

Drinking water as a source of human exposure to xenobiotics: The case of disinfection by-product N-nitrosodimethylamine (NDMA)

Andrea I. Schäfer¹, William Mitch², Sophie Walewijk³, Albert Munoz⁴, Emma Teuten¹, Martin Reinhard³

¹ School of Engineering, University of Edinburgh,
Edinburgh, EH9 3JL, UK
Phone: +44 (0)131 650 7109, Fax: +44(0) 131 650 6781

E-mail: andrea.schaefer@ed.ac.uk
² Department of Chemical Engineering, Yale University, New Haven, CT 06520
Phone: 203-432-4386, Fax: 203-432-4387

E-mail: william.mitch@yale.edu
³ Department of Civil and Environmental Engineering, Stanford University, Stanford, California 94305-4020
E-mail: reinhard@stanford.edu

⁴ Environmental Engineering, University of Wollongong, NSW 2125, Australia

Abstract

One of the most concerning xenobiotics currently under discussion by regulators and treatment experts is N-Nitrosodimethylamine (NDMA). NDMA is a carcinogen known to induce cancer in a variety of animals, causing DNA damage at low doses. Human exposure occurs through cigarettes, food, personal care products and drinking water, in addition to endogenous formation in the stomach.

The daily tolerable limit for intake has been identified to be 4.0 - 9.3 ng/kg.day (Fitzgerald and Robinson 2007). Water at the WHO proposed guideline value of 100 ng/L would contribute about 2.9 ng/kg.day of this intake, while intake from food varies from 5.7 – 44.2 ng/kg.day. Smoking and workplace are additional exposure routes. This outlines that the exposure is often higher than tolerable limits. In the food and drinks industry this has in recent decades resulted in improved manufacturing processes.

Awareness of NDMA in drinking water is a relatively recent issue. NDMA stems from precursors in raw water and can be generated during treatment. Generally removal of precursors is more achievable than the removal of NDMA itself. For example, the potent NDMA precursor dimethylamine is rapidly removed in biological pre-treatment, while many other precursor amines are more persistent. These precursor amines include some ion exchange resins and coagulants, used in water treatment processes, which have been shown to generate NDMA during chlorination. Ozonation has also been shown to produce NDMA in treatment. UV oxidation is the preferred method for removal of NDMA in water treatment, although reverse osmosis membranes are possible alternatives if effective retention can be achieved.

Keywords: N-Nitrosodimethylamine (NDMA), membrane filtration, advanced oxidation, regulation, risk assessment, exposure.

1 INTRODUCTION

N-Nitrosodimethylamine (NDMA) is an environmental contaminant that has been shown to initiate cancer through methylation of DNA in animal studies. While it has not been definitively identified as a human carcinogen, incidents of certain types of cancer were, as an example, significantly higher in rubber workers with high exposure to NDMA, than in workers with lower exposure. NDMA is classified as a 'probable human carcinogen' by the

International Agency for Research on Cancer (World Health Organization International Agency for Research on Cancer 1987).

Human exposure to NDMA is typically assumed to occur through exposure to food, cosmetics, cigarette smoke and industrial exposure. Little attention was given to the presence of NDMA in drinking water until the early 1990s, following its detection in the water supply in Ohsweken, in Ontario, Canada (Jobb et al. 1993). Subsequent routine monitoring indicated a persistent, fluctuating presence. Following the detection of NDMA in drinking water wells near rocket engine testing facilities in California, a statewide survey of drinking water facilities indicated that NDMA can form as a disinfection byproduct (Mitch et al. 2003). More widespread analyses at drinking water facilities, predominantly in North America, have revealed that NDMA is often present above the detection limit at facilities practicing chloramination, albeit with mean concentrations typically below 10 ng/L (Charrois et al. 2007). Surveys across the world are currently in progress and NDMA is found in many locations.

Despite a recent analysis by Fristachi and Rice (Fristachi and Rice 2007) suggesting that <1% of the dietary contribution of NDMA originates from water, there has been a surge of interest in NDMA in drinking water. Meta analyses have indicated that long term consumption of chlorinated drinking water is associated with an increased risk of cancers of the bladder, colon, rectum oesophagus and breast (Doyle et al. 1997, Koivusalo et al. 1997, Villanueva et al. 2005). The exact agent responsible for this increased cancer risk is uncertain, although carcinogenic nitrosamines cannot be ruled out and the application of the precautionary principle is advisable.

While generally viewed as a contaminant of concern, concentrations of NDMA in drinking water are regulated in few countries. Only the governments of California, USA, and Ontario, Canada have set tolerable limits of 10 ng/L and 9 ng/L, respectively. The World Health Organisation (WHO) is currently considering a guideline value of 100 ng/L, which is the calculated health-based value (HBV) associated with an upper-bound excess lifetime cancer risk of 10⁻⁵ (World Health Organization 2006). A consequence of regulation is the requirement to remove NDMA from drinking water supplies.

This chapter summarises the human sources of NDMA, putting recent exposure into a historical context. Sources and concentrations of NDMA in drinking water are described and the potential impact of NDMA in drinking water on human health is discussed. The discussions are intended to give a thorough case study of the issues surrounding xenobiotics well as an assessment of the relative risk of such compounds through water intake.

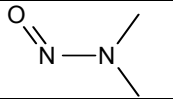
2 CHARACTERISTICS, FORMATION AND SOURCES OF NDMA

2.1 Chemical and physical properties of NDMA

N-nitrosodimethylamine (NDMA) belongs to the family of compounds known as nitrosamines and is the simplest dialkyl nitrosamine. Table 1 presents the physico-chemical properties of NDMA.

Table 1 Physico-chemical properties of NDMA.

Physical/chemical Property	Unit	Value	Reference
Formula		C ₂ H ₆ N ₂ O	(United States Environmental Protection Agency 1980)

Chemical Structure			(Ontario Ministry of the Environment 1991)
Molecular Weight	g/mol	74.08	(Weast 1983)
Vapour Pressure (at 25°C)	Pa	1080	(Weast 1983)
Henry's law constant (at 25°C)	Pa.m ³ /mol	3.34	(Mirvish et al. 1976)
Octanol Water Partition coefficient	Log K _{ow}	-0.57	(Hansch and Leo 1985)
Organic Carbon Water Partition coefficient	Log K _{oc}	1.07	(Thomas 1982)

2.2 Formation Pathways of NDMA

There are three formation pathways of greatest relevance to food and drinking water:

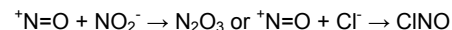
- Acid-nitrite or NO_x nitrosation in food products
- Dichloramine-oxygen pathway during drinking water chloramination
- Free chlorine-nitrite pathway during chlorination in of nitrite-rich waters

Other pathways have been identified, including the ozonation of a specific fungicid degradation product (Schmidt and Brauch 2008) and formation associated with radicals generated during breakpoint chlorination (Schreiber and Mitch 2007). However, these are likely of limited importance.

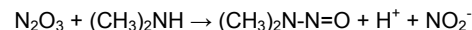
Acid-nitrite or NO_x nitrosation in food products: The nitrosation mechanism has been used to explain endogenous nitrosamine formation during ingestion of meats preserved with nitrite (Mirvish 1971). The nitrosyl cation (*N=O) forms from acidification of nitrite in the stomach:



The nitrosyl cation is partially stabilized by interaction with anions, including nitrite and chloride:



These partially stabilized forms of nitrosyl cations are highly potent nitrosating agents, that transfer nitrosyl cations to the lone pairs of amines in the rate-limiting step for nitrosamine formation (Casado et al. 1996):



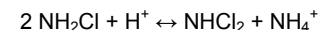
Formation rates were maximized near pH 3.4 (Mirvish 1971). Elevated anion concentrations, including the saliva constituent thiocyanate, were found to enhance formation rates (Fan and Tannenbaum 1973). Due to the pH dependency of the reaction, this formation mechanism would not be important for drinking water disinfection, even in the presence of elevated anion concentrations.

Nitric oxide (NO) and nitrogen dioxide (NO₂) in air pollution can form N₂O₃. Dissolution of N₂O₃ into amine-containing solutions can rapidly form nitrosamines.

Dichloramine-oxygen pathway during chloramination: Early research recognized the association between chloramination (used in treatment as well as distribution systems in various countries) and nitrosamine formation. However, attempts were made to link this formation with monochloramine, the predominant chloramine species under typical chloramination conditions (Choi and Valentine 2002, Mitch and Sedlak 2002). Briefly, this research suggested that monochloramine reacted with dimethylamine to form NDMA via

an unsymmetrical dimethylhydrazine (UDMH) intermediate over the course of days at overall yields of <3%.

However, noting that, chloramination of dimethylamine formed much more NDMA than did chloramination of UDMH, more recent research has indicated that nearly all nitrosamine formation could be explained by a reaction of dichloramine with organic amine precursors (Schreiber and Mitch 2006). This pathway posits a reaction between dichloramine and unchlorinated dimethylamine to form a chlorinated UDMH intermediate. Oxidation of the intermediate by chloramines to form uncharacterized products competes with oxidation with dissolved oxygen to form NDMA. Under typical chloramination conditions, monochloramine is the predominant species, yet dichloramine is always present according to the equilibrium:



The dichloramine model was robust over a variety of conditions and could even account for NDMA formation when preformed monochloramine was applied to dimethylamine solely from the traces of dichloramine that formed from disproportionation of monochloramine.

Free chlorine nitrite pathway. Previous research suggested that chlorination in the presence of nitrite would form a ClNO₂ intermediate (Choi and Valentine 2003). Reaction of ClNO₂ with nitrite would form the nitrating and nitrosating agent, dinitrogen tetroxide (N₂O₄). NDMA and dimethylnitramine formed simultaneously and rapidly during chlorination in the presence of nitrite and dimethylamine (Schreiber and Mitch 2007).

However, this pathway is less relevant to drinking water systems as free chlorine and nitrite rarely coexist in these systems. In nitrifying sections of distribution systems, the practice of boosting the free chlorine dose may promote nitrosamine formation via this pathway. On the other hand, both dimethylnitramine and NDMA were observed in chlorinated pools, with dimethylnitramine concentrations correlating with nitrite concentrations (Walse and Mitch 2008).

2.3 Precursors for and occurrence, and fate of NDMA in drinking water and wastewater facilities

The specific identity of NDMA precursors has not been identified. However, while organic nitrogen is elevated in water impacted by both wastewater and algal blooms (Westerhoff and Mash 2002), NDMA precursors are particularly associated with municipal wastewater-impacted water supplies (Gerecke and Sedlak 2003, Mitch and Sedlak 2004). Dimethylamine was reduced to <2 nM concentrations via biological wastewater treatment, such that it was not an important precursor (Mitch and Sedlak 2004). Tertiary amines would be degraded to secondary amines via all three of the most important NDMA formation pathways (Mitch and Schreiber 2008). However, although trimethylamine, like dimethylamine, is a urine constituent, trimethylamine was also removed readily by biological wastewater treatment.

As a class, tertiary amines with dimethylamine functional groups were determined to be potent NDMA precursors (Mitch and Sedlak 2004). However, specific tertiary amines with dimethylamine functional groups that may be responsible for NDMA formation within wastewater-impacted drinking water supplies have not been identified.

More recently, ozonation has been associated with significant levels of NDMA formation (Kosaka et al. 2009). Reported values before and after ozonation were 16-290 and 14-280 ng/L, respectively. Some sources were attributed to industrial effluents which resulted in an extremely high concentration of 10 000 ng/L in one case.

Although their permanent positive charges renders them unlikely to react with oxidants, quaternary amine polymers used as coagulants (Mitch and Sedlak 2004, Park et al. 2009) and for anion exchange resins (Kemper et al. 2009) during water treatment have been noted as NDMA precursors. Whether the NDMA formation results from reactions with quaternary amine functional groups or tertiary or secondary amine impurities in the treatment polymers is unclear.

In contrast to the long history of NDMA measurements in food, concentrations of NDMA in drinking waters have only been measured since the 1990s. Some reported values are shown in Table 2. While the mean concentrations are low, concentrations have exceeded 100 ng/L following disinfection. However, in most situations utilities cognizant of elevated NDMA concentrations have employed remedial techniques to reduce NDMA concentrations supplied to the consumer. Dillon et al (Dillon et al. 2008) have surveyed a number of UK drinking waters and detected concentrations of up to 5.8 ng/L. Those numbers are consistent with river water concentrations detected in Japan (Asami et al. 2009).

Table 2 Concentrations of NDMA reported in drinking water.

Location	Date	[NDMA] (ng/L)		Treatment method	Reference
		range	mean		
Water Factory 21, California, USA	2001	nd - 200	7 ± 16	UV	(Orange County Water District 2001)
Ohswaken, Ontario, Canada	1994	nd - 52	3 ± 8	UV	(Ontario Ministry of the Environment and Energy 1994)
Alberta, Canada	2004	nd - 12 ± 4		Chloramination	(Charrois et al. 2007)
Alberta, Canada	2004	nd - 100 ± 9		Chlorination	(Charrois et al. 2007)

In a recent survey, untreated wastewater was shown to contain a median NDMA concentration of 80 ng/L (Sedlak et al. 2005). NDMA occurrence in wastewater is particularly significant in cases where water of wastewater origin percolates into aquifers used as drinking water supply or where wastewater is treated such that it can be directly injected into potable aquifers (Anderson 2003, Drewes et al. 2008, Mitch et al. 2003, Sedlak and Kavanaugh 2005). For example, 50% of the water produced by Orange County Sanitation District Plant 1 augments potable water supplies (Sedlak and Kavanaugh 2005). Other cases are found in Virginia and Texas, and in Namibia and South Africa (Anderson 2003).

2.4 Origin and Occurrence of NDMA in food, drinks and cigarette smoke

High concentrations of nitrosamines were widely reported in foods in the 1970s, particularly in cured meats and fish, cheese, beer and dried milk (Lijinsky 1999). Since NDMA is a potent liver carcinogen, this was good reason for concern. Subsequently, the mechanisms for NDMA formation in these foods were determined. Those are nitrosation of naturally occurring amine by sodium nitrite (a preservative added to fish, meat and cheese), or by gaseous nitrogen oxides (formed during flue drying of milk and malt used in brewing). Once the routes to NDMA formation in food were understood, steps were taken to reduce its presence. Consequently, the NDMA levels reported in these foods stuffs has been significantly reduced. As an example, Table 3 compares early reports of NDMA concentrations in food, with those measured more recently. Reports from the 1990s - 2000s show more than an order of magnitude less NDMA than studies from the 1970s - 1980s. Preparation methods are important, for example, cooking meat at high

temperatures (frying or baking) gives a significant increase in NDMA (Yurchenko and Mölder 2007).

Synergistic effects of dietary components may increase the likelihood of tumours arising from NDMA. Alcohol and high diets rich in fats have been shown to increase the occurrence of liver tumours in laboratory animals fed NDMA (Anderson et al. 1992, Hietanen et al. 1990). Furthermore, cadmium in the diet has been shown to promote NDMA carcinogenesis (Wade et al. 1987).

Table 3 Concentrations of NDMA reported in foods.

Product	Unit	Year	NDMA Concentration		Reference
			range	mean	
Cured fish	ng/g	1971 2001 - 2005	nd - 26	0.54 - 1.99	(Fazio et al. 1971) (Yurchenko and Mölder 2007)
Cured meat	ng/g	1975 2004	nd - 35	7.3 ± 0.93	(Sen et al. 1975) (Byun et al. 2004)
Bacon	ng/g	1973 1993 -1994	nd - 30 nd - 3		(Sen et al. 1973) (Glória et al. 1997a)
Cheese	ng/g	1978 1995	nd - 68 nd - 0.84	0.28	(Gough et al. 1978) (Dellisanti et al. 1996, Glória et al. 1997a)
Dried milk	ng/g	1981	0.45 - 4.2	1.69 ± 0.17	(Lakritz and Pensabene 1981)
Beer	ng/L	1995 1978 - 1979 2000 - 2006	nd - 0.18 nd - 78,000 nd - 660		(Oliveira et al. 1995) (Lachenmeier and Fúgel 2007) (Lachenmeier and Fúgel 2007)

Many studies indicate that endogenous NDMA formation from amines and nitrites/nitrates in the stomach is important, and the contribution of endogenous NDMA formation was estimated to be significant by Fristachi and Rice (Fristachi and Rice 2007). This occurs because nitrates are reduced to nitrites in the oral cavity, and many amines in foods are rapidly nitrosated in the presence of nitrite, under the acidic conditions pertaining to the stomach. Nitrosamines can also form from bacterial nitrosation of amines. However it is very difficult to accurately estimate endogenous NDMA formation. This has consequences on the intake of nitrites and nitrates in drinking water also, for which health effects are currently unknown.

In vitro experiments frequently use excessively high nitrite concentrations, making extrapolation to realistic physiological concentrations complicated. Investigation of the endogenous NDMA formation *in vivo* is particularly difficult due to its rapid metabolism. Furthermore, co-ingestion of foods rich in some antioxidants, such as strawberries, garlic and green tea, significantly inhibit nitrosation under gastric conditions (Choi et al. 2007, Choi et al. 2002). For example, human excretion of NDMA was 26 times lower following green tea ingestion. These factors make predicting endogenous formation of NDMA in humans difficult, and we will not address it further herein.

3 HUMAN EXPOSURE TO NDMA

The daily tolerable limit for NDMA intake has been identified to be 4.0 - 9.3 ng/kg.day using a rat liver tumour study and a range of modifying factors. This translates to 280-650

ng/day for a 70 kg person (Fitzgerald and Robinson 2007). For estimations below a person of 70 kg has been assumed.

3.1 Exposure to NDMA through water

The main source of NDMA in drinking water is from its unwanted formation of a disinfection byproduct. Many disinfection methods, including chlorination, chloramination and ozonolysis, can result in the formation of NDMA. However, the highest concentrations of NDMA are generated during chloramination (up to 100 ng/L), in which the oxidant chloramine nitrosates numerous amines present in water supplies. Recent evidence on ozonation is also indicating high levels of NDMA formation.

Exposure of humans to NDMA from drinking water varies considerably depending on the concentrations in the water supply. While it was recently suggested that on average <1% of the dietary contribution of NDMA originates from its presence in water, some communities are likely exposed to much higher amounts due to high NDMA concentrations in some drinking water supplies, particularly those that treat the water with chloramines.

Considering the recommended consumption of 2 L of water per day, the maximum concentrations shown in Table 2 (200 ng/L which is twice the proposed WHO guideline value) indicate that exposure from NDMA from drinking water would be up to 5.7 ng/kg.day in situations where these concentrations have not been mitigated by further treatment processes. If the WHO guidelines are used for estimations then a maximum of 2.9 ng/kg.day can be expected from water.

In addition to exposure to NDMA in water through ingestion, dermal sorption from water is another possible uptake mechanism. The rate of penetration of NDMA through the skin has been estimated as 10^{-4} cm/h. Assuming a skin surface area of 1.8 m², a 10 minute shower in water containing 200 ng/L NDMA would expose a person to just 0.06 ng of NDMA. High concentrations of NDMA have also been measured in swimming pools and hot tubs (Walse and Mitch 2008). Even when considering the maximum NDMA concentrations reported by Walse and Mitch (Walse and Mitch 2008), a 20 minute exposure is predicted to result in exposure to 0.03 and 0.3 ng NDMA uptake through the skin for swimming and bathing in hot tubs, respectively.

Hence the dermal uptake of NDMA from water is likely negligible compared to other sources, such as food (or drinking water). Uptake of NDMA through open wounds, or inhalation through volatilisation may increase the exposure dose, but this is unlikely to make it significant compared to other exposure routes.

3.2 Exposure to NDMA through food, drinks and smoking

The estimated daily exposure to NDMA from selected food and drinks compared with water and cigarettes is outlined in Table 5. The total daily intake varies from about 400 – 3100 ng/day, which is for a 70 kg person 5.7 – 44.4 ng/kg.day. This is higher than the daily tolerable limit specified above. Fristachi and Rice (Fristachi and Rice 2007) estimated a lower mean daily intake from food of 110 ng/person (1.6 ng/kg.day). Uncertainties remain and improvement in production processes is likely to reduce those figures further. Main contributions are food products, namely bacon/ham, cheese and poultry. Average concentrations of NDMA are in the order of 1 µg/kg for meat products (Biaudet et al. 1994), which can be used to estimate exposure based on consumption. Munoz has summarised reported values from various sources including detailed assessment of food types extensively (Munoz 2005). Figures vary widely depending on nationality (see Table 4) given different dietary habits. The relative toxicity of NDMA consumed in food compared to that from water is uncertain, although an article published in 1956 reported that NDMA administered in the basal diet was more potent than that in drinking water.

Table 4 Estimation of daily intake of NDMA in various countries (adapted from (Biaudet et al. 1994, Tricker et al. 1991)).

Country	NDMA* (ng/kg.day)	Major NDMA source (% contribution)	Reference
United Kingdom	7.6	Cured meats (81%) ¹	(Gough et al. 1978)
	8.6	Beer, cured meats	(Ministry of Agriculture Fisheries and Food (MAFF) 1987)
Netherlands	5.4	Beer (71%)	(Stephany and Schuller 1980)
	1.4	Not evaluated ²	(Ellen et al. 1990)
Germany	15.7 (8.1)	Beer (65%), cured meats (10%)	(Spiegelhalder et al. 1980)
	7.6 (5)	Beer (40%), cured meats (18%)	(Spiegelhalder and Preussmann 1983)
	4 (2.4)	Beer (31%), cured meats (36%)	(Spiegelhalder et al. 1980)
Japan	25.7	Dried fish (91%)	(Maki et al. 1980)
	7.1	Beer (30%), fish products (68%)	(Yamamoto et al. 1984)
Sweden	1.7	Beer (32%), cured meats (61%)	(Österdahl 1988)
Finland ³	1.4	Beer (31%), smoked fish (25%)	(Pentilla et al. 1990)
France	2.7	Alcohol (33.5%)	(Biaudet et al. 1994)

* Data for women in parenthesis; ¹ Beer was not included in this study; ² Determined by a 24-hr duplicate diet analysis; ³ Based on limited data.

Drinks can contribute significantly to NDMA intake. For example, Gloria et al. (Glória et al. 1997b) found NDMA in beer at concentrations of 0.05 to 0.55 µg/kg, originating from the fermentation process. Assuming a daily beer consumption of about 0.3 L/day the range of beer related NDMA intake is 0.3 – 3.3 ng/kg.day, which has decreased significantly in recent years due to improvements in the brewing process. In fact, Tricker et al (Tricker et al. 1991) indicated that 31% of the intake of men is from beer, while this figure used to be 65%. In whiskey, NDMA originates from the kilning of malt and concentrations reported were on occasion exceeding the 'action level' of 5 µg/kg (Ministry of Agriculture Fisheries and Food (MAFF) UK 1995) with a median of 0.3 µg/kg and values declining in new (rather than extensively aged) products due to improved production processes.

Smoking is a further source of NDMA, among other carcinogens. An intake range of 5 – 76 ng/cigarette has been reported (Tricker et al. 1991). For an average 20 cigarettes per day smoker, daily NDMA intake from smoking would be 1.4 – 21.7 ng/kg.day. Hence, cigarettes (and some drinks) are potentially a significantly greater source of NDMA than other sources for some individuals.

3.3 Exposure to NDMA through other sources

NDMA has been reported in a range of cosmetics and personal care products with concentrations of up to 24 ng/g (Spiegelhalder and Preussmann 1984). However, only 1–4% of the NDMA in cosmetic preparations was estimated to penetrate through the skin (Brain et al. 1995). At the maximum concentration reported by Spiegelhalder and Preussmann, 10 g of product would be expected to result in 2 -10 ng of uptake of NDMA through the skin. Based on this limited amount of data cosmetics and toiletries are probably only a negligible source of NDMA for average consumers although monitoring would be a wise precaution. No data is available on the formation of harmful substances on the skin following application and exposure to sunlight.

A significant contributor to NDMA related health problems is workplace exposure. Industrial exposure affects workers, particularly in the rubber industry, where vulcanisation and salt bath processes are applied. Concentrations reach up to $100 \mu\text{g}/\text{m}^3$ in the air. This compares to concentrations of up to $0.07 \mu\text{g}/\text{m}^3$ measured in a smoky bar (Stehlik et al. 1982), indicating that occupational sources can be a significant source of NDMA exposure albeit limited to a high occupational risk group. A correlation between risk of occupational NDMA exposure and certain types of cancer has been identified.

3.4 Comparison of NDMA Intake from various sources

Comparison of various intakes outlines a number of key points. Firstly, intake from food is substantial and in mean values constitutes 98% of intake (see Figure 1). Secondly, this intake varies significantly with location, occupation, lifestyle and dietary habits. Hence the intake of a vegan with no consumption of cheese or meat products who does not drink alcohol or smoke will have the main NDMA intake originate from water, while for a person with high cheese and meat diet and a moderate to high alcohol consumption the contribution of water would be negligible. Bearing in mind that the contribution of water is 5.9% (see Table 5) when considering maximum NDMA load in food and water at the WHO guideline value, it becomes clear that water can indeed make a significant contribution.

Table 5 Estimation of mean and maximum daily intake of NDMA by Australians based on consumer statistics in 2000 and NDMA food concentrations from literature (Tricker et al. 1991).

Type of Product	Amount per capita per day consumed	Units	NDMA Load (ng/kg.day)		Mean Contribution (%)	
			Mean	Max	Mean	Max
Food						
Cheese	29.6	g/day	1.4	28.7	24.0	60.4
Sausage Products	26.0	g/day	0.2	3.5	3.4	7.4
Bacon, Ham	26.0	g/day	2.5	6.4	42.9	13.5
Fish	22.2	g/day	0.3	2.5	5.1	5.3
Poultry	84.4	g/day	1.1	3.0	18.9	6.3
Powdered Milk	27.4	g/day	0.2	0.3	3.4	0.6
Food subtotal			5.7	44.4		
Drinks & Cigarettes						
Water	2.0	L/day	0.02	2.80	0.3	5.9
Beer	0.3	L/day	0.03	0.18	0.5	0.4
Cigarettes	7.4	cig/day	0.08	0.15	1.4	0.3
D & C Subtotal			0.13	3.13		
Total			5.8	47.1		

Figure 1 summarises the intake of NDMA through water, cigarettes, and a variety of foods as detailed in Table 5. Exposure routes are based on mean values and the average Australian diet. Clearly in this case water is not a significant contributor.

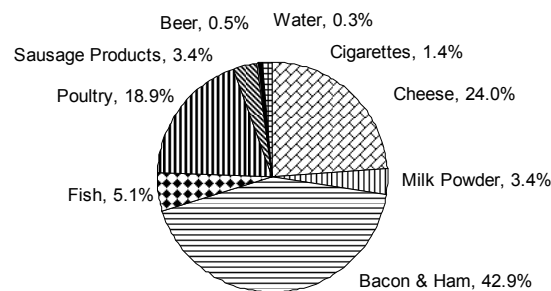


Figure 1 Intake distribution of NDMA based on mean intake distribution.

Given that the awareness of NDMA has made significant contributions to reduction of NDMA by improved manufacturing processes outlines that awareness and regulation of NDMA in drinking water will have a measurable health impact.

4 REGULATION OF NDMA IN DRINKING WATER

There are a number of regulatory and policy approaches regarding the issue of pollutants which occur in wide ranges of contaminant concentrations, and ingestion habits. Mean values for NDMA used to calculate mean daily intakes based on average consumption values are somewhat meaningless when applied to individuals within a population. This is particularly true for NDMA, for which ingestion of the main dietary sources (cured meats and beer) vary from nothing to multiples the average amounts, depending on personal habits. Furthermore, looking at the relative contributions of NDMA from different sources is only marginally meaningful. It is the absolute amounts that are consumed that need to be addressed, and looking at ways to ensure that these are minimised and water plays an increasing role in those.

Given that NDMA can form during water and wastewater treatment, and that in some severe cases drinking water may provide as much or more dietary NDMA as food, some degree of formal monitoring of NDMA in drinking water must be required, particularly when disinfection techniques promoting formation are practiced.

Currently, NDMA in drinking water is regulated in very few countries worldwide, although it is now limited to 9 ng/L and 10 ng/L by the state and provincial governments in California and Ontario, respectively. These values exceed the 0.7 ng/L drinking water concentration suggested by the US EPA to result in a 10^{-6} lifetime cancer risk (United States Environmental Protection Agency 2008). Further, the World Health Organisation is considering a guideline value of 100 ng/L to be included in the second addendum to the 3rd edition of the World Health Organization (WHO) Guidelines for Drinking Water Quality (Dillon et al. 2008). This is in agreement with German regulations for carcinogenic substances that have some level of uncertainty associated with their evaluation that in the case of NDMA resulted at 100 ng/L (Umweltbundesamt 2003). There is presently no standard in the UK or the EU. Since NDMA is likely a human carcinogen, its presence as a contaminant in drinking water is of concern, and consideration should be given to its wider regulation as well as the feasibility of monitoring and treatment options to prevent the occurrence of NDMA in water supplies.

5 CONTROL OF NDMA IN WATER

Two fundamentally different approaches to NDMA control have been pursued for drinking water treatment. One approach seeks to minimize NDMA formation while the other approach attempts to remove NDMA after its formation, but upstream of the drinking water distributions system.

5.1 Minimization of NDMA Formation

As the predominant mechanism responsible for NDMA formation during disinfection involves a reaction between dichloramine and unchlorinated organic nitrogen precursors, removal or deactivation of organic nitrogen precursors, or minimization of dichloramine would reduce NDMA formation. Chloraminating utilities employing cationic coagulation polymers, such as polyDADMAC, are attempting to reduce NDMA formation by reducing their polymer dosage (Wilczak et al. 2003); however, these attempts must be balanced by the need to ensure proper coagulation.

In the case of wastewater-impacted source waters, the organic nitrogen precursors may be deactivated by a period of free chlorination (Schreiber and Mitch 2005) or ozonation (Lee et al. 2007). As the dichloramine-associated formation mechanism requires an initial nucleophilic attack by the lone electron pair of organic amines on dichloramine, pre-treatment with a strong oxidant, such as free chlorine or ozone would oxidize the lone pair, preventing the formation. Interestingly, ozone was not effective at destroying NDMA itself.

Lastly, previous research indicated that dichloramine formation during chloramination, and the associated NDMA formation, could be reduced by altering the method by which the chlorine and ammonia reagents are added (Schreiber and Mitch 2005). Chloramine formation reactions are fast compared to the timescale of reagent mixing. When chlorine is added downstream of ammonia, the chlorine to ammonia molar ratio can exceed one at the point of chlorine addition prior to complete mixing of chlorine into the flow stream. These conditions promote dichloramine formation at the point of chlorine addition. When chlorine is added upstream of ammonia, the opposite conditions pertain, and monochloramine formation is favored. Moreover, as noted above, the short contact time with free chlorine before ammonia addition would aid in deactivating organic nitrogen precursors.

In certain waters, such as non-nitrified secondary municipal wastewaters in some wastewater recycling operations, ammonia is present in the influent water. In these situations, chloramines could be preformed under conditions promoting monochloramine formation (i.e., high pH with chlorine added prior to ammonia), and then applied to the process stream. This process was successfully pilot-tested at a wastewater recycling facility (Mitch et al. 2005).

5.2 Membrane Filtration

Historically reverse osmosis (RO) membranes were designed to remove salt from seawater (Glaser 1998). Over the next decades, a range of specialized membranes have become available for a variety of purposes, including nanofiltration (NF) membranes which were designed for use as water softeners (Verliefde 2007). Today, RO and NF membranes are widely used in water treatment because they are able to remove various contaminants other than salts, including harmful trace organics, viruses, and dissolved organic matter. Sedlak found that NDMA precursors were 98% removed by RO (Deeb et al. 2006, Sedlak and Kavanaugh 2005). However, RO and NF membranes are not always effective at removing small, neutral, and hydrophilic compounds such as NDMA. RO and NF only partially remove NDMA (Bellona et al. 2008, Deeb et al. 2006, Drewes et al. 2008, Mitch et al. 2003, Plumlee et al. 2008, Sedlak and Kavanaugh 2005, Steinle-Darling et al. 2007).

The more porous microfiltration (MF) and ultrafiltration (UF) membranes are unable to remove NDMA, however, they can reject its precursors moderately efficiently (50%) (Sedlak and Kavanaugh 2005). More information on mechanisms of Xenobiotics removal by membranes is provided in the chapter by Semiao and Schäfer.

To predict retention by RO and NF understanding of mechanisms is required. Although the actual rejection mechanisms for RO and NF are complex and not yet fully understood, key factors have been identified. These factors can be categorized as size exclusion, charge exclusion and solute-membrane affinity (Wijmans and Baker 1995), and they are related to the properties of the following solute, membrane, solution (liquid matrix) and operating conditions (Bellona et al. 2004, Nghiem et al. 2004):

- Solute properties: molecular mass (MW) or molecular diameter, acid dissociation constant (pK_a), polarity (Hydrogen acceptor and donor characteristics) and hydrophobicity ($\log K_{ow}$)
- Membrane properties: molecular weight cut off (MWCO), surface charge (zeta potential), and roughness.
- Water chemistry: pH, ionic strength, solute-solute interactions with other substances in a particular organic matter and colloidal matter.
- Operating conditions: pressure, flow rate and recovery.
- Fouling status of the membrane.

Figure 2 shows a schematic indicating solute-matrix-membrane interactions and their impact on organics rejection by membranes. The grey path follows the case for a negatively charged membrane and NDMA at pH values encountered during wastewater treatment and in environmental waters. Depending on the membrane, NDMA is smaller or larger than the molecular weight cut off (MWCO).

Size exclusion depends on the MW and chemical structure of the solute as it relates to the membrane MWCO and/or pore size. The MWCO is defined as the molar mass above which more than 90% of a given compound is rejected. Compounds used for MWCO determinations are typically aqueous sugar or polyethylene glycol solutions. However, today there is no generally accepted industry standard (Novasep 2009), and MWCO ratings are not always comparable. As a first approximation, any solute that is larger than the MWCO will be efficiently rejected. NDMA has a MW of 73 Da, which is smaller than the MWCO of NF membranes (typically 200-500 Da). Although RO membranes are usually considered non-porous (i.e. no MWCO), some manufacturers report MWCO of approximately 100 Da for their RO membranes (Koch Membranes 2008). Because the MWCO of RO membranes (non-existent to 100 Da) is closer to NDMA's MW (73 Da) than that of NF membranes (200-500 Da), tight RO membranes would be expected to better remove NDMA than NF membranes.

Holding other properties constant, a compound that is more charged is better rejected by NF and RO. The pK_a of NDMA is less than 1 (Lee et al. 2008), which renders this amine compound uncharged at ambient pH. Therefore membrane charges do not contribute to NDMA rejection.

Finally, NDMA is expected to sorb poorly on the membrane and instead stay in the water phase due to its hydrophilicity ($\log K_{ow} = -0.57$). For these reasons, NDMA is predicted to be poorly rejected by NF membranes and poorly to moderately rejected by RO membranes depending on their "looseness", i.e. MWCO (Figure 2).

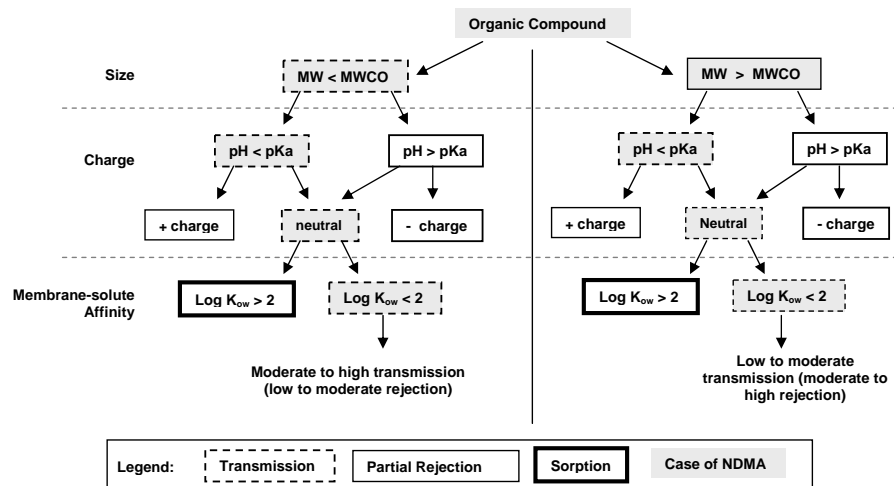


Figure 2 Predicting NDMA removal using a solute-matrix-membrane interaction scheme (adapted from (Bellona et al. 2004)). It is assumed that the membrane is negatively charged. The grey boxes highlight the case of NDMA. Left hand side represents NF and "loose" RO; right hand side represents "tight" RO.

The available data show that RO and NF membranes do not achieve complete NDMA removal. Table 6 summarizes the available literature on NDMA removal by membranes in field and laboratory experiments. The data indicate a wide range of NDMA rejection values (10-70%), likely caused by different membrane-solute-matrix interactions. For example, in her laboratory studies Steinle-Darling showed a decrease in NDMA rejection due to membrane fouling and water chemistry (Steinle-Darling et al. 2007). This is in agreement with other studies showing that fouling decreases rejection of small, uncharged contaminants (Ng and Elimelech 2004, Zhu and Elimelech 1997).

To date, there is very little published data on NDMA rejection by NF membranes. An example is a study by Bellona et al. who determined the rejection of Filmtec NF90 (Bellona et al. 2004, Drewes et al. 2008) to be 42-47% NDMA. NF90 appears to be a borderline case because, based on the membrane's salt rejection and surface chemistry (Tang et al. 2007), NF90 could be classified as an RO membrane.

Advances in material science, such as membrane coatings, show promises in improving NDMA rejection by membranes. For example, a polyether polyamide block copolymer (PEBAX) coating increased NDMA rejection by LFC3 and BW-30 RO membranes by 6% and 15% respectively, to 76% in both cases (Steinle-Darling et al. 2007). Further optimization of membranes may lead to greater removal efficiencies of small pollutants and greater reliance on membrane technology for organics removal.

Table 6 Literature NDMA rejection by RO and tight NF membranes.

Rejection of NDMA (%)	Membrane	MWCO**	Inlet NDMA concentration (ng/L)	Outlet NDMA concentration (ng/L)	Source

Laboratory Study – distilled water matrix:

54	RO: ESPA3	200 ²	200	92	(Steinle-Darling et al. 2007)
70	RO: LFC3	N/A	200	60	(Steinle-Darling et al. 2007)
61	RO : BW-30	N/A	200	78	(Steinle-Darling et al. 2007)

Field Studies at water reuse facilities (pilot and full scales) – pre-treated secondary wastewater matrix:

24-56	RO (ESPA2)	250-500 ³	18-57	14-41	(Plumlee et al. 2008)
32	RO (ESPA2)	250-500 ³	30	20	(Bellona et al. 2008, Drewes et al. 2008)
40-65*	RO (ESPA2')	250-500 ³	25-100	12-50	(Sedlak and Kavanaugh 2005)
42-50*	RO	N/A	50-70	30-45	(Sedlak and Kavanaugh 2005)
10-70*	RO	N/A	200-330	100-170	(Sedlak and Kavanaugh 2005)
50	RO	N/A	N/A	N/A	(Mitch et al. 2003)
~50	RO: TFC	N/A	(wastewater concentration) 20-170		(Deeb et al. 2006)
30	ULPRO (TFC-HR)	N/A	60	40	(Bellona et al. 2008, Drewes et al. 2008)
50-55	ULPRO (TMG-10)	100 ⁶	20-40	10-20	(Bellona et al. 2008, Drewes et al. 2008)
42-47	NF (NF90)	300 ⁴ , 200 ⁵	10-20	4-12	(Bellona et al. 2008, Drewes et al. 2008)

N/A means data not available; * numbers were approximated from graphs; ** MWCO sources are: ¹ (Plumlee et al. 2008); ² (Fonseca et al. 2007) the authors classified this membrane as NF; ³ estimation in (Kim et al. 2008); ⁴ (Kim et al. 2008); ⁵ Filmtec; ⁶ (Drewes et al. 2005)

Currently regulatory limits may be achieved by treating water with advanced oxidation (UV) or by blending it with water containing lower levels of NDMA.

5.3 UV Treatment

UV treatment is the most common NDMA removal technique. However, treatment can employ UV fluences near 1000 mJ/cm², nearly an order of magnitude above those employed for disinfection (Mitch et al. 2003). NDMA exhibits a strong absorption band at 227 nm ($\epsilon = 7000 \text{ M}^{-1} \text{ cm}^{-1}$) associated with a $\pi \rightarrow \pi^*$ transition. Laboratory studies indicate that low and medium pressure lamps exhibit comparable photonic efficiencies for NDMA degradation (Sharpless and Linden 2003). Addition of 100 mg/L hydrogen peroxide (H₂O₂) to promote hydroxyl radical (OH[•]) formation results in no significant benefit regarding NDMA degradation. However, some wastewater recycling facilities employ a UV/H₂O₂ advanced oxidation process (AOP) downstream of reverse osmosis membranes because of the combination of UV for NDMA removal and OH[•] for destruction of other contaminants that may pass through the membranes.

6 CONCLUSIONS

NDMA occurs in many foods, cigarettes, drinks, certain industrial processes and in some water supplies. While the regulation of NDMA in water supply can be described as an emerging issue with significant difficulties with regards to the implementation of monitoring procedures, the main aim of this chapter has been to present the available knowledge on NDMA in water regarding sources, occurrence, fate, effects, risk assessment and risk management opportunities.

An increased awareness about the presence of traditionally high NDMA concentrations in some foods, and the understanding of how it was formed, has effectively led to large reductions in its occurrence. With the growing concern about NDMA in drinking water, hopefully the next decade will see an increase in monitoring, elevated removal efficiency by treatment processes and a decrease in its presence and consequently risk of exposure from water supplies. The avoidance of NDMA formation during treatment will play an important role in this process. Given the difficulty in removing NDMA in water treatment, this compound is an excellent model compound to deal with the implications of xenobiotics occurrence in water supplies.

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