Model 2 (Final NDMA Influent Adjusted)

| Predictor | P-value | Beta Coef. |
|---|---|---|
| NDMA FP in Plant influent | 0.02 | 0.02 |
| UV254 | 0.01 | 15.3 |
| logPre-chlorination time in minutes | 0.02 | -1.5 |
| Ozone* | 0.01 | -5.9 |
| DS max (time from plant effluent to DS sampling point in minutes) | 0 | 0.02 |
| Biofilter | 0.03 | 5.8 |

*denotes categorical variable

Sucralose has been shown to be a surrogate for wastewater discharges in surface water, which is indicative of a high amount of NDMA precursors. However, NDMA FP is the actual measure of NDMA precursors, and hence it is more effective in explaining the amount of NDMA formed than sucralose concentration. PolyDADMAC can be a source of NDMA precursors as well, but again NDMA FP is a better measurement of all precursors. The fact that GAC, pH and $Cl_2$/N ratio drop out of the model is indicative that these variables are associated with the NDMA FP in the plant influent.

In this model, the amount of time the chloraminated water spent in the distribution system becomes significant. However, the coefficient of this variable is very small, suggesting that the practical effect on the final NDMA concentration in the distribution system is not very large. The coefficient for this variable is 0.02, which means that NDMA will increase 0.02 ng/L for every minute in the distribution system. Additionally, when NDMA FP in the plant influent is considered, the presence of a biofilter is associated with an increase in NDMA concentration in finished water. When NDMA FP in the plant influent is not considered, the use of a biofilter is associated with a decrease in amount of NDMA formed in the distribution system. This suggests that when we account for the precursors coming into the plant, the biofilter tends to be a source of NDMA precursors. Biofiltration can remove some precursors, however it can also transform others to more potent forms thus increasing total NDMA formation. (Krasner et al. 2013) When incoming precursors are not considered, biofiltration is usually associated with a lower NDMA concentration meaning that biofilters may be used at plants with a lower concentration of total precursors.

Figure 4-4: Model 2 (Final NDMA Influent Adjusted) Predictive Equation

$$NDMA_{DS} = 15.3(UV254\ abs._{PI}) - 1.5(\log \text{Pre-chlorination time in minutes}) + 5.8(\text{Biofilter use=1, no Biofilter use=0}) - 5.9(\text{Ozone use=1, No Ozone use=0}) + 0.02\ (\text{time from plant effluent to } DS_{max} \text{ in minutes}) + 0.03(NDMA\ FP_{PI}) + 0.9$$

*$DS_{max}$ is the point in the distribution system at maximum hold time.

When NDMA FP in the plant influent is accounted for the most highly significant factors correlated to NDMA in the distribution system at maximum detention time, based on their p-values, are UV254 absorbance in the plant influent, the use of ozone, and chloramination time (measured as time from the plant effluent to the DS sampling point). However, pre-chlorination time still remains very significant.

Model 3 (Percent Reduction Model)

In addition to modeling NDMA concentration as a factor of drinking water treatment plant source water quality and treatment techniques, a model can be developed to determine which factors are most associated with a decrease of NDMA precursors. The percentage reduction in the NDMA formation between the plant influent and the NDMA concentration in the distribution system indicates whether or not certain treatment techniques are effective a decreasing the amount of NDMA formed in finished water. The percent reduction model measures the difference between what we would expect to be formed (NDMA FP in the plant influent) without any treatment and the actual formation at the end of the treatment train. The factors most significantly associated with percentage change in NDMA in the multivariable model are shown in Table 4-3.

In this model, plants with a high UV254 absorbance in the influent were more likely to have a large percent change ($p=0.02$). This may be due to the fact that a high UV254 absorbance signifies a large quantity of aromatic organic chemicals, some of which may be NDMA precursors. Waters with high precursor loading, may also have a higher percent change as those

precursors are destroyed by treatment techniques. The quarter in which the plant was sampled was also significant (p=0.04), with samples taken in quarter 1 (January, February and March) showing a higher percent change. This could be due to a difference in types of precursors seen during this time of year, or due to the fact that more precursors are present in the winter and spring months. NDMA FP in the plant influent is significantly correlated with quarter, suggesting precursor loading is different during different months.

Table 4-3: Model 3 (Percent Reduction Model)

| Predictor | P-value | Beta Coef. |
|---|---|---|
| Quarter | 0.04 | -4.8 |
| UV254 | 0.02 | 98 |
| logPre-chlorination time (minutes) | 0.04 | 13.7 |

Pre-chlorination time was significant in all 3 models, and is the only significant variable in the percentage reduction model that is a treatment technique. Oxidation by free chlorine prior to ammonia addition has been shown in bench-scale tests to be very effective at reducing NDMA precursors, achieving upwards of 50% reduction of precursors using half the chlorination dose (~70 mg/min*L) typically used for deactivation of Giardia (Krasner et al. 2013). In this model, pre-chlorination time is associated with a reduction in possible NDMA formation in treatment plants (p=0.04). Correlations were calculated between NDMA FP in the plant influent and the variables to determine if any of these were good indicators of NDMA FP. Similar to the NDMA outcome model, percent change was also highly correlated with NDMA FP in the plant influent.

This further confirms that waters with high precursor loading were more likely to see a large percent change.

In addition to percent change, NDMA in the distribution system and sampling month, NDMA FP in the plant influent was correlated with UV254 concentration, use of powdered activated carbon (PAC), and use of ozone. This suggests that UV254 absorbance may be a good surrogate for NDMA precursors. While TOC concentration reflects the amount of total organic carbon present, which may include aliphatic and aromatic compounds, UV254 absorbance is generally representative specifically of aromatic compounds. While, some precursors of NDMA are currently known, there are many others that are not. This work suggests that many NDMA precursors will likely have aromatic groups. When NDMA FP in the plant influent is high, it is likely other water quality indicators measuring the load of organic pollutants, such as UV254, will also be high. In this case, it is likely that a plant will employ additional treatment techniques to reduce organic pollutants and natural organic matter. The use of ozone and PAC may increase in these circumstances, as treatment plants attempt to reduce organic contaminants.

Figure 4-5: Model 3 (Percent Reduction Model) Predictive Equation

$$Percent\ Change = 98(UV254\ abs._{PI}) - 4.8(Quarter) + 13.7(\log Pre\text{-}chlorination\ time\ (min)) + 48.9$$

The most significant factor in predicting a decrease in NDMA formation, based on its p-value, is pre-chlorination time. UV254 absorbance in the plant influent remains a significant predictor in this model, suggesting that it can also be used to predict changes in NDMA formation. These

results indicate the UV254 absorbance in the plant influent and pre-chlorination time are the best predictors of NDMA formation and that increasing pre-chlorination time is the best way for a wide range of plants to reduce NDMA formation.

Treatment Effects Analysis

Certain treatment techniques have been shown in bench-scale tests to be effective at either increasing or decreasing NDMA formation. However those techniques may not have been as significant in the models presented here. The observational nature of the data used in this study may confound seeing causal effects. To determine if these treatment techniques were impacting NDMA formation in situ, NDMA FP was measured at points along a treatment train at certain plants before and after polyDADMAC addition, the use of ozone and GAC treatment.

PolyDADMAC

There were statistically significant differences in NDMA FP concentrations before and after polyDADMAC treatment on the percentage change. Influent NDMA FP was the most significant predictor of percent change, likely due to the fact that a high influent NDMA FP creates the potential for a larger change. When influent FP is removed as a predictor, ammonia concentration in the plant influent and water temperature were both associated with a lower percent change. This suggests that when ammonia concentration increases, the effect of polyDADMAC as a precursor is reduced and the same is true for water temperature.

Ozone

There were also significant changes in NDMA FP before and after ozone treatment on the percentage change scale. A higher NDMA FP concentration in the plant influent was associated with a larger percent change. When NDMA FP in the plant influent was removed, TOC was the only other significant predictor. Plants with a higher TOC concentration in the plant influent were more likely to have a larger percent change than plants with low TOC concentrations.

GAC

Use of granular activated carbon filtration was effective in reducing NDMA FP. The percent change and change score for NDMA FP before and after treatment with a GAC filter were both statistically significant. Unlike with polyDADMAC dose and the use of ozone, none of the other plant pretreatment characteristics were correlated with these changes. This suggests that the use of GAC will be effective at removing NDMA precursors, regardless of their initial load. Use of GAC was associated with higher NDMA in the distribution system using the NDMA outcome model. This may be due to the fact that plants with worse water quality and thus worse NDMA values in the distribution system are more likely to use GAC filtration.

Model Stability

Plants sampled in year two may have been subject to selection bias. Therefore, tests were completed to determine if this bias may have impacted the results. The difference in NDMA concentrations in the distribution system sampled between year 1 and year 2 was not statistical significant when using year as a predictor and NDMA concentration in the distribution system as the outcome variable. However, the percent change values for the plant influent and NDMA concentration in the distribution system were different between year 1 and year 2.

When the variables that were significant from the year 1 and year 2 combined data set were tested using only the data from year 1, the coefficients of the predictors were also similar. The coefficients of the significant variables from the models with NDMA concentration as the outcome variable were also significant using the year 1 and year 2 data set on year 1 variables only and vice versa suggesting that the both models are stable between the two years.

Due to the fact that this regression was completed using real world samples, the study design is not purely experimental. Therefore, the results can only suggest a correlation between certain water quality and treatment technique factors rather than causation. However, it appears that certain water quality indicators such as UV254 concentration in the plant influent are very strongly associated with an increase in NDMA concentration. Additionally, certain treatment techniques such as the use of polyDADMAC, Ozone and GAC impact the amount of NDMA precursors present. Water temperature, pH, use of pre-chlorination, chlorine to ammonia weight

ratio and the use of biofiltration are also useful when trying to predict the amount of NDMA that is formed in dirnking water treatment plants.

Conclusions

The large amount of data collected from treatment plants allows for a better understanding of which treatment processes and water quality indicators are most correlated with NDMA formation. A linear mixed effects model with a random intercept was used to account for the repeated measurements of samples at the same plant during different quarters. This type of model has not been used previously with THM models due to the fact that those studies did not sample such a large number and range of plants. The variability between plants was also accounted for, as some plants tend to form high amounts of NDMA and some tend to be low formers. Three models were created and an analysis was done to determine if specific treatment processes were changing NDMA precursor concentrations.

- Model 1 (Final NDMA Concentration) used the NDMA concentration in the DS at the maximum detention time as the outcome variable. The factors that were most correlated with this outcome were: UV254 absorbance in the plant influent, sucralose concentration in the plant influent, polyDADMAC concentration used, pre-chlorination time, use of GAC, pH during chloramination, $Cl_2/NH_3$ weight ratio and biofilter use. The most influential factors were UV254 absorbance in the plant influent, pre-chlorination time and biofilter use.

- Model 2 (Final NDMA Influent Adjusted) used NDMA FP in the plant influent as a variable in addition to the variables tested in Model 1. It used the same outcome variable as Model 1 (NDMA concentration in the DS at the maximum detention time). This model was used to account for the fact that some plants may have more precursors coming into the plant and determine which variables were still significant when this was the case. The factors that were significant in predicting this were: NDMA FP in the plant influent, UV254 absorbance in the plant influent, use of ozone, time from the point of chlorination to the DS sampling location, pre-chlorination time and use of a biofilter. The most influential factors were chloramination time, UV254 absorbance in the plant influent, and use of ozone.
- Model 3 (Percent Reduction Model) uses the percent change between NDMA FP in the plant influent and final NDMA formed in the DS at maximum detention time to assess which variables were correlated with a reduction of NDMA potential during treatment. The variables that could be used to predict this reduction were: the quarter during which the plant was sampled, pre-chlorination time and UV254 absorbance in the plant influent. The most influential factor was UV254 absorbance in the plant influent.
- Lastly, the Treatment Effects Analysis was used to determine if the use of polyDADMAC, ozone and GAC were effective at removing precursors. Water was collected before and after each treatment and was tested for NDMA FP. PolyDADMAC was effective at adding precursors, while ozone and GAC were effective at removing them.

Overall, this analysis made it clear that UV254 in the plant influent was very effective at predicting NDMA concentration, regardless of the type of model. Since UV254 absorbance tends to represent the presence of aromatic compounds, this makes sense as many NDMA precursors have this functionality. Additionally, pre-chlorination time is clearly significant in reducing the amount of NDMA formed in all models. This information may be useful to treatment plant operators in both estimating the likelihood of the presence of NDMA precursors and determining steps to reduce formation. Future research is needed to augment the analysis using data from more treatment plants and over a greater number of years to increase the sample size and thus statistical power.

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# Chapter V: Conclusions and Recommendations

*Veterinary Antibiotics*

Among the many sources of NDMA precursors, it appears that veterinary antibiotics from large-scale animal agriculture operations may be a new source that has not been previously considered. Like many other NDMA precursors, the formation of NDMA from veterinary antibiotics is impacted by the nature of the chloramination conditions. The pH at which the water is chloraminated appears to be very import. pH between 8 and 9 is exceptionally better for the formation of NDMA as was seen in this and other studies. The chlorine to ammonia weight ratio, temperature and hold time was also impactful on NDMA formation rates. While some of the precursors may be capable of producing NDMA from a newly proposed nucleophilic mechanism ( Le Roux 2012), others may not be likely to form NDMA in this way.

In the future, research is needed to confirm that water sources impacted by run-off from large scale animal agriculture operations does indeed result in an increase in NDMA formation. A survey of antibiotic concentrations downstream of farming operations should be completed while corresponding NDMA formation is measured.

*Natural Organic Matter*

Natural organic matter may be an NDMA precursor in some cases, but it is likely co-occurring NDMA precursors disbursed throughout the NOM that are causing the formation. Instead, NOM was seen, in this and other studies, to reduce NDMA formation from precursor chemicals. High

molecular weight NOM (>10 kDa) and medium molecular weight NOM (5 K- 10 K) reduced NDMA formation from the antibiotic tetracycline in this study. Polar and charged NOM was shown to reduce formation of NDMA from tetracycline as well. The mechanism for this is likely to sorption of tetracycline's polar functional groups to the polar groups in the NOM via hydrogen bonding. Research is needed to assess the impact of NOM character on non-polar NDMA precursors. Additionally, other fractions of NOM, such as an anionic fraction should be tested with various types of NDMA precursors to determine the effect of these NOM constituents on NDMA formation.

*NDMA Modeling*

Other disinfection byproducts of treated drinking water, such as trihalomethanes have been predicted using various models in previous literature. Models were created experimentally, by varying certain parameters that had been shown to affect formation. They were also created using already available data about treatment plants and trihalomethane formation via linear regression. However, only one model has been created for NDMA in the past and this model was only a function of chloramine concentration. In this study, data from about 20 treatment plants in the U.S. and Canada was collected over two years and NDMA concentrations were measured. Two models were created and individual treatment effects were measured for ozone, GAC and polyDADMAC treatment. The first model identified UV254 absorbance in the plant influent, sucralose concentration in the plant influent, polyDADMAC concentration used, the use of GAC, pH during chloramination, chlorine to ammonia weight ratio and biofilter use as associated with NDMA concentration in the distribution system. Meaning, that all of these

variables had an effect on the final NDMA that a treatment plant formed. A second model assessed the amount of change between potential NDMA in the plant influent and final NDMA formed in the distribution system. In this model, quarter in which the samples were taken, UV254 absorbance and time of pre-chlorination were all significant in affecting the change in NDMA concentration. Lastly, GAC, ozone and polyDADMAC all impacted the amount of NDMA precursors present. GAC and ozone reduced NDMA precursors and polyDADMAC increased them. These models created predictive equations that can be used to estimate the amount of NDMA a plant will form given the various parameters. Future research should be conducted using data from more years and from more treatment plants to increase the power of the study.

Reflections

NDMA will be a growing challenge in plants that utilize chloramine disinfection. While it is uncertain which of the two proposed mechanisms is responsible for the majority of NDMA formation, each is effective under certain scenarios. As certain areas of the U.S. and the globe experience unprecedented drought and communities attempt to deal with the realities of a changing climate, new sources of water are being proposed. Certain water treatment processes, such as water reclamation, or water recycling, have been shown to form much higher amounts of NDMA than water originating from less contaminated sources. If these new water sources are to be considered as part of the portfolio of water resources in drought-starved regions, the NDMA issue must be solved. Research is neeeded to determine how to reduce NDMA in recycled water, in order to render this a useful resource. This dissertation sheds new light on new types of

precursors, the effect of NOM character on slowing the formation of NDMA from precursors and which treatment aspects may increase or decrease formation. All of these are pieces of a puzzle which will help water providers reduce the amount of NDMA formed in drinking water and allow them to provide safe water to the millions of people who depend on it.