

N-Nitrosodimethylamine (NDMA) as a Drinking Water Contaminant: A Review

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ABSTRACT

N-Nitrosodimethylamine (NDMA) is a member of a family of extremely potent carcinogens, the *N*-nitrosamines. Until recently, concerns about NDMA mainly focused on the presence of NDMA in food, consumer products, and polluted air. However, current concern focuses on NDMA as a drinking water contaminant resulting from reactions occurring during chlorination or via direct industrial contamination. Because of the relatively high concentrations of NDMA formed during wastewater chlorination, the intentional and unintentional reuse of municipal wastewater is a particularly important area of concern. Although ultraviolet (UV) treatment can effectively remove NDMA, there is considerable interest in the development of less expensive alternative treatment technologies. These alternative technologies include approaches for removing organic nitrogen-containing NDMA precursors prior to chlorination and the use of sunlight photolysis, and *in situ* bioremediation to remove NDMA and its precursors.

Key words: *N*-nitrosodimethylamine (NDMA); nitrosation; unsymmetrical dimethylhydrazine (UDMH); chlorination; photolysis; bioremediation

INTRODUCTION

N-NITROSODIMETHYLAMINE (NDMA) IS A MEMBER of a family of extremely potent carcinogens, the *N*-nitrosamines (U.S. EPA, 2002). Their cancer potencies are

much higher than those of the trihalomethanes. Much of the recent focus on NDMA as a drinking water contaminant can be traced to the detection of NDMA in drinking water wells near a rocket engine testing facility in Sacramento County, CA, that used unsymmetrical dimethylhy-

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drazine (UDMH)-based rocket fuel. With groundwater NDMA concentrations as high as 400,000 ng/L on site and 20,000 ng/L off site, it became necessary to close downgradient drinking water wells (DHS, 2002; MacDonald, 2002). The U.S. EPA established a cleanup level of 0.7 ng/L for NDMA in groundwater (U.S. EPA, 2001), based on a risk assessment target of an increased lifetime cancer risk of 10^{-6} in drinking water (U.S. EPA, 2002). The subsequent discovery of NDMA at concentrations up to 3,000 ng/L downgradient of another rocket engine testing facility in the San Gabriel Valley (CA) spurred the California Department of Health Services to sponsor a survey of NDMA in California drinking waters (DHS, 2002).

The results of this survey demonstrated that NDMA occurrence was not limited to regions proximal to facilities that used UDMH-based fuels. Rather, NDMA detected at other sites also appeared to be associated with chlorine disinfection of water and wastewater. Especially in locations where chlorinated wastewater effluent was used for aquifer recharge, NDMA was present at elevated concentrations. For example, two drinking water production wells, under the influence of recharge water from the advanced wastewater treatment system of the Orange County Water District's Water Factory 21, suspended operations due to the presence of NDMA in 2000 (OCWD, 2000a). Groundwater injection of treated wastewater from Water Factory 21 was reduced from 7 to 1 million gallons per day pending the installation of an expensive ultraviolet treatment system to remove the NDMA prior to injection (OCWD, 2000b). Even more recently, NDMA was detected in treated drinking water from sources that were not impacted by wastewater effluent or industrial sources, especially when monochloramine was used to maintain a chlorine residual (DHS, 2002).

Although NDMA is listed as a priority pollutant (CFR, 2001), a federal maximum contaminant level (MCL) has not been established for drinking water. Moreover, NDMA is not even on the Candidate Contaminant List, which sets the priorities for future regulation of drinking water (U.S. EPA, 1998). However, other regulatory agencies have established NDMA guidelines. The Ontario Ministry of the Environment and Energy established an Interim Maximum Acceptable Concentration of 9 ng/L for NDMA (MOE, 2000). After discovering the widespread presence of NDMA, the California Department of Health Services set an interim action level of 20 ng/L, which was later reduced to 10 ng/L (DHS, 2002).

Despite heightened recent concern, NDMA is not really an emerging contaminant. Since the 1960s, toxicologists have studied the health effects of nitrosamines. The concern focused on their widespread occurrence in food and consumer products, particularly beer, meats cured with nitrite, tobacco smoke, and rubber products includ-

ing baby bottle nipples (IARC, 1978). Concerns about human exposure to NDMA from industrial sources also were voiced previously. During the 1970s, NDMA was detected in the air and water adjacent to a factory near Baltimore (MD) that produced UDMH from NDMA (Shapley, 1976; Fine *et al.*, 1977; Fine, 1978). More alarming was the detection of NDMA in the air upwind of the plant in downtown Baltimore ($0.1 \mu\text{g}/\text{m}^3$), and at other sites in Belle, WV ($0.1 \mu\text{g}/\text{m}^3$), and New York City ($0.8 \mu\text{g}/\text{m}^3$), areas with no known industrial sources of NDMA. On the basis of those observations, some researchers suggested that NDMA formed in the polluted atmosphere could be responsible for elevated urban cancer rates (Shapley, 1976). However, it was subsequently determined that a factory using dimethylamine was located near Belle, WV, and that air concentrations of NDMA in areas not impacted by industrial processes were orders of magnitude lower than the initial reports (Hanst *et al.*, 1977; Cohen and Bachman, 1978; Fine, 1978).

Prior review articles (IARC, 1978; ASTDR, 1989) have focused on the occurrence and toxicology of NDMA in food and consumer products. In addition to research occurring after 1989, this review covers material from prior review articles that is relevant to water treatment.

ANALYSIS

Prior to the recent interest in low-level NDMA occurrence, analysis of the compound usually was performed by liquid-liquid extraction and gas chromatography/mass spectrometry (GC/MS) or gas chromatography with a thermionic detector. The detection limit of the method was approximately 1,000 ng/L. The most common technique currently used for analysis of low concentrations of NDMA involves extraction, preconcentration, and analysis by gas chromatography with tandem mass spectrometry in the chemical ionization mode (GC/CI/MS/MS) or gas chromatography with high resolution mass spectrometry (GC/HRMS). These methods typically have detection limits around 1 ng/L. Although a standard method for low-level quantification of NDMA has not been published, several methods have been shown to yield accurate and reproducible results. In the first step, residual chlorine in the sample is quenched with ascorbic acid or sodium thiosulfate to prevent an artifact due to reaction of chlorine with methylene chloride to form NDMA (Cohen and Bachman, 1978). Deuterated NDMA is added for use in isotope dilution to reduce the uncertainty associated with extraction efficiency. In some methods, the sample is extracted in methylene chloride by the separatory funnel method according to U.S. EPA Method 3510C (U.S. EPA, 1996). Unfortunately, this

method yields low recoveries, and may generate difficult-to-handle emulsions when used for wastewater effluent samples. Extraction efficiencies can be improved to approximately 50% by the addition of up to 100 g/L of sodium chloride (Yoo *et al.*, 2000). Other methods employ continuous liquid-liquid extraction via U.S. EPA Method 3520C (U.S. EPA, 1998), which involves extraction of the sample with 100–300 mL methylene chloride for approximately 6–18 h. Continuous liquid-liquid extraction avoids problems associated with emulsions in wastewater samples, and can yield extraction efficiencies of up to 60% (Mitch *et al.*, 2003). The methylene chloride extracts are then concentrated to 1 mL or less using rotary evaporators or nitrogen blowdown.

There have been several attempts to use solid-phase extraction to improve extraction efficiency and to reduce the volume of methylene chloride required for extractions. Jenkins *et al.* (1995) reported a NDMA solid-phase extraction method involving the use of carbonaceous Ambersorb 572 resin that reduces the volume of methylene chloride required to 400 μ L. Recoveries were approximately 30%. This method suffers from difficulties arising from fragmentation of the resin and subsequent recovery for extraction (Tomkins and Griest, 1996). Tomkins and Griest (1996) described solid phase extraction using a carbon-based Empore disk that resulted in 60% recovery. Unfortunately, the carbon-based Empore extraction disks are no longer available.

Following extraction, NDMA is separated by capillary gas chromatography (most often with DB-5 or DB-1701 columns) followed by detection by one of several methods: thermal energy analyzers (Fine *et al.*, 1977; Kimoto *et al.*, 1981), chemiluminescent nitrogen detectors (Tomkins *et al.*, 1995), and high-resolution mass spectrometers (Taguchi *et al.*, 1994). Although these methods are still used, the most common method used for determination of low concentrations of NDMA involves the use of chemical ionization followed by tandem mass spectroscopy.

Analytical methods also have been described for NDMA precursors. Mitch *et al.* (2003) describe methods for analyzing total concentrations of the organic nitrogen precursors for NDMA formation during chlorination of water and wastewater. Although several methods for the detection of dimethylamine (and other primary and secondary amines) have been previously described (Scully *et al.*, 1988; Hwang *et al.*, 1994, 1995; Lopez *et al.*, 1996; Sacher *et al.*, 1997; Abalos *et al.*, 1999; Liu *et al.*, 2001), a method recently was developed specifically for use in water or wastewater (Mitch *et al.*, 2003).

Obtaining blanks that are free from NDMA and NDMA precursors can be problematic. Deionized or distilled water can be contaminated with several ng/L of

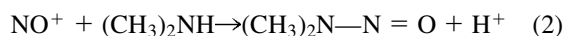
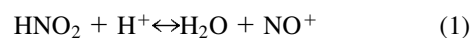
NDMA (Kimoto *et al.*, 1981) as well as NDMA precursors (Gerecke and Sedlak, 2003). A UV lamp can be used to destroy NDMA in deionized water prior to use or NDMA-free water can be obtained by purchase of HPLC grade water.

SOURCES AND OCCURRENCE

NDMA can be released directly from industrial sources as a contaminant of products such as liquid rocket fuel, or it can be formed in solution from chemical reactions. Available data suggest that there are two major pathways for NDMA formation: (1) nitrosation, and (2) formation by oxidation of UDMH. Although the two pathways differ in their mechanisms of formation, the organic nitrogen precursors involved in both reactions may be identical.

Nitrosation: NDMA formation via nitrite

Nitrosation involves the formation of nitrosyl cation or similar nitrogen-containing species, such as dinitrogen trioxide (N_2O_3), during acidification of nitrite (reactions 1 and 2; Mirvish, 1975). The nitrosyl cation then reacts with an amine, such as dimethylamine, to form NDMA. This reaction occurs most rapidly at pH 3.4, reflecting a balance between the protonation of nitrite (pK_a of $HNO_2 = 3.35$) and the increased fraction of dimethylamine in the reactive, deprotonated form with increasing pH (pK_a of $H_2N(CH_3)_2^+ = 10.7$).



This nitrosation mechanism is believed to be responsible for the observed formation of NDMA in vegetables, fish, and especially meat products cured with nitrite to prevent the growth of *Clostridium botulinum*, the bacterium that generates botulism toxin (IARC, 1978). Nitrate also can contribute to nitrosation because it can be reduced to nitrite by bacteria in the mouth (Preussmann, 1984). *In vivo* nitrosation occurs when nitrite enters the acidic environment of the stomach (Shapley, 1976). Nucleophilic anions, particularly thiocyanate (a constituent of saliva), enhance the rate of nitrosation through catalytic NDMA formation from nitrite (Fan and Tannenbaum, 1973). Although the U.S. Food and Drug Administration reduced the concentrations of nitrite allowed for curing meat to a maximum of 120 ppm, several meat processors add reducing agents such as ascorbic acid to quench nitrosating agents and minimize *in vivo* NDMA formation (Preussmann, 1984).

Although the rate of nitrosation is slow at neutral and

basic pH, several studies indicate that photochemical reactions (Ohta *et al.*, 1982), formaldehyde (Keefer and Roller, 1973) and fulvic acid (Weerasooriya and Disanayake, 1989) can catalyze nitrosation at circumneutral pH. For example, Ayanaba and Alexander (1976) observed that the addition of high concentrations of nitrite to lake water containing dimethylamine resulted in the formation of NDMA. Although the concentration of NDMA increased as pH decreased, NDMA formation was observed even at pH 6.2. Denitrifying bacteria that colonize the organs of sick patients also are known to catalyze the nitrosation reaction at circumneutral pH values (Leach *et al.*, 1987). Furthermore, catalysis of nitrosation by the yeast *Candida albicans* in the mouth is thought to be potentially responsible for some oral cancers (Krogh *et al.*, 1987).

Reactions similar to nitrosation also can occur in the atmosphere. Combustion often results in the formation of nitrogen-containing species (i.e., NO_x or nitroso radicals) that react with species such as dimethylamine to produce nitrosamines. Relatively slow NDMA formation may occur in the atmosphere due to reaction of NO_x (principally atmospheric nitrous acid) with dimethylamine released by industrial sources (Hanst *et al.*, 1977; Cohen and Bachman, 1978). However, atmospheric NDMA may accumulate only at night because it degrades quickly by sunlight photolysis (Hanst *et al.*, 1977; Tuazon *et al.*, 1984).

Gas-phase nitrosation may explain the occurrence of NDMA in cigarette smoke, malt beverages, dried foods, and rubber products (Preussmann, 1984; ATSDR, 1989). NDMA can be formed during food drying or during the barley malting process as a result of NO_x in the exhaust of air heaters (Preussmann, 1984; ATSDR, 1989; Sen *et al.*, 1996). For example, concentrations of NDMA detected in beer dropped by nearly an order of magnitude when malting houses switched to the use of indirect heaters to prevent contact of the barley with heater exhaust or when they applied sulfur dioxide to the flue gas as a quenching agent. Prior to these modifications, beer was estimated to be the major dietary contributor to daily NDMA ingestion. Occupational exposures to NDMA are high in the tire and rubber industries where nitroso radicals in engine exhaust react with amine-containing accelerators used for vulcanization (Preussmann, 1984). NDMA also was observed in the wastewater effluents of a variety of industrial plants manufacturing amines, herbicides, pesticides, pharmaceuticals (Cohen and Bachman, 1978) and rubber. For example, NDMA has been detected at concentrations up to 2 mg/L in the wastewater effluent of a tire factory in Ontario (Ash, 1995).

Nitrosation reactions in food and consumer products may represent a significant exposure source. The esti-

mated daily intake of NDMA for an average German diet was 0.2 μg/day (Tricker *et al.*, 1994). The most important dietary source of NDMA may be preserved meat and fish products, beer, and tobacco (Fine, 1978; ATSDR, 1989). NDMA is occasionally detected in cheese and bakery products (Uibu *et al.*, 1978) as the result of the drying process for cheeses or catalysis of nitrosation reactions by yeast. The formation of NDMA in amine-containing toiletry and cosmetic products, such as shampoo, has been attributed to the use of nitrite (Spiegelhalder and Preussmann, 1984). NDMA volatilizing from upholstery also is detectable in the interior air of automobiles (ATSDR, 1989).

Unsymmetrical dimethylhydrazine (UDMH) oxidation: NDMA formation from chlorine and other oxidants

During the 1980s, the formation of NDMA was reported when hypochlorite was used to treat waste UDMH-containing rocket fuel (Brubaker *et al.*, 1985, 1987). NDMA also has been observed as a byproduct of UDMH oxidation by cupric ion (Banerjee *et al.*, 1984), potassium permanganate, iodate (Castegnaro *et al.*, 1986), hydrogen peroxide, and oxygen (Lunn *et al.*, 1991; Lunn and Sansone, 1994). The formation of NDMA from oxidation of UDMH is maximized at neutral and high pH (Lunn *et al.*, 1991).

The formation of NDMA during water chlorination was reported in laboratory experiments in 1980 (Kimoto *et al.*, 1980, 1981). The formation of NDMA was later documented after chlorination at full-scale drinking water treatment plants and at wastewater treatment plants (Jobb *et al.*, 1994; Ash, 1995; Child *et al.*, 1996). Because NDMA is formed when UDMH is oxidized, any chlorination reactions that produce UDMH also should produce NDMA. The reaction between monochloramine and dimethylamine to form UDMH (Yagil and Anbar, 1962) and the reaction of monochloramine with trimethylamine to form a 1,1,1-trimethyl hydrazinium salt (Omietski and Sisler, 1956) have been known for some time. Delalu *et al.* (1981; Delalu and Marchand, 1987, 1989a, 1989b) described the kinetics of the formation of UDMH from the reaction of monochloramine and dimethylamine and the subsequent oxidation of UDMH at high concentrations of reactants. However, they did not attempt to measure the formation of NDMA.

Until recently, NDMA formation during chlorination was assumed to occur via the nitrosation pathway (Kimoto *et al.*, 1981; Jobb *et al.*, 1994; OCWD, 2000b). However, Mitch and Sedlak (2002a) and Choi and Valentine (2002a, 2002b) demonstrated that NDMA formation during chlorination could occur through UDMH as an in-

intermediate (Fig. 1). The rate of UDMH formation via this process increases with pH (Yagil and Anbar, 1962). Although stable at high pH, the UDMH intermediate is oxidized nearly instantaneously at circumneutral pH to form NDMA at low yields (<1%) (Mitch and Sedlak, 2002a). The maximum rate of formation occurs at circumneutral pH. Due to the preliminary slow step, the overall rate of formation is extremely slow, resulting in formation of NDMA over a period of days. Mitch and Sedlak (2002b) demonstrated that chloramination of amines via this pathway was a plausible explanation to account for the formation of NDMA during wastewater chlorination. However, it was unclear whether dimethylamine concentrations in secondary effluent are sufficient to account for NDMA formation or whether other organic nitrogen compounds are more important precursors.

Bromide ion is frequently a trace component of drinking water and wastewater. It is readily oxidized by free chlorine and monochloramine although the rate of reaction with monochloramine is several orders of magnitude slower (Trofe *et al.*, 1980). In the presence of excess ammonia, bromamines are readily produced when hypochlorite is added to water. Given the similarity of bromamine to chloramine chemistry and the generally increased reactivity of bromamines compared to chloramines, it is not surprising that Choi and Valentine (2002b, 2002c) observed a catalytic effect of bromide on NDMA formation.

The two-step mechanism elucidated by Mitch and Sedlak (2002a) and Choi and Valentine (2002a, 2002b) is consistent with observations (Najm and Trussell, 2001;

Berger *et al.*, 2002; Najm and Ma, 2002; Wilczek *et al.*, 2002) that the use of monochloramine in water treatment greatly increases NDMA formation. Because NDMA formation is slow (Mitch and Sedlak, 2002a; Mitch *et al.*, 2003), the use of monochloramine to maintain a chlorine residual can result in increasing concentrations of NDMA within the distribution system. However, the problem is not restricted to chloramines. In the absence of ammonia, hypochlorite also can produce NDMA through reaction with secondary amines, but the rate of formation is approximately an order of magnitude lower than that observed with monochloramine (Mitch and Sedlak, 2002a).

Several studies have documented NDMA formation in waters treated with ion-exchange resins having quaternary amine functional groups that could serve as NDMA precursors (Fiddler *et al.*, 1977; Gough *et al.*, 1977; Kimoto *et al.*, 1980). In many of these studies, a chlorine or monochloramine residual in the water probably reacted with resin functional groups. However, Najm and Trussell (2001) found that even distilled water leached significant concentrations of NDMA (up to approximately 60 ng/L after 4 h of contact) from anion exchange resins. These concentrations doubled in the presence of 1 mg/L nitrite, suggesting a mechanism other than UDMH oxidation was involved. Although NDMA may form from the reaction of hypochlorite with amine-containing polymers used in water treatment, two studies indicated that the concentrations formed are not likely to be significant under normal drinking water conditions (Child *et al.*, 1996; Najm and Trussell, 2001).

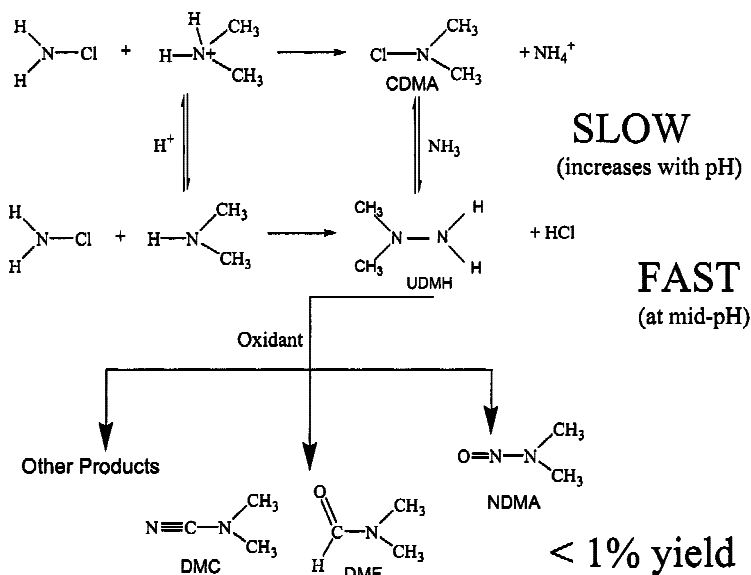


Figure 1. Pathway for NDMA formation during chloramination of dimethylamine via a UDMH intermediate (Mitch and Sedlak, 2002a).

NDMA OCCURRENCE IN DRINKING WATERS, WASTEWATERS, AND RECYCLED WATERS

The discovery of elevated concentrations of NDMA in treated drinking water in Ohsweken, Ontario, in 1989 prompted a survey of 145 Ontario drinking water plants (Jobb *et al.*, 1994; MOE, 1998). This survey indicated that the NDMA concentration in the treated water from most plants was less than 5 ng/L, although some samples exceeded 9 ng/L. Similar results were obtained by the California Department of Health Services during a survey of NDMA concentrations in drinking water systems conducted in 2001 (DHS, 2002). The results showed that 3 of the 20 chloraminated supplies surveyed contained NDMA concentrations greater than 10 ng/L, while none of the eight water supplies that used only free chlorine disinfection exhibited NDMA levels above 5 ng/L. One of the four drinking water supplies surveyed that employ anion exchange treatment also showed NDMA concentrations in excess of 10 ng/L. Other sampling programs confirmed that the majority of treated drinking water samples contain less than 10 ng/L of NDMA (Tomkins *et al.*, 1995; Tomkins and Griest, 1996). No sampling was conducted within water distribution systems, although the concentrations are anticipated to gradually increase in the presence of chlorine or chloramine residuals.

In contrast to results from drinking water treatment plants, effluents from conventional and advanced wastewater treatment plants contain relatively high concentrations of NDMA. NDMA is often present in raw sewage prior to chlorination. For example, NDMA concentrations as high as 105,000 ng/L have been reported in effluents from printed circuit board manufacturers using NDMA-contaminated dimethyldithiocarbamate to remove metals (OCSD, 2002). These industrial inputs resulted in concentrations of NDMA of approximately 1,500 ng/L in raw sewage. As a result of removal processes that occur during secondary treatment, NDMA concentrations in unchlorinated secondary effluent often are less than 20 ng/L, although industrial inputs can lead to large spikes in NDMA influent and effluent concentrations.

Chlorination of secondary wastewater effluent typically results in the formation of between 20 and 100 ng/L NDMA (Mitch and Sedlak, 2002b). Consistent with the UDMH-intermediate mechanism, nitrification of wastewater to completely remove ammonia prior to hypochlorite addition reduces NDMA formation by approximately an order of magnitude (Mitch and Sedlak, 2002e). In wastewater recycling plants receiving secondary wastewater effluent, NDMA concentrations in microfiltration effluent may increase by approximately 30–50 ng/L as a

result of chlorination before the membrane to prevent biological growth (L. McGovern, personal communication). NDMA also has been detected in dried municipal sewage sludge used for agricultural fertilizer, but in this case the formation pathway may be biologically mediated nitrosation during anaerobic digestion (Brewer *et al.*, 1980; ATSDR, 1989).

ORGANIC NITROGEN PRECURSORS: SOURCES AND OCCURRENCE

Both of the NDMA formation mechanisms involve reactions between an inorganic, nitrogen-containing species (e.g., N_2O_3 , NH_2Cl) and an organic nitrogen species. Not surprisingly, dimethylamine has been demonstrated to be the most effective organic nitrogen precursor of NDMA formation by both the nitrosation pathway (Fiddler *et al.*, 1972) and the UDMH pathway (Mitch and Sedlak, 2002b). Both pathways also can produce NDMA from tertiary amines containing dimethylamine functional groups (e.g., trimethylamine and dimethylethanolamine) but at lower yields. Nitrosation of trimethylamine-*N*-oxide, a common constituent of urine (Zuppi *et al.*, 1997), resulted in some NDMA formation, but much less than did trimethylamine (Fiddler *et al.*, 1972). Many other organic nitrogen-containing molecules, including the primary amine monomethylamine, the quaternary amine tetramethylamine, and amino acids or proteins, did not form significant concentrations of NDMA after chloramination (Mitch and Sedlak, 2002b). Fiddler *et al.* (1972) found that nitrosation of quaternary amines that contained trimethylamine functional groups resulted in four orders of magnitude lower NDMA concentrations than did trimethylamine. Significant organic nitrogen precursors for NDMA formation therefore appear to be limited to dimethylamine and tertiary amines with dimethylamine functional groups.

The lower yields of NDMA from species other than dimethylamine are not unexpected given the need to break a C—N bond prior to NDMA formation. In the case of the nitrosation pathway, Ohshima and Kawabata (1978) described a complex reaction scheme for NDMA formation from trimethylamine-*N*-oxide and trimethylamine that accounts for the dealkylation required to form the dimethylamine portion of NDMA using the proposed pathways of earlier researchers such as Smith and Loeppky (1967) and Lijinsky and Singer (1975). A dealkylation scheme for NDMA formation during chloramination of tertiary amines containing dimethylamine functional groups may involve chlorine transfer to the nitrogen atom followed by elimination of HCl to form an iminium ion (Ellis and Soper, 1954). Hydrolysis of the

iminium ion results in formation of the secondary amine. Finally, Mitch and Sedlak (2002b) demonstrated that chloramination of other secondary amines or tertiary amines containing functional groups other than dimethylamine resulted in the formation of their respective nitrosamines in quantities similar to those associated with NDMA formation from dimethylamine and trimethylamine.

Dimethylamine is present in food, and can be liberated from food during digestion (Tricker *et al.*, 1994). Nitrogen-containing organic molecules, such as the cell membrane structural lipid phosphatidyl choline (lecithin) and amino acids, are broken down by bacterial flora in the gastrointestinal tract to trimethylamine (Simenhoff *et al.*, 1976; Tricker *et al.*, 1994). After absorption into the bloodstream, a portion of the trimethylamine is demethylated to dimethylamine and excreted via the urine, gastric juice, or bile. The remainder is oxidized to trimethylamine-*N*-oxide, which is excreted in the urine in concentrations usually twice as high as those of dimethylamine (Zuppi *et al.*, 1997). Tricker *et al.* (1994) found that dimethylamine is present in human urine (average concentration is approximately 40 mg/L) and feces (average concentration is 0.41 $\mu\text{g}/\text{mL}$). Dimethylamine also has been detected in the feces of dairy cattle (van Rheen, 1962).

Amines also are produced outside of the body by microbes via the vitamin B₆-mediated degradation of amino acids (Metzler, 1977). Ayanaba and Alexander (1974) demonstrated that addition of relatively high concentrations of trimethylamine or tetramethylthiuram disulfide (thiram) to lake water or municipal sewage resulted in the microbiological production and eventual consumption of dimethylamine. Trimethylamine-*N*-oxide is present in seafood, and may be broken down to trimethylamine by bacteria (Ohshima and Kawabata, 1978).

As a result of excretion and industrial activities, dimethylamine concentrations in primary wastewater effluent typically range from 20 to 80 $\mu\text{g}/\text{L}$ (Mitch and Sedlak, 2002c). Dimethylamine is readily degraded by bacteria. As a result, concentrations in secondary wastewater effluents are generally low (i.e., average = 4 $\mu\text{g}/\text{L}$; Mitch and Sedlak, 2002c). Mitch and Sedlak (2002c) concluded that dimethylamine could only account for approximately 10% of the NDMA formed when secondary wastewater effluent was chloraminated. However, other authors, using a less sensitive HPLC method, have found no significant loss of dimethylamine upon secondary biological treatment (Hwang *et al.*, 1995; Abalos *et al.*, 1999).

In unpolluted waters, dimethylamine concentrations are generally less than 0.1 $\mu\text{g}/\text{L}$ (Gerecke and Sedlak, 2003). These concentrations can not account for NDMA

formation during chlorination (Mitch *et al.*, 2003). However, dimethylamine, methylamine and morpholine were detected at concentrations up to 3 $\mu\text{g}/\text{L}$ in the Rhine and Elbe Rivers in Germany (Sacher *et al.*, 1997) where the input of wastewater effluents may be significant. Under these conditions, dimethylamine from unintentional reuse of municipal wastewater effluent could be an important NDMA precursor.

Resins used in water and wastewater treatment also may be sources of dimethylamine and other organic nitrogen-containing NDMA precursors. NDMA itself may be a contaminant of carbonaceous resins and activated carbon at levels up to approximately 10 $\mu\text{g}/\text{kg}$ (Kimoto *et al.*, 1981). Najm and Trussell (2001) found that extraction of strong-base anion-exchange resins containing dimethyl-ethanol or trimethyl quaternary functional groups with distilled water in the absence of chlorine resulted in concentrations of NDMA up to approximately 50 ng/L. Moreover, while NDMA was not detected in effluent from resins containing triethyl or tripropyl functional groups, *N*-nitrosodiethylamine and *N*-nitrosodi-*n*-propylamine were detected, respectively (Najm and Trussell, 2001). NDMA precursors can leach from functional groups on quaternary amine-containing exchange resins (Cohen and Bachman, 1978; Kimoto *et al.*, 1980; Najm and Trussell, 2001). At elevated temperatures (i.e., 78°C), some of the quaternary amine functional groups on resins demethylate to form trimethylamine (Fiddler *et al.*, 1972).

Resins and granular activated carbon may promote NDMA formation by surface-catalyzed reactions. Angeles *et al.* (1978) suggested that mixed bed resins promote nitrosation of precursors because proton displacement on cationic resins creates acidity, which promotes nitrosation reactions on adjacent anionic resins (usually containing amine precursors) to which nitrite may adsorb. An enhancement of nitrosation reactions was observed when a nitrifying biofilm was active on granular activated carbon (DiGiano *et al.*, 1986), possibly as a result of biological catalysis. However, NDMA formation by this pathway is unlikely to be significant under typical drinking water treatment conditions.

Other industrial products containing dimethylamine functional groups that could serve as precursors include fungicides such as thiram (tetramethylthiuram disulfide) (IARC, 1978) Graham *et al.*, 1995), pesticides, and herbicides such as 2,4-D, which are formulated as a dimethylamine salts (Fine, 1978; Child *et al.*, 1996), drugs such as ranitidine (IARC, 1978), and amine-containing accelerators for vulcanization of tires (Fig. 2). The dithiocarbamates, which are a family of compounds used as fungicides, herbicides, and as chelating agents to remove cationic metals from industrial wastewater, contain

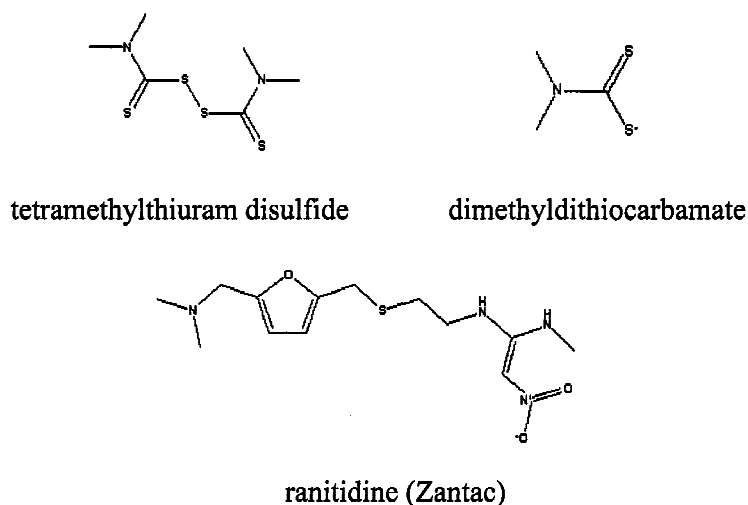


Figure 2. Industrial products that could be precursors for NDMA formation: the pesticide tetramethylthiuram disulfide (thiuram), the fungicide, herbicide, and metal chelator dimethyldithiocarbamate (DTC), and the H-2 receptor antihistamine pharmaceutical ranitidine (Zantac).

readily hydrolyzable dimethylamine functional groups (Weissmahr and Sedlak, 2000).

Amine-based polymers (Child *et al.*, 1996; MOE, 1998; Najm and Trussell, 2001) and unknown contaminants of alum (Jobb *et al.*, 1994) also have been identified as sources of NDMA precursors. In the case of wastewater treatment, treatment polymers containing dimethylamine groups become associated with particles, and can form a significant fraction of the total organic nitrogen precursors during wastewater treatment (S. Carr, personal communication).

TREATMENT

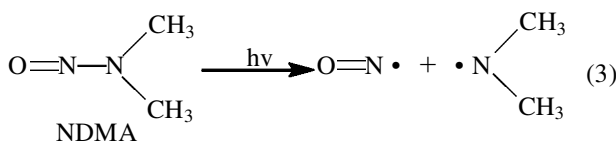
Removal of NDMA

The vapor pressure of NDMA is estimated to be relatively high at 360 Pa at 20°C (Klein, 1982). Due to the high water solubility of NDMA, the estimated Henry's Law constant for NDMA is low at $2.6 \times 10^{-4} \text{ atm M}^{-1}$ 20°C (ATSDR, 1989; Mirvish *et al.*, 1976). Therefore, volatilization from natural waters and air stripping are unlikely to result in significant removal of NDMA from solution. As a small, uncharged molecule, NDMA is poorly removed via reverse osmosis membranes. Within wastewater recycling plants, NDMA was removed with approximately 50% efficiency by thin-film composite reverse osmosis membranes (L. McGovern, personal communication).

Due to the presence of polar functional groups, NDMA is hydrophilic, with a $\log K_{ow}$ value of -0.57 (ATSDR, 1989). As a result, NDMA sorbs poorly to soil, activated

carbon, and other sorbents. Bituminous coal granular-activated carbon was used in interceptor trenches to remove NDMA arising from groundwater contamination at the Rocky Mountain Arsenal (Fleming *et al.*, 1996). Fleming *et al.* (1996) found that sorption onto hydrophilic sorbents such as silica, acrylic resins, and zeolite were insignificant. Amborsorb 572 carbonaceous resin was found to be the most effective sorbent, followed by coconut shell carbon. However, the Freundlich isotherm K and $1/n$ constants for Amborsorb 572 ($9.65 \times 10^{-3} \text{ mg/g}$ and 1.17, respectively) were low, which resulted in prohibitive treatment costs. Consistent with these observations, the transport of NDMA was not retarded through soil columns (Dean-Raymond and Alexander, 1976).

Currently, the most commonly applied aqueous NDMA treatment method is photolysis by ultraviolet (UV) radiation. NDMA absorbs light strongly between 225 and 250 nm (Fig. 3; $\lambda_{max} = 228 \text{ nm}$ where $\epsilon = 7380 \text{ M}^{-1} \text{ cm}^{-1}$). This wavelength is at the lower end of the transparency of water to UV. The absorption results in a π to π^* transition (Polo and Chow, 1976; Stefan and Bolton, 2002) followed by cleavage of the N—N bond, most likely via hydrolysis to dimethylamine and nitrous acid, or by forming nitroso and dimethylamine radicals (reaction 3).



The major products of the reaction are dimethylamine and nitrite, while minor products include nitrate, for-

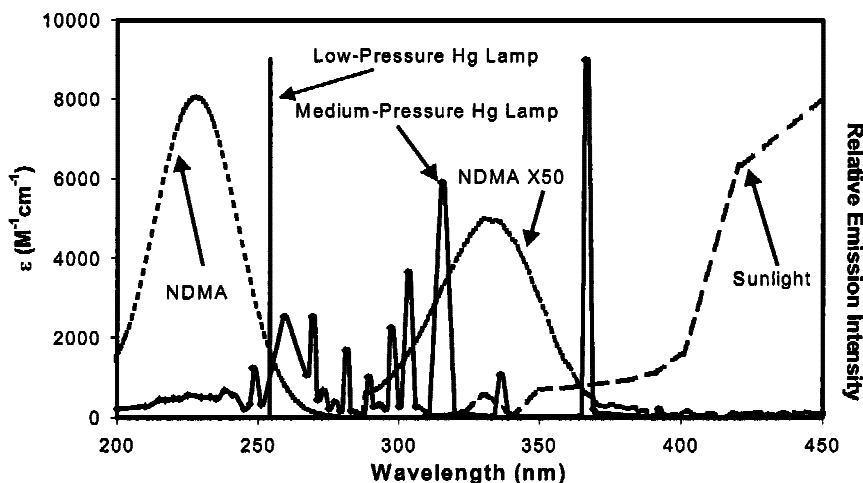


Figure 3. Emission spectra for low- and medium-pressure mercury lamps, sunlight spectrum at the surface of the Earth and absorption spectrum of 1 μM NDMA.

maldehyde, formate, and perhaps methylamine (Stefan and Bolton, 2002). The quantum yield at pH 7 is 0.13 (Stefan and Bolton, 2002). Dimethylamine is resistant to further photolytic reactions, while nitrite is readily oxidized to nitrate. NDMA also has a secondary absorption peak between 300 and 350 nm ($\lambda_{\text{max}} = 332$ nm, where $\epsilon = 109 \text{ M}^{-1} \text{ cm}^{-1}$) within which excitation occurs via an n -to- π^* transition (Stefan and Bolton, 2002). This secondary peak overlaps well with the intensity of UV produced by medium-pressure mercury lamps (Stefan and Bolton, 2002). However, whether low- or medium-pressure lamp systems are more efficient for NDMA destruction is still unclear. Under conditions typically encountered in drinking water treatment systems, the UV dosage required for a one order of magnitude decrease in NDMA concentration is approximately 1,000 mJ/cm^2 , which is approximately 10 times higher than that required for equivalent virus removal. Therefore, UV treatment for NDMA will be feasible but more expensive than UV treatment for disinfection.

UV treatment has been used to remove NDMA at a drinking water plant in Ohsweken, Ontario (Jobb *et al.*, 1994), in effluent from a tire factory upgradient of the Ohsweken plant (Ash, 1995), and at Water Factory 21 in Orange County, CA (OCWD, 2000a). Three technologies have been used for UV treatment of NDMA: low-pressure UV lamps emitting mainly monochromatic light at 254 nm, medium-pressure lamps emitting polychromatic light, and pulsed UV systems. Pulsed UV systems have the advantage of an emission spectrum that more closely matches the adsorption spectrum of NDMA (Liang, 2002). However, the technology is less proven than low- and medium-pressure UV lamps.

Because UV photolysis may not destroy NDMA precursors, some have suggested that reformation of NDMA may occur within drinking water distribution systems if chlorination is performed after the UV treatment (Jobb *et al.*, 1994). However, the concentration of dimethylamine liberated when low concentrations of NDMA are photolyzed usually will be small. If significant concentrations of NDMA are formed upon chlorination following UV treatment, the formation likely results from other NDMA precursors. Addition of hydrogen peroxide to generate hydroxyl radical for NDMA oxidation does not significantly increase NDMA destruction efficiency (Jobb *et al.*, 1994; Liang, 2002).

Photolysis of NDMA also occurs in sunlight as a result of NDMA's secondary absorption band between 300 and 350 nm. Sunlight photolysis was used by the OCWD as part of their initial attempt to reduce concentrations of the compound at Water Factory 21; placing treated water in shallow sunlit basins with residence times of approximately 1 day resulted in removal of approximately half of the NDMA (M. Wehner, personal communication). Sunlight photolysis also may be an important loss mechanism for NDMA applied in irrigation water (ATSDR, 1989).

Atmospheric photolysis of NDMA removes NDMA from the sunlit atmosphere within a few hours (Shapley, 1976; Hanst *et al.*, 1977; Cohen and Bachman, 1978; Tuazon *et al.*, 1984). NDMA is believed to decay via equation (1) with a quantum yield of 1 for $\lambda \geq 290$ nm (Tuazon *et al.*, 1984). The major product is dimethylnitramine via the reaction of NO_2 with the dimethylamino radical. Lesser products include formaldehyde and methylnitramine. The half-life for the atmospheric reac-

tion of NDMA with hydroxyl radical was estimated to be approximately 3 days compared with only 5 min for direct photolysis (Tuazon *et al.*, 1984).

Ozone does not appear to react with NDMA by a direct mechanism either in the atmosphere (Tuazon *et al.*, 1984) or in water (Liang, 2002). Hydroxyl radicals produced from ozone and hydrogen peroxide can be used to treat NDMA (Liang, 2002). However, the efficiency of ozonation and other advanced oxidation processes (AOPs) will be limited by the presence of hydroxyl radical scavengers.

Zero-valent iron catalyzes NDMA transformation by hydrogenation (Gui *et al.*, 2000; Odziemkowski *et al.*, 2000). This reduction reaction leads to the formation of dimethylamine and ammonia as final products. Although a field feasibility study conducted with canisters demonstrated NDMA reduction, the relatively slow kinetics of the reaction suggested that it would not be a cost effective treatment option (Cox, 2002). The addition of 0.25% nickel to the iron increased the reduction rate by nearly a factor of 340. However, the reaction rate for the nickel-iron mixture decreased within 100 pore volumes.

The potential for phytoremediation of NDMA is currently unknown. However, the high aqueous solubility of the compound is well-suited for the treatment. Lettuce and spinach readily took up ^{14}C -labeled NDMA from irrigation water (Dean-Raymond and Alexander, 1976). ^{14}C activity in the plants decreased with time, suggesting that the NDMA was converted to $^{14}\text{CO}_2$ in the plants.

Bioremediation could hold significant potential for the *in situ* treatment of NDMA contaminated water. Bacterial monooxygenase enzymes may be similar to the cytochrome P-450 enzymes that catalyze the NADPH-dependent oxidation of NDMA in both plants and animals (Tu and Yang, 1985; Yamazaki *et al.*, 1992; Stiborova *et al.*, 2000). Mineralization (conversion to CO_2) of NDMA by undefined consortia has been observed in two studies (Kaplan and Kaplan, 1985; Gunnison *et al.*, 2000). Biodegradation also has been reported in anaerobic and aerobic incubations of native microbial soil consortia, with half-lives ranging from 12 to 55 days (Tate and Alexander, 1975; Oliver *et al.*, 1979; Gunnison *et al.*, 2000). Biodegradation proceeded slightly faster under aerobic conditions than under anaerobic conditions (Mallik and Tesfai, 1981). In two cases, the NDMA biodegradation rate may have slowed after the first few weeks of NDMA application (Tate and Alexander, 1975; Mallik and Tesfai, 1981); however, these studies suffered from poor quantification of the effect of confounding factors such as volatilization (ATSDR, 1989). Although these studies documented degradation intermediates, including methylamine and formaldehyde, none of these studies was able

to identify the responsible micro-organisms nor elucidate degradation pathways.

Despite the existence of NDMA-degrading bacteria in soil, there is limited evidence for the biodegradation of NDMA under field conditions. For example, at the Rocky Mountain Arsenal, no significant loss of NDMA was observed during passage through the aquifer (Gunnison *et al.*, 2000). However, after groundwater was passed through an *ex situ* granular activated carbon (GAC) treatment system and reinjected into the subsurface, NDMA removal was observed. Because NDMA adsorption to GAC is negligible, the GAC at the Rocky Mountain Arsenal site may have removed competitive substrates from solution, allowing NDMA biodegradation to proceed. In another study, the addition of glucose or nutrient broth to microcosms hindered NDMA mineralization, indicating that substrate competition may occur (Kaplan and Kaplan, 1985). It is likely that a complex interaction exists between dissolved organic nutrients necessary for the growth of bacteria capable of degrading NDMA and a tendency of these micro-organisms to consume these nutrients in preference to NDMA. In addition to the lack of clear evidence for bioremediation of NDMA in groundwater, there is no information regarding the potential for biological removal of NDMA within drinking water treatment systems such as biofiltration units.

Removal of NDMA precursors

Unlike NDMA, many nitrogen-containing NDMA precursors, including dimethylamine and trimethylamine, are charged at circumneutral pH. Precursors may therefore have significantly different properties than NDMA. As a result of their protonation, precursors should be even less susceptible to treatment by air stripping or adsorption compared to NDMA. Hwang *et al.* (1994) found that dimethylamine and other aliphatic amines were removed poorly by sorption to granular activated carbon (Freundlich isotherm constants for dimethylamine onto Calgon F-400 GAC were $K = 7.73$ mg/g and $1/n = 0.26$).

Although direct photolysis of NDMA is an effective treatment technique, the lack of the nitroso functional group on the nitrogen-containing precursors may make precursors unreactive. Hwang *et al.* (1994) found that the reaction of dimethylamine with ozone was slow. However, there are preliminary indications that hydroxyl radicals formed in UV-hydrogen peroxide or ozone-hydrogen peroxide systems can remove NDMA precursors (Liang, 2002).

NDMA precursors are readily removed by biological treatment. Secondary biological treatment of municipal

wastewater was found to reduce NDMA precursors in wastewater by an average of 60%, and to reduce dimethylamine concentrations by at least an order of magnitude (Mitch and Sedlak, 2002c). Although biological nitrification and denitrification reduced NDMA formation during application of hypochlorite by precluding monochloramine formation, these extended biological treatments were not found to significantly reduce organic NDMA precursor concentrations (Mitch and Sedlak, 2002c). Typical secondary treatment systems appear capable of removing the majority of biodegradable precursors.

NDMA precursors also are removed in advanced treatment systems. Microfiltration reduces the concentration of particle-associated NDMA precursors in activated sludge wastewater effluent (Mitch and Sedlak, 2002c). Reverse osmosis treatment reduces NDMA precursor concentrations by at least an order of magnitude, removing not only colloidal NDMA precursors, but also charged, dissolved precursors such as protonated dimethylamine.

AREAS OF FUTURE RESEARCH

As indicated by this review, a substantial amount of research has been performed on the source, behavior, and treatment of NDMA. However, additional research needs to be performed to develop more cost-effective means of minimizing NDMA exposure. Several research needs are listed below:

- Characterization of other *N*-nitroso compounds and other products formed from the reaction of organic nitrogen and monochloramine should be performed.
- Characterization of the precursors responsible for NDMA formation during chlorination of drinking water should be elucidated better. In particular, additional research is needed to determine the relative importance of NDMA formation during passage of water through ion exchange units or during post-treatment chlorination of precursors leached from ion exchange units relative to precursors from other sources.
- Characterization of organic nitrogen-containing NDMA precursors during wastewater treatment is needed. Only about 10% of the formation of NDMA from organic nitrogen precursors in the low molecular weight fraction of secondary wastewater effluent can be accounted for by dimethylamine. Other dissolved precursors in wastewater must be identified. In addition, the role of treatment polymers as potential NDMA precursors should be explored.

- Methods are needed to improve the removal of organic nitrogen-containing NDMA precursors prior to chlorination.
- NDMA formation did not occur during ozone disinfection (Najm and Trussell, 2001). However, an investigation regarding the effect of ozonation on NDMA precursors should be undertaken because monochloramine may be applied to maintain a disinfection residual following ozonation. Furthermore, the ability of alternative disinfectants such as chlorine dioxide to form NDMA should be investigated.
- Measurement of the quantum yield for aqueous NDMA photolysis by sunlight is needed to predict the rate of removal of NDMA upon sunlight exposure in infiltration basins, during irrigation or in surface waters.
- The uptake of NDMA by plants and its subsequent fate should be further evaluated to determine the potential for phytoremediation.
- The pathway for microbial degradation of NDMA and the associated kinetics should be evaluated to identify conditions conducive to *in situ* bioremediation. The potential for NDMA removal in biofiltration treatment units should be evaluated as a treatment strategy in drinking water treatment plants.

ACKNOWLEDGMENTS

We thank Mr. Timothy Durbin for help with this manuscript. Support for Mr. Bill Mitch was provided by the WaterReuse Association and the National Water Research Institute. Support for Mr. Jonathan Sharp was provided by funding from the University of California Toxics Substances Research and Teaching Program and by NIEHS Grant ES04705.

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