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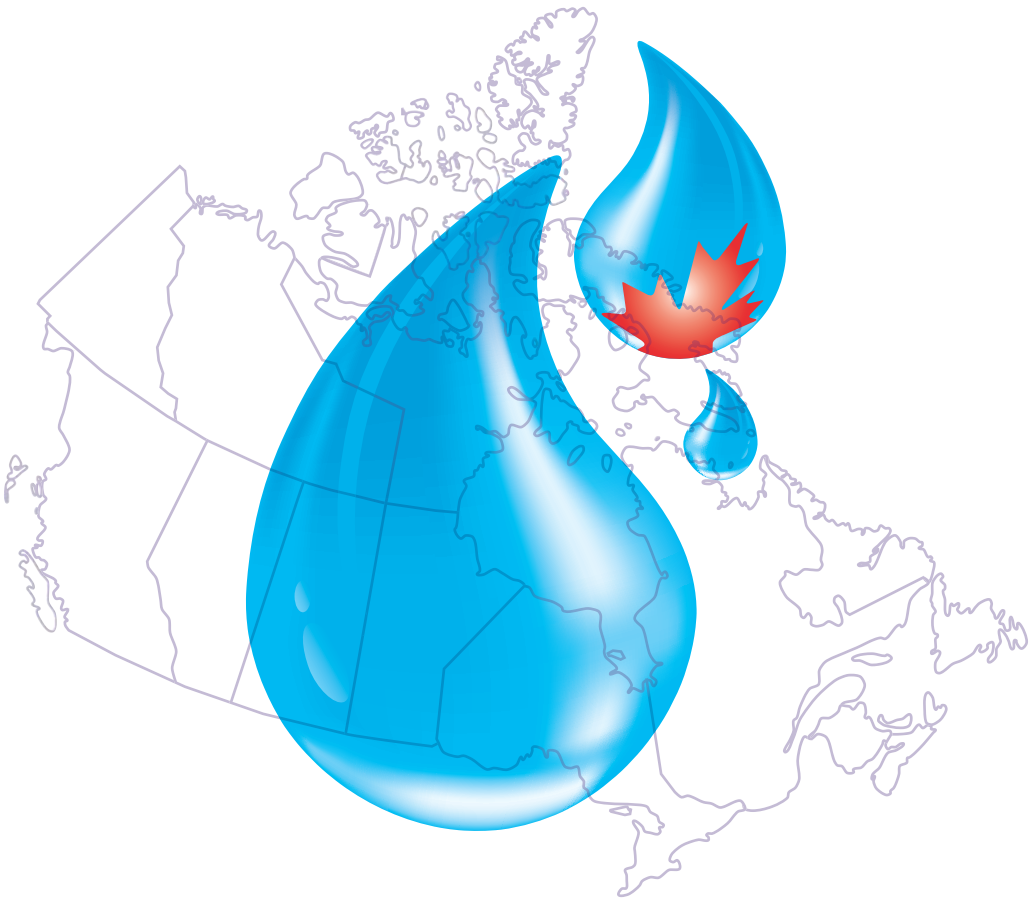
Guidelines for Canadian Drinking Water Quality

Guideline Technical Document

N-Nitrosodimethylamine (NDMA)



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Guidelines for Canadian Drinking Water Quality

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N-Nitrosodimethylamine (NDMA)

Prepared by the
Federal-Provincial-Territorial Committee on
Drinking Water
of the
Federal-Provincial-Territorial Committee on
Health and the Environment

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January, 2011

N-Nitrosodimethylamine (NDMA) in Drinking Water[1]

Part I. Overview and Application

1.0 Guideline

The maximum acceptable concentration (MAC) for N-*nitrosodimethylamine (NDMA) in drinking water is 0.000 04 mg/L (0.04 µg/L).*

2.0 Executive summary

Levels of NDMA in Canadian drinking water are generally very low. There are no industrial or commercial uses for NDMA in Canada. NDMA can be found in both surface water and groundwater sources, but it is found in drinking water primarily from its formation during the treatment process, in particular chloramination.

This Guideline Technical Document reviews and assesses all identified health risks associated with NDMA in drinking water, incorporating all relevant routes of exposure from drinking water—namely, ingestion as well as skin absorption from showering and bathing; inhalation was not found to be significant. It assesses new studies and approaches and takes into consideration the availability of appropriate treatment technology. From this review, the guideline for NDMA in drinking water is established at a maximum acceptable concentration (MAC) of 0.000 04 mg/L (0.04 µg/L). The guideline for NDMA is established based on cancer end-points and is considered protective of all health effects.

2.1 Health effects

NDMA is considered highly likely to be carcinogenic to humans, based primarily on clear evidence of carcinogenicity in animals. Consequently, there have been few studies on other possible adverse health effects. The maximum acceptable concentration for NDMA in drinking water was established based on the incidence of liver cancer in male and female rats, through the calculation of a lifetime unit risk.

2.2 Exposure

Canadians can be exposed to NDMA through its presence in water, air and food. Drinking water is considered to be only a minor source of exposure to NDMA compared with other sources. Overall, the concentration of NDMA measured in Canadian water supplies is normally well below the MAC.

[1] This Guideline Technical Document was originally prepared in Canada as a background document for the development of the World Health Organization (WHO) *Guidelines for Drinking-water Quality* (WHO, 2008) and has been revised to address Canadian policies and perspectives.

2.3 Treatment

The presence of NDMA in drinking water is primarily associated with water treatment. It can be formed as a result of chloramination, and to a lesser extent chlorination, as well as the use of some coagulants and anion exchange resins. Consequently, the best approaches to reduce the concentration of NDMA in drinking water are to remove the organic nitrogen precursors (including humic substances) from the source water, or to modify the disinfection strategy to minimize its formation, without compromising the efficacy of the disinfection process. Any modification to the disinfection strategy needs to consider the potential formation of other disinfection by-products in a holistic manner and include pilot testing. Once NDMA is present in drinking water, its reduction using ultraviolet (UV) irradiation is technically feasible, but may be difficult for smaller utilities.

3.0 Application of the guideline

Note: Specific guidance related to the implementation of drinking water guidelines should be obtained from the appropriate drinking water authority in the affected jurisdiction.

Drinking water operators should strive to keep NDMA concentrations low by implementing strategies to prevent its formation during treatment without compromising the effectiveness of disinfection. NDMA is considered a probable human carcinogen. Specific subpopulations, such as children and pregnant women, are not at a greater risk of developing adverse health effects from exposure to NDMA compared with the general population.

The drinking water guideline is based on lifetime exposure to NDMA from drinking water. For drinking water supplies that occasionally experience short-term exceedances above the MAC, it is suggested that a plan be developed and implemented to address these situations. For more significant long-term exceedances that cannot be addressed through treatment, it is suggested that alternative sources of drinking water be considered.

The guideline for a carcinogen is normally established at a level at which the increased cancer risk is considered to be "essentially negligible" for a person exposed to that level in drinking water over a lifetime (70 years). In the context of drinking water guidelines, Health Canada has defined this term as a range from one new cancer above background per 100 000 people to one new cancer above background per 1 million people (i.e., 10^{-5} to 10^{-6}) exposed to a contaminant at the MAC over a lifetime. In the case of NDMA, the MAC is established at a concentration that would present an "essentially negligible" risk of one new cancer above background per 100 000 people (i.e., 10^{-5}) exposed to NDMA at the MAC over a lifetime, which takes into consideration treatment limitations.

3.1 Monitoring

In general, monitoring of NDMA should be conducted on an annual basis. Where the characteristics of raw water or the treatment and disinfection strategies create the potential to produce NDMA, quarterly monitoring of treated water from surface and groundwater sources is recommended. This may be reduced to an annual frequency if drinking water monitoring consistently does not show the presence of NDMA in the finished water. Monitoring should be conducted at the treatment plant and at the points of the distribution system with the longest disinfectant retention time.

Factors to consider when determining the need for monitoring of NDMA include the presence of NDMA precursors or of nitrogen-containing compounds; the type of coagulant used; the type of anion exchange resins used; and the disinfection practices (i.e., chloramination or booster chloramination). Increased frequency of monitoring may be required for facilities using surface water sources during periods when water characteristics are more favourable to the formation of by-products, which will vary according to the specific system.

Part II. Science and Technical Considerations

4.0 Identity, use, sources and fate in the environment

4.1 Identity, uses and sources in the environment

N-Nitrosodimethylamine (NDMA) is the simplest dialkylnitrosamine, with a molecular formula of $C_2H_6N_2O$ (ATSDR, 1989). NDMA is also known as dimethylnitrosoamine, *N*, *N*-dimethylnitrosoamine, *N*-methyl-*N*-nitrosomethanamine, *N*-nitroso-*N*, *N*-dimethylamine, DMN and DMNA. NDMA is a volatile, combustible, yellow, oily liquid. Its physicochemical properties are listed in Table 1.

Table 1. Physicochemical properties of NDMA

Property	Value[a]
Relative molecular mass	74.08
Melting point	-50°C
Boiling point	151–154°C
Vapour pressure	1080 Pa at 25°C
Water solubility	Miscible
Log *n*-octanol/water partition coefficient (K_{ow})	0.57
Henry's law constant (K_{aw})	3.34 Pa·m^3/mol at 25°C

[a] Includes experimental and calculated values listed in Callahan et al. (1979); Clayton and Clayton (1981); ATSDR (1989); Budavari et al. (1989); OME (1991); DMER and AEL (1996).

NDMA is produced as a by-product of industrial processes that use nitrates or nitrites and amines under a range of pH conditions (ATSDR, 1989; IPCS, 2002). It is inadvertently formed when alkylamines, mainly dimethylamine (DMA) and trimethylamine, come into contact and react with nitrogen oxides, nitrous acid or nitrite salts or when transnitrosation via nitro or nitroso compounds occurs (ATSDR, 1989). Therefore, NDMA may be present in the environmental discharges of such industries as rubber manufacturing, leather tanning, pesticide manufacturing, food processing, foundries and dye manufacturing, as well as in effluent from sewage treatment plants. These discharges account for its presence in a number of media, including air, soil and water. Almost all of the releases are to water. NDMA can also occur in drinking water through the degradation of dimethylhydrazine (a component of rocket fuel) (Siddiqui and Atasi, 2001; Mitch et al., 2003b). In addition, NDMA has been detected in diesel vehicle exhaust emissions (Goff et al., 1980).

NDMA may form directly in sewage as a result of the biological and chemical transformation of alkylamines in the presence of nitrate or nitrite (Ayanaba and Alexander, 1974; ATSDR, 1989). It may also be released into the environment as the result of application of sewage sludge to soils rich in nitrate or nitrite. It has been demonstrated that disinfection of wastewater effluent by chlorine produce NDMA (Mitch and Sedlack, 2004). It may also be released into the environment as the result of application of sewage sludge to soils rich in nitrate or nitrite. The NDMA precursor, DMA, may enter surface water streams from agricultural runoff, as it has been detected in the faeces of dairy cattle (van Rheenan, 1962).

NDMA may also be formed during the treatment of drinking water (OME, 1994). Water treatment plants incorporating a chlorination or chloramination process in the presence of nitrogen-containing organic matter form NDMA as a disinfection by-product (Richardson, 2003). NDMA precursors such as DMA and trimethylamine may be present after drinking water treatment with nitrogen-based cationic polyelectrolytes (Wilczak et al., 2003) or ion exchange resins (Kimoto et al., 1980). For further details on NDMA's formation during disinfection processes, see Section 7.0.

NDMA may be released into the environment as a result of the use of certain pesticides contaminated with this compound (Pancholy, 1978). NDMA is present in various technical and commercial pesticides used in agriculture, hospitals and homes as the result of its formation during the manufacturing process and during storage. The following DMA formulation pesticides may contain NDMA as a microcontaminant: benazolin, bromacil, dicamba, 2,4-dichlorophenoxyacetic acid (2,4-D), mecoprop and 4-(2-methyl-4-chlorophenoxy)acetic acid (MCPA) (IPCS, 2002).

In the 1990s, in testing in Canada of over 100 samples of formulated pesticidal products (DMA salt of phenoxy acid herbicides) potentially contaminated by NDMA, the compound was detected in 49% of the samples with an average concentration of 0.44 µg/g; only six samples contained concentrations above 1.0 µg/g (1.02–2.32 µg/g). Concentrations of NDMA in pesticides have decreased over time. In 1994, approximately 1 million kilograms of DMA-formulated phenoxy acid herbicides for commercial use were applied to the terrestrial environment in Canada (Moore, 1999). Based on the amount of DMA-formulated phenoxy acid herbicides applied in 1994, the average NDMA concentration of 0.44 µg/g and the 49% detection rate, it has been estimated that approximately 200 g of NDMA may have been released into the environment through the use of these herbicides (IPCS, 2002).

There are no industrial or commercial uses of NDMA in Canada or the United States. NDMA was used in Canada in the past, and may still be used in other countries, in rubber formulations, as a fire retardant and in the organic chemical industry as an intermediate, catalyst, antioxidant, additive for lubricants and softener of copolymers (ATSDR, 1989; Budavari et al., 1989).

4.2 Environmental fate

NDMA has a low vapour pressure (1080 Pa at 25°C). If emitted to, or formed in, air, it is not likely to adsorb to airborne particulate matter and is expected to be almost entirely in the vapour phase. In daylight, it degrades rapidly by direct photolysis to form dimethylnitramine. The photolytic half-life of NDMA vapour exposed to sunlight ranges between 0.5 and 1.0 h (Hanst et al., 1977). Half-lives for the reaction with hydroxyl radicals in air range from 25.4 to 254 h (Atkinson, 1985). Modelling of environmental partitioning used a half-life for NDMA in air of 5 h (Environment Canada and Health Canada, 2001). The short half-life for NDMA in air suggests that it is not persistent in this medium.

Since NDMA is miscible in water and has a low vapour pressure and a low *n*-octanol/water partition coefficient (log K_{ow} of 0.57), it is not likely to bioaccumulate, adsorb to particulates or volatilize to any significant extent (Thomas, 1982; ATSDR, 1989; OME, 1991). Oxidation, hydrolysis, biotransformation and biodegradation are not significant factors affecting the fate of NDMA in lake water (Tate and Alexander, 1975). Photodegradation is the main process for removing NDMA from the aquatic environment. The efficiency of removal of NDMA depends on the characteristics of the particular water environment. Typically, photodegradation of NDMA is much slower in waters with high concentrations of organic

substances and suspended solids than in clear water bodies. The rate of degradation through photolysis may be significantly decreased in the presence of interferences with light transmission, such as ice cover on receiving water bodies (IPCS, 2002; WHO, 2008). This observation is supported in the groundwater compartment, where, in the absence of light, NDMA has the potential to persist (OME, 1991). A half-life for NDMA in surface water at 25°C of 17 h was assumed by DMER and AEL (1996) in their modelling of environmental partitioning for Environment Canada and Health Canada (2001). Howard et al. (1991) reported a half-life range for NDMA in groundwater of 1008–8640 h, based on estimated unacclimated aqueous aerobic biodegradation.

On soil surfaces, photolysis and volatilization rapidly remove NDMA. Oliver (1979) reported that 30–80% of an unreported concentration of NDMA volatilized from the soil within the first few hours of application to the soil surface. As outlined by Haruta et al. (2008), NDMA rapidly disappears from soils receiving reclaimed wastewater, though microbial degradation and volatilization.

Once incorporated into subsurface soil, however, NDMA will be highly mobile, with the potential to migrate into groundwater supplies. Subsurface biodegradation is slightly slower under anaerobic conditions (ATSDR, 1989). Soil type only slightly affects the biodegradation of NDMA. Aeration of soil improved biodegradation compared with waterlogged soil. Pre-exposure of bacteria to NDMA increased biodegradation in soil (Mallik and Tesfai, 1981).

5.0 Exposure

Canadians can be exposed to NDMA through its presence in food, water, and air. In addition, certain segments of the population may be exposed through the use of specific consumer products or in occupational settings.

5.1 Water

Releases of NDMA into water in Canada have been measured primarily in Ontario and vary considerably. Evidence for this variation in NDMA levels is provided by a 1996 incident in which a chemical plant released wastewater containing NDMA into the St. Clair River at a concentration of 0.266 µg/L (Environment Canada, 1997). In April 1997, concentrations of NDMA in the wastewater at this same chemical plant varied considerably from the previous year's measurements, since NDMA levels at the point of release to surface water ranged from 0.096 to 0.224 µg/L. NDMA releases are expected to decrease, as the company installed a wastewater treatment plant in 1998 (IPCS, 2002).

In a 1990 survey of sewage treatment plant effluent in Ontario, NDMA was detected in 27 of 39 samples, with a maximum concentration of 0.22 µg/L (OME, 1991). In 390 samples of raw surface water from 101 water treatment plants sampled for NDMA in Ontario from 1990 to July 1998, concentrations were detectable (>0.001 µg/L) in the raw water at 37 plants. The average concentration in raw water was 1.27×10^{-3} µg/L (IPCS, 2002). The highest concentration of NDMA in raw water taken at two water treatment plants in 1996 was 0.008 µg/L (IPCS, 2002).

In 1990, concentrations of NDMA in 24 groundwater samples taken from various locations in Ontario were below detection limits (detection limits ranged from 0.001 to 0.010 µg/L) (OME, 1991). Concentrations of NDMA in the municipal aquifer in Elmira ranged from 1.3 to 2.9 µg/L and were attributed to contamination from a nearby chemical facility (Kornelsen et al., 1989). The municipal wells using this aquifer were closed in 1989 (Ireland, 1989).

In 313 samples of treated water analysed from 100 locations within Ontario between 1994 and 1996, NDMA was detected in at least one sample at 40 of these 100 sites at levels greater than the detection limit of 0.001 µg/L. The mean concentration was 0.0027 µg/L. The highest concentrations were measured in samples from drinking water treatment plants using a specific pre-blended polyamine/alum water treatment coagulant (OME, 1996). These included a concentration of 0.04 µg/L at the water treatment plant in Huntsville, Ontario. NDMA was detected in all 20 samples collected from four water treatment plants using the specific coagulant. The mean concentration of NDMA in these 20 samples was 0.012 µg/L, whereas the mean concentration in the remaining 293 samples for the locations where the specific coagulant was not used was 0.002 µg/L.

More recent data from Ontario's Drinking Water Surveillance Program report levels of NDMA in finished drinking water exceeding the province's standard of 0.009 µg/L in three cases between 1998 and 1999. These exceedances ranged from 0.012 to 0.027 µg/L (OME, 2009).

Recent surveys conducted in Canada at different drinking water treatment plants and distribution systems reported levels of NDMA ranging from < 1 to 12 ng/L, with one exception where levels were reported to exceed 100 ng/L in the distribution system (Charrois et al., 2004, Tugulea et al., 2008). Drinking water and source water samples were tested as part of the validation of the analytical methods developed by Charrois et al. (2004). One series of samples was from an Alberta city that used chloramination and UV disinfection. The source water had no detectable NDMA (detection limits ranged from 0.0004 to 0.0016 µg/L), but the finished water contained NDMA at 0.067 µg/L, and water in the distribution system contained 0.16 µg/L. Further investigation confirmed that distribution system samples had much higher levels of NDMA than the finished water at the treatment plant. There is a need for more studies that measure NDMA levels in the distribution systems of water treatment facilities using chloramine.

Another study by Charrois et al. (2007) sampled 23 locations in 20 distribution systems for NDMA in Alberta in 2004. The authors reported concentrations of NDMA in at least one location in each of 6 systems, ranging from below the method detection limit of 5 ng/L to 100 ng/L. In 5 of the 6 systems, chloramine was used as a secondary disinfectant or there was naturally occurring ammonia present in the source water.

In a 2009 Canadian survey of 33 plants (Tugulea et al., 2010), low concentrations of NDMA were detected at 3 plants. Concentrations of NDMA ranging from 1-2 ng/L were found in both the treated water and the distribution system samples of each plant. All 3 plants where NDMA was detected were using chloramine as a secondary disinfectant.

A survey of NDMA concentrations in drinking water systems in California was conducted by the California Department of Health Services in 2001 (DHS, 2002). In 3 of 20 chloraminated supplies, NDMA concentrations exceeded 0.01 µg/L, whereas all 8 supplies that used only free chlorine had levels below 0.005 µg/L.

The presence of NDMA in drinking water is usually associated with its formation during water treatment rather than with its presence in the source water. Factors affecting this formation include the nature and amount of precursor compounds and the disinfection strategy used. Chloramination is the secondary disinfection process that is most often associated with the formation of NDMA, the predominant species of nitrosamines formed during this process. The nitrosamine formation pathways relevant to drinking water disinfection are discussed in Section 7.0. Nitrosamine formation is expected to continue within chloraminated distribution systems.

5.2 Air

There is little information on the presence or concentrations of NDMA in ambient (i.e., outdoor) air in Canada or elsewhere. Available Canadian data are limited to the province of Ontario, where short-term measurements have been taken in the immediate vicinity of potential point sources of discharge to the atmosphere, for comparison with background measurements from other urban locations.

No data on airborne concentrations at rural locations have been identified. At industrial and urban locations in Ontario in 1990, based on seven samples taken in five cities, concentrations of NDMA were all below the detection limit (detection limits ranged from 0.0034 to 0.0046 $\mu g/m^3$) (OME, 1990). In surveys of ambient air conducted in the vicinity of a chemical production facility in Elmira, Ontario, in 1990, concentrations of NDMA ranged from not detected (detection limits ranged from 0.0029 to 0.0048 $\mu g/m^3$) to 0.230 $\mu g/m^3$ in 41 samples; concentrations in 20 of the 41 samples were at or above the detection limit (OME, 1990). The highest concentrations were measured within the perimeter of the production facility, and the maximum concentration measured beyond this perimeter was 0.079 $\mu g/m^3$. Similar concentrations of NDMA were found in samples taken in the vicinity of an industrial site in Kitchener, Ontario, in 1992 (OME, 1992).

Available data indicate that levels of NDMA were elevated in indoor air contaminated with environmental tobacco smoke in the United States (Brunnemann and Hoffmann, 1978) and Austria (Stehlik et al., 1982; Klus et al., 1992). The maximum concentration of NDMA in environmental tobacco smoke–contaminated indoor air was 0.24 $\mu g/m^3$, whereas NDMA was not detected (i.e., <0.003 $\mu g/m^3$) when the indoor air of a residence of a non-smoker was sampled in the same manner (Brunnemann and Hoffmann, 1978). Concentrations of NDMA in environmental tobacco smoke–contaminated indoor air in these countries (United States and Austria) were generally between 0.01 and 0.1 $\mu g/m^3$ (Health Canada, 1999).

5.3 Food

NDMA can be formed during food processing, preservation or preparation from precursor compounds already present in, or added to, the specific food items. The foodstuffs that have been most commonly contaminated with NDMA can be classified into several broad groups (IPCS, 2002):

- foods preserved by the addition of nitrate or nitrite, such as cured meat products (in particular, bacon) and cheeses (as these methods of preservation introduce nitrosating species into the food);
- foods preserved by smoking, such as fish and meat products (as oxides of nitrogen in the smoke act as nitrosating agents);
- foods dried by combustion gases, such as malt, low-fat dried milk products and spices (as combustion gases can contain oxides of nitrogen);
- pickled and salt-preserved foods, particularly pickled vegetables (as microbial reduction of nitrate to nitrite occurs); and
- foods grown or stored under humid conditions, leading to nitrosamine formation by contaminating bacteria.

It should be noted, however, that most data on levels of NDMA in foodstuffs have been derived from studies conducted in the 1970s and 1980s and may not be reliable for estimating current exposure to this substance, because of the limited analytical methodology available at the time. Moreover, efforts have been made to reduce the potential for exposure to NDMA in foodstuffs in Canada and other countries through continued reduction of allowable nitrite levels

during preservation, suspension of the use of nitrate for certain food groups and increased use of nitrosation inhibitors, such as ascorbate or erythorbate (Cassens, 1997; Sen and Baddoo, 1997).

Levels in Canadian foods in the late 1970s and early 1980s have been fully reviewed in IPCS (2002). NDMA concentrations in meat ranged from less than the detection limit of 0.1 µg/kg to 17.2 µg/kg; for various fish and seafood, the range was from <0.1 to 4.2 µg/kg. For cheese, the range was <1 µg/kg to a maximum of 68 µg/kg in a sample of wine cheese. NDMA was not detected in milk products, with the exception of skim milk powder, in which it was present at concentrations below 0.7 µg/kg (IPCS, 2002). A 1981 report (Sen and Seaman, 1981) indicated the presence of NDMA in powdered infant formulas containing skim milk powder, with levels ranging from trace amounts to 1 µg/kg in three of eight samples tested. NDMA was not detected in baby food, apple juice, ketchup, sauces, margarine or butter (IPCS, 2002). Cooked bacon was reported to contain as much as 17.2 µg/kg, but controls on the use of nitrate and nitrite are believed to have reduced NDMA levels in bacon. Malt beverages such as beer and whiskey contain NDMA, but, again, levels have been dropping. Canadian beer analysed in 1988–1989 had a mean NDMA concentration of only 0.10 µg/L. Concentrations in imported beer averaged 0.71 µg/L in 1991–1992 and 0.15 µg/L in 1994 (Sen et al., 1996).

In addition to the presence of NDMA in various food sources, NDMA can also form endogenously from the nitrosation of secondary amines found in various foods. This process involves the reaction of nitrite and nitrate in foods with stomach acid to form nitroso groups, which can then react with amines to form NDMA. Although the mechanisms of NDMA formation have been well studied, data are insufficient to assess the quantities formed endogenously in humans (Fristachi and Rice, 2007).

5.4 Consumer products

Exposure to NDMA can result from the use of consumer products. NDMA has been detected in a variety of personal care and cosmetic products (e.g., shampoos, hair conditioners and toners, bath and shower gels, creams and oils, face tonics, cleansers). This is likely due to the reaction of nitrosating agents such as nitrite or nitrogen oxides, which occur frequently in these products (Spiegelhalder and Preussmann, 1984), with amine-containing compounds used extensively in ingredients of personal care products (ECETOC, 1990).

Rubber-containing products that come into contact with human skin are another potential source of exposure to NDMA, since dialkylamines used by rubber manufacturers as accelerators and stabilizers during rubber vulcanization can react with nitrosating agents during processing to form nitrosamines (Biaudet et al., 1997). NDMA has been detected in a diverse selection of workplace, consumer and medical products containing rubber, including rubber bottle nipples (Health Canada, 1999; Fristachi and Rice, 2007).

Lastly, the nitrosation of natural constituents of tobacco during curing and fermentation results in the formation of three major classes of *N*-nitroso compounds in tobacco and tobacco products: volatile, non-volatile and tobacco-specific *N*-nitrosamines (Hoffmann et al., 1984; Tricker et al., 1991). In addition, the combustion of cigarette tobacco results in the pyrolytic formation of volatile *N*-nitrosamines, including NDMA (Tricker and Preussmann, 1992). The yields of these volatile *N*-nitrosamines in cigarette smoke from combustion of tobacco depend on many chemical and physical parameters, including the amounts of organic nitrogen and nitrate present. Furthermore, nicotine serves as a specific precursor for the formation of NDMA (Hoffmann et al., 1987).

5.5 Contribution of drinking water to total exposure

Canadian data for environmental media, used to estimate population exposure to NDMA, are limited in both spatial and temporal scope. In a worst-case estimation of exposure to NDMA in contaminated air, water and food, the daily intake of a 20- to 59-year-old was approximated to be 0.005–0.016 µg/kg bw per day (Environment Canada and Health Canada, 2001). Daily intake of NDMA from ingestion of drinking water for the same age group was estimated at 0.0003–0.001 µg/kg bw per day (Environment Canada and Health Canada, 2001), based on a mean NDMA concentration of 0.012 µg/L and a maximum concentration of 0.04 µg/L obtained from 20 samples from four water treatment plants using a pre-blended polyamine/alum product during the treatment process (OMEE, 1996). Comparing the low- and high-end values for daily intake of NDMA from ingestion of drinking water the total exposure to NDMA in contaminated air, water and food indicates that human exposure to NDMA via drinking water is very low.

In a detailed study that examined NDMA exposure from a number of different sources, The authors estimated the proportional oral intake of NDMA attributable to drinking water over a 75-year lifetime to be less than 1% (Fristachi and Rice, 2007). Although the concentrations of NDMA in foods are low and hence exposure from foods is relatively low, foods were estimated to be a much more significant source of exposure to NDMA than was drinking water (Fristachi and Rice, 2007). However, it should be noted that higher concentrations, as observed in contaminated groundwater, could result in significantly higher exposures via drinking water (OEHHA, 2006).

5.6 Multi-route exposure through drinking water

In order to assess the potential exposure to NDMA via inhalation and dermal absorption resulting from activities such as showering and bathing, the relative contribution of each exposure route was assessed through a multi-route exposure assessment. This approach was derived from physiologically based pharmacokinetic modelling (Krishnan, 2004). Both the dermal and inhalation routes of exposure for a volatile organic chemical are considered significant if they contribute to at least 10% of the drinking water consumption level.

5.6.1 Dermal exposure

To determine whether dermal exposure represents a significant route of exposure for NDMA, tier 1 of the multi-route exposure assessment determines whether or not this route of exposure contributes a minimum of 10% of the drinking water consumption level (i.e., 10% of 1.5 L = 0.15 L). In order for a chemical to contribute at least 0.15 litre-equivalents (L_{eq}), the skin permeability coefficient (K_p) for the chemical must be greater than 0.024 cm/h. The K_p for NDMA can be calculated using the following formula, described in Krishnan (2004):

$$\log K_p = -0.812 - 0.0104\ MW + 0.616 \log K_{ow}$$

$$= -0.812 - 0.0104\ (74.08) + 0.616\ (0.57)$$

$$K_p = 0.058\ \text{cm/h}$$

where:

- MW is the molecular weight of NDMA (74.08);
- $\log K_{ow}$ is the log *n*-octanol/water partition coefficient (0.57).

Since the skin permeability coefficient for NDMA is greater than 0.024 cm/h, dermal absorption is considered to be significant during showering and bathing. As such, it is necessary to perform a tier 2 calculation to determine what value of L-eq is needed to account for dermal exposure.

The L-eq for dermal exposure to NDMA in drinking water can be calculated using the following formula, described in Krishnan, 2004:

$$\begin{aligned} \text{Dermal L-eq} &= 6.3(K_p) \\ &= 6.3(0.058) \\ &= 0.3654 \end{aligned}$$

$$\text{Dermal L-eq} \approx 0.4 \text{ (rounded)}$$

This L-eq should be considered in calculation of the MAC, and the value of 1.5 L/d normally considered for ingestion of drinking water becomes 1.9 L/d for total exposure from drinking water.

5.6.2 Inhalation exposure

A two-tier assessment was also used to evaluate the inhalation route of exposure. Similar to the approach used for dermal exposure, tier 1 of the assessment determines whether the inhalation of NDMA during bathing or showering is likely to contribute at least 10% of the drinking water consumption level. For a tier 1 goal of 0.15 L-eq, the air to water NDMA concentration ($F_{air:water}$) value should be greater than 0.000 89. Using Henry's law constant (K_{aw}), the $F_{air:water}$ value for NDMA was determined using the following equation (Krishnan, 2004):

$$\begin{aligned} F_{air:water} &= \frac{0.61 \times K_{aw}}{1 + (80.25 \times K_{aw})} \\ &= \frac{0.61 \times 3.3 \times 10^{-5}}{1 + (80.25 \times 3.3 \times 10^{-5})} \\ &\approx 2.0 \times 10^{-5} \end{aligned}$$

where:

- K_{aw} is the unitless Henry's law constant of 3.3×10^{-5} at 25°C;
- 0.61 is 61% transfer efficiency (McKone and Knezovich, 1991);
- 80.25 is the ratio of the volume of air in an average bathroom (6420 L) to the average volume of water (80 L) used during the showering/bathing event (Krishnan, 2004).

Since the $F_{air:water}$ value is less than 0.000 89, exposure to NDMA via inhalation from bathing or showering is not considered to be significant. Tier 2 of the assessment, which calculates the volume of water (in L-eq) to account for inhalation exposure, is not needed (Krishnan, 2004).

6.0 Analytical methods

The U.S. Environmental Protection Agency (EPA) has approved one method, EPA Method 521, for the analysis of NDMA and has identified it as the method to use under the Unregulated Contaminants Monitoring Rule 2. EPA Method 521 uses solid-phase extraction with capillary column gas chromatography and chemical ionization tandem mass spectrometry. The method lists a detection limit of 0.28 ng/L and a lowest concentration minimum reporting level of 1.6 ng/L (U.S. EPA, 2004).

Standard Methods for the Examination of Water and Wastewater has one method for the analysis of NDMA under Method 6410B, which uses liquid–liquid extraction with gas chromatography/mass spectrometry (APHA et al., 2005). However, this method does not identify any method detection limit.

Other methods have been published with different extraction and concentration methods, such as liquid–liquid extraction and solid-phase extraction (Cheng et al., 2006). A number of studies are currently being conducted to improve the detection of NDMA and other nitrosamines; however, none is currently approved for routine monitoring.

7.0 Treatment considerations

The presence of NDMA in drinking water is usually associated with its formation during water treatment rather than with its presence in the source water. NDMA formation in water is largely a function of the nature and amount of precursor compounds and the disinfection strategy used.

7.1 NDMA formation during disinfection

The formation of NDMA is primarily associated with chloramination. Research has identified three nitrosamine formation pathways relevant to drinking water disinfection. For the first two pathways, the organic nitrogen precursors (i.e., DMA and trimethylamine) are likely to be similar, although DMA and trimethylamine concentrations in source waters are generally insufficient to account for NDMA formation (Gerecke and Sedlak, 2003; Mitch and Sedlak, 2004; Mitch and Schreiber, 2008).

In the first pathway, chloramination has been associated with the formation of nitrosamine (Mitch et al., 2003a), possibly involving the reaction of dichloramine with organic nitrogen precursors over the course of days (Schreiber and Mitch, 2006a). Although monochloramine predominates in chloraminated systems, low concentrations of dichloramine generally co-occur. Organic nitrogen precursors are typically associated with wastewater effluents, and utilities employing wastewater-impacted source waters may be at particular risk (Schreiber and Mitch, 2006b). Organic nitrogen precursors are also produced as a consequence of the general oxidation of NOM such as humic substances (Chen and Valentine, 2007). Industrial emissions of nitrosamines may be a concern for these water supplies (Sedlak et al., 2005). Other precursors of importance to drinking water systems include quaternary amine–based cationic coagulation polymers (Wilczak et al., 2003) and anion exchange resins (Najm and Trussell, 2001).

In the second pathway, chlorination in the presence of nitrite can rapidly form nitrosamines (Choi and Valentine, 2003; Schreiber and Mitch, 2007). This pathway is likely to be less important, as free chlorine and nitrite do not co-occur in significant concentrations in drinking water plants, but it could be more of a concern in the distribution system.

The third pathway for NDMA formation involves ozonation of the degradation products of the fungicide tolylfluanide, as documented by Schmidt and Brauch (2008).

There is little research investigating NDMA formation within distribution systems. In the case of NDMA formation through the first pathway, nitrosamine formation is expected to continue within chloraminated distribution systems because of the slow reaction time associated with dichloramine. It has been shown that NDMA levels in the distribution system increased with increased distribution residence time (Barrett et al., 2003; Wilczak et al., 2003; Charrois and Hrudey, 2007).

Breakpoint chlorination and free chlorine contact time have significant implications in the formation of NDMA. In a bench-scale experiment, Charrois and Hrudey (2007) reported a 93% reduction of NDMA formation to an effluent level of 3 ng/L when allowed a free chlorine contact time of 2 h prior to chloramination, compared with no free chlorine contact time. In a laboratory study of secondary disinfection, breakpoint chlorination reduced NDMA formation. Chlorination at a Cl:N molar ratio of 0.5 produced concentrations of NDMA greater than 200 ng/L, compared with negligible levels of NDMA when chlorinating at a Cl:N molar ratio of 4 (Schreiber and Mitch, 2005). When ammonia is already present in the source water, precursor deactivation can be achieved with free chlorine by applying a chlorine dose that exceeds the breakpoint (Schreiber and Mitch, 2007).

7.2 Preventing NDMA formation

Existing treatment facilities and processes should be optimized to reduce the formation of disinfection by-products, including NDMA, without compromising the effectiveness of disinfection. Strategies to prevent NDMA formation during disinfection focus on the removal of its most important precursors, the organic nitrogen precursors (i.e., DMA and trimethylamine) and dichloramine.

Application of strong oxidants, including free chlorine (Schreiber and Mitch, 2005; Charrois and Hrudey, 2007), chlorine dioxide or ozone (Lee et al., 2007a), upstream of chloramination can deactivate organic precursors. In a laboratory study with both synthetic and natural water, oxidation by either ozone or chlorine dioxide showed reduction of NDMA formation potential (Lee et al., 2007a).

As stated previously, some treatment processes may result in the formation of NDMA. To minimize NDMA formation, drinking water utilities should pay special attention when selecting polyelectrolyte coagulants and ion exchange resins and should minimize the use of quaternary amine–based coagulation polymers (Wilczak et al., 2003).

7.3 Treatment technology

NDMA is the nitrosamine species predominantly formed during chloramination, but it can also be a by-product of chlorination. In laboratory- and full-scale tests, the levels of other nitrosamines formed (*N*-nitrosoethylmethylamine, *N*-nitrosodiethylamine) were one or two orders of magnitude lower than the concentrations of NDMA (Sacher et al., 2008). More research on the toxicity and treatment characteristics of the other nitrosamines is required.

In order to reduce NDMA levels in the finished water, it is important to study the influence of treatment on the formation of NDMA and other disinfection by-products. In particular, the treatment study (including pilot testing) should assess the disinfection strategy for its potential to form disinfection by-products. This assessment will help ensure that the treatment strategy implemented minimizes the formation of all potential disinfection by-products.

7.3.1 Municipal scale

The most commonly used treatment method for the reduction of already formed NDMA is photolysis by ultraviolet radiation (UV) (Mitch et al., 2003a). NDMA can be removed by activated carbon adsorption, reverse osmosis, ozone oxidation or biodegradation or by the advanced oxidation process (AOP) of UV with hydrogen peroxide (UV/H_2O_2). (Siddiqui and Atasi, 2001; Mitch et al., 2003a), although these methods are not highly efficient. NDMA is biodegradable; however, the rate of degradation is in the order of days, which makes it impractical for drinking water treatment processes. Sharpless and Linden (2003) and Liang et al. (2003) concluded that the addition of hydrogen peroxide as an AOP is of limited economic benefit when it is used only for NDMA removal.

7.3.1.1 UV irradiation and advanced oxidation

The most common process currently used for NDMA reduction is UV irradiation. The UV dose required for 90% reduction of NDMA is about 1000 mJ/cm^2, approximately 10 times higher than that required for virus inactivation (Mitch et al., 2003a). NDMA reduction using UV irradiation is technically feasible but expensive, and it may be difficult for smaller utilities.

The principal by-products of UV photolysis of NDMA are DMA and nitrite (Bolton and Stefan, 2000; Mitch et al., 2003a). When UV/ H_2O_2 is applied, nitrate is the major degradation product, and the concentration of DMA is significantly lower than with direct photolysis (Bolton and Stefan, 2000).

A study conducted to compare the ability of low- and medium-pressure mercury UV lamps to degrade NDMA in "synthetic" drinking water spiked at a concentration of 75 µg/L demonstrated that both types of lamps gave effective degradation with similar efficiencies (Sharpless and Linden, 2003). The addition of hydrogen peroxide at 100 mg/L gave a 30% increase in the degradation rate for the low-pressure lamp but did not improve the efficiency of the medium-pressure lamp.

A study by Lee et al. (2005) demonstrated that irradiation with a 13 W low-pressure mercury lamp required approximately 15 min for complete degradation of a 7.5 µg/L NDMA solution at pH 7; a 750 µg/L solution required 5 h. The subsequent analysis showed that the degradation products from this treatment process were methylamine and DMA, and their relative concentrations depended on the reaction conditions.

Liang et al. (2003) conducted a bench-scale study to determine the effectiveness of pulsed UV in oxidizing NDMA, as pulsed UV can deliver higher UV intensities compared with continuous-wave UV technology. High removal rates were observed with pulsed UV, but the viability of such systems needs to be further studied.

AOP studies for degradation of NDMA were very dependent on the hydroxyl scavenging rates of the natural waters. In experiments with ozone and hydrogen peroxide, Lee et al. (2007b) observed NDMA oxidation of 55% and 78% with ozone doses of 160 µM and 320 µM, respectively, with an ozone to H_2O_2 ratio of 2:1, pH of 7.9 and an initial concentration of 1 µM (74 µg/L) NDMA. Ozone doses of 40 and 160 µM provided NDMA reductions of 10% and 25%, respectively, at pH 7 with an initial NDMA concentration of 1 µM.

A bench scale study (Zhao et al., 2008) suggests that UV degradation or AOP treatment may provide a source of precursors that can form NDMA during subsequent chlorination steps. The study also indicates that because of the different pattern of NDMA formation, the natural organic matter and anthropogenic organic contaminants of different source waters may affect NDMA removal. Although UV and AOP can reduce concentration of NDMA in water, the

selection of that treatment option will require pilot study/consideration regarding the potential formation of NDMA subsequent to chlorination steps.

7.3.1.2 Reverse osmosis and adsorption

NDMA is poorly removed by reverse osmosis (RO). A laboratory-scale study using three different membranes resulted in rejection rates of 54%, 61% and 70% (Steinle-Darling et al., 2007). This study also indicated that additional coating and/or foulant accumulation can be significant and, depending on conditions, can increase or decrease rejection. This underlines the importance of assessing membranes individually through pilot testing.

NDMA sorbs poorly to soil, activated carbon or other sorbents. Various laboratory tests conducted to compare the effectiveness of various carbonaceous adsorbents and zeolites for NDMA reduction (Fleming et al., 1996; Zhu et al., 2001; Kommineni et al., 2003) found these adsorbents to be largely ineffective.

7.3.2 Residential scale

Generally, it is not necessary to use drinking water treatment devices with municipally treated water. Where consumers choose to use a device, it is important to note that Health Canada does not recommend specific brands of drinking water treatment devices, but it strongly recommends that consumers look for a mark or label indicating that the device has been certified by an accredited certification body as meeting the appropriate NSF/American National Standards Institute (ANSI) standards. These standards have been designed to safeguard drinking water by helping to ensure the material safety and performance of products that come into contact with drinking water. Meeting these standards ensures that a drinking water treatment device does not introduce additional contaminants into the drinking water.

Certification organizations provide assurance that a product conforms to applicable standards and must be accredited by the Standards Council of Canada (SCC). In Canada, the following organizations have been accredited by the SCC to certify treatment devices and materials as meeting NSF/ANSI standards:

- Canadian Standards Association International (www.csa-international.org);
- NSF International (www.nsf.org);
- Water Quality Association (www.wqa.org);
- Underwriters Laboratories Inc. (www.ul.com);
- Quality Auditing Institute (www.qai.org); and
- International Association of Plumbing and Mechanical Officials (www.iapmo.org).

An up-to-date list of accredited certification organizations can be obtained from the SCC (www.scc.ca).

NSF International (NSF) has developed several standards for residential water treatment devices designed to reduce the concentrations of various types of contaminants in drinking water, but NDMA is not currently included in any NSF standard. Research is ongoing in the private and public sectors to test and adopt efficient methods for the reduction of NDMA in drinking water. At this time, there are no residential-scale treatment devices specifically for NDMA reduction. Reverse osmosis filtration, although not very efficient, can provide some reduction. Because NDMA reduction is dependent on membrane type, testing of various RO filters should be done to select the most appropriate system for the water being treated. Products that use RO technology can lose removal capacity through usage and time and should be maintained or replaced as per the manufacturer's recommendations. Although UV is a technology that can

reduce NDMA levels, residential UV treatment units do not operate at high enough doses to reduce NDMA concentrations in water.

8.0 Kinetics and metabolism

8.1 Absorption

Although quantitative data in humans have not been identified, studies conducted with laboratory animals indicate that ingested NDMA is absorbed rapidly and extensively (i.e., >90%) (Daugherty and Clapp, 1976; Diaz Gomez et al., 1977; Kunisaki et al., 1978), primarily from the lower intestinal tract (Phillips et al., 1975; Hashimoto et al., 1976; Agrelo et al., 1978; Pegg and Perry, 1981). Detection of NDMA in the urine of rats and dogs exposed by inhalation indicates that the nitrosamine is absorbed through the lungs; however, reliable quantitative information on the absorption of NDMA following inhalation was not identified. Although quantitative data were not identified, absorption through the skin may be inferred from the results of a study in which small amounts (i.e., 0.03%) of NDMA were detected in the urine of rats following epicutaneous (dermal) administration of a solution containing 350 µg NDMA (Spiegelhalder et al., 1982).

8.2 Distribution and excretion

Once absorbed, NDMA and its metabolites are distributed widely (Daugherty and Clapp, 1976; Anderson et al., 1986) and likely passed to offspring through mothers' milk (Diaz Gomez et al., 1986). The nitrosamine and its metabolites have been detected in the fetuses of pregnant rodents injected with the substance (Althoff et al., 1977; Johansson-Brittebo and Tjälve, 1979). Pharmacokinetic analyses of NDMA injected intravenously into a number of laboratory species have revealed that the nitrosamine is cleared rapidly from the blood, with metabolism involving both hepatic and extrahepatic components. NDMA and its metabolites may be excreted in the urine or exhaled as carbon dioxide.

8.3 Metabolism

Quantitative information from studies on the metabolism of NDMA in humans was not identified. However, there appear to be differences in the rate of metabolism of NDMA between species (Jeong-Sook et al., 1987; Gombar et al., 1990). Despite potential quantitative differences in NDMA metabolism, there appear to be few qualitative differences in the metabolism of NDMA between humans and laboratory animals. The metabolism of NDMA involves either the α-hydroxylation or denitrosation of the nitrosamine (Figure 1). Both pathways are considered to proceed through a common intermediate radical [$CH_3(CH_2\cdot)NBN{=}O$] generated by the action of the cytochrome CYP2E1-dependent mixed-function oxidase system (Haggerty and Holsapple, 1990; Lee et al., 1996). Along the α-hydroxylation pathway, the hydroxymethylnitrosamine ($HOCH_2CH_3HBN{=}O$) formed from the intermediate radical decomposes to formaldehyde (itself ultimately converting to carbon dioxide) and monomethylnitrosamine ($CH_3NHN{=}O$); the monomethylnitrosamine, owing to its instability, undergoes rearrangement to the strongly methylating methyldiazonium ion ($CH_3N^+{\equiv}N$), which alkylates biological macromolecules such as DNA, RNA and proteins. It is the α-hydroxylation pathway that is believed to form the active metabolites responsible for NDMA's genotoxicity and carcinogenicity (Lee et al., 1996). Metabolic conversion of the intermediate radical via denitrosation leads to the formation of methylamine (CH_3NH_2) and formaldehyde (Figure 1).

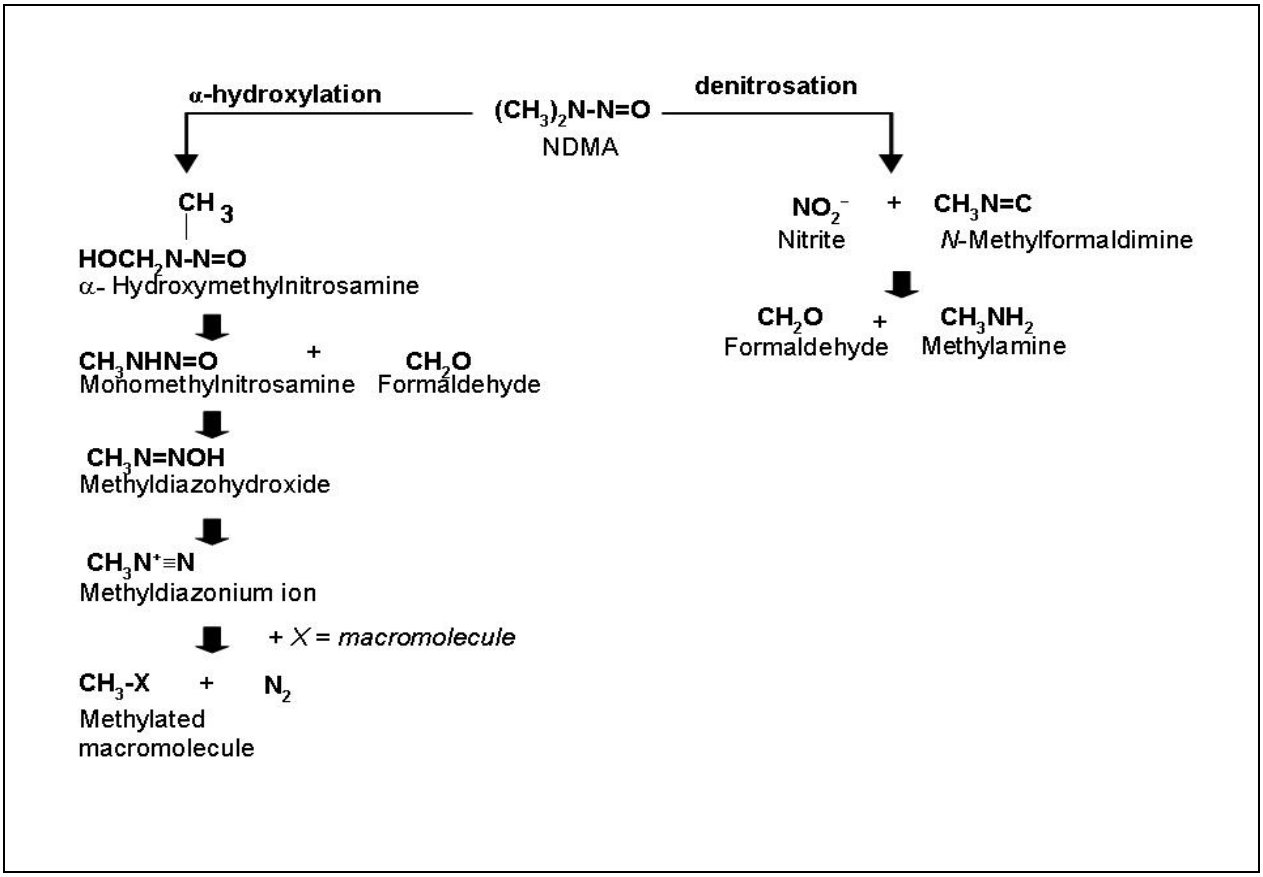

Figure 1: Pathways of NDMA metabolism (adapted from ATSDR, 1989; IPCS 2002)

9.0 Health effects

9.1 Effects in humans

9.1.1 Acute and short-term toxicity

Two deaths (one adult and one child) linked to the acute ingestion of unknown quantities of NDMA in tainted lemonade, as well as a third adult fatality attributed to the consumption of at least four doses of approximately 250–300 mg of NDMA over a 2-year period, have been reported (Cooper and Kimbrough, 1980; Fussgänger and Ditschuneit, 1980; Pedal et al., 1982). Liver failure was observed in all three cases; the two acutely exposed decedents also exhibited cerebral haemorrhage.

9.1.2 Epidemiology: cancer effects

Relevant epidemiological studies include case–control investigations in which the potential risks of cancer of the stomach (Risch et al., 1985; González et al., 1994; La Vecchia et al., 1995; Pobel et al., 1995), upper digestive tract (Rogers et al., 1995) and lung (Goodman et al., 1992; De Stefani et al., 1996) associated with the ingestion of NDMA have been assessed. In some of these reports, the estimated intake of NDMA was based upon recollection of an individual's typical diet consumed in the year preceding the onset of illness, as well as the reported levels of this nitrosamine in the foodstuffs consumed (Goodman et al., 1992; González et al., 1994; Pobel et al., 1995).

In other studies (Rogers et al., 1995; De Stefani et al., 1996), subjects were asked to recall their typical diet in the 5 and 10 years, respectively, prior to the onset of illness.

In three of four case–control studies, there was a positive relationship with evidence of exposure–response for the intake of NDMA and gastric cancer (González et al., 1994; La Vecchia et al., 1995; Pobel et al., 1995), although not in an additional study in which oral, laryngeal and oesophageal cancers were investigated separately (Rogers et al., 1995). In two case–control studies in which matching or control for confounders was more extensive than that for the investigations of gastric cancer mentioned above, there were clear exposure–response relationships for NDMA and lung cancer (Goodman et al., 1992; De Stefani et al., 1996). In almost all studies, associations between the cancers of interest and nitrate, nitrite and NDMA were examined.

A population-based cohort study of 9985 adult Finnish men and women with a follow-up period of 24 years showed a relative risk of 2.12 (95% confidence interval = 1.04–4.33) for colorectal cancer associated with NDMA intake (Knekt et al., 1999). Head and neck and stomach cancers were also studied, but the relative risks were not statistically significant. No significant association was observed between nitrate or nitrite intake and cancers of the gastrointestinal tract. There appears to be no qualitative difference between rodents and humans in the formation of DNA adducts following exposure to NDMA. In a case of suspected NDMA poisoning in a human male, methylation of liver DNA was evident at both the $N^7$and O^6 positions of guanine (Herron and Shank, 1980). Using an immunohistochemical technique, Parsa et al. (1987) detected the formation of O^6-methylguanine in human pancreatic explants incubated *in vitro* with NDMA.

9.2 Effects in experimental animals and *in vitro*

9.2.1 Acute toxicity

NDMA is highly acutely toxic after oral administration to rats, with lethal doses (LD_{50}s) ranging from 23 to 40 mg/kg bw (ATSDR, 1989). It is also highly acutely toxic via inhalation; 4-h median lethal concentrations (LC_{50}s) are 240 mg/m^3 (78 parts per million [ppm]) for rats and 176 mg/m^3 (57 ppm) for mice (ATSDR, 1989). A lowest-observed-effect concentration (LOEC) of 49 mg/m^3 (16 ppm) was identified for inhalation in dogs exposed to NDMA for 4 h (ATSDR, 1989). In all three species, acute inhalation exposure produced haemorrhagic necrosis in the liver. An increased blood clotting time was also reported for the NDMA-exposed dogs (ATSDR, 1989). Following intraperitoneal exposure, LD_{50}s of 43 mg/kg bw in rats and 20 mg/kg bw in mice have been reported (IARC, 1978). In other laboratory species, acute exposure to NDMA at levels of 30–60 mg/kg bw produced effects in the liver (hepatotoxicity), kidney (tumours) and testes (necrosis of the seminiferous epithelium) (Magee and Barnes, 1962; Schmidt and Murphy, 1966; Hard and Butler, 1970a,b; McLean and Magee, 1970; OME, 1991).

9.2.2 Short-term exposure

Hepatic effects (i.e., hepatocyte vacuolization, portal venopathy, necrosis/haemorrhage), often associated with reduced survival, have been observed in a number of mammalian species exposed orally (by gavage, unless otherwise stated) under various conditions (e.g., in rats receiving 1, 3.8 or 5 mg NDMA/kg bw per day for 30, 7–28 or 5–11 days, respectively; in mice receiving 5 mg/kg bw per day in drinking water for 7–28 days; in hamsters receiving 4 mg/kg bw per day in drinking water for 1–28 days; in guinea-pigs, cats and monkeys receiving 1 mg/kg bw per day for 30 days or 5 mg/kg bw per day for 5–11 days; in dogs receiving 2.5 mg/kg bw per day, 2 days per week, for 3 weeks; and in mink receiving 0.32 mg/kg bw per day for 23–34 days) (as reviewed in IARC, 1978; ATSDR, 1989).

In addition to effects in the liver, "congestion" (excessive blood/fluid content) in a variety of organs (i.e., kidneys, lung, spleen, myocardium) has been reported in rats receiving 3.8 mg NDMA/kg bw per day in the diet for 1–12 weeks (Khanna and Puri, 1966). Gastrointestinal haemorrhage has been observed in rats receiving dietary doses of 10 mg NDMA/kg bw per day for 34–37 days (Barnes and Magee, 1954) and in mink receiving 0.3 or 0.6 mg NDMA/kg bw per day in the diet for 23–34 days (Carter et al., 1969). Effects in the kidneys (including glomerulus dilatation and slight thickening of the Bowman's capsule) were observed in mink receiving 0.2 mg NDMA/kg bw per day from the diet (period not specified) (Martino et al., 1988).

9.2.3 Long-term exposure and carcinogenicity

NDMA has consistently shown potent carcinogenicity in all laboratory animal studies. As a result, there has been little attempt to study other toxic end-points, and there are inadequate data available to make a meaningful assessment of end-points other than carcinogenicity.

Although most studies would be considered limited by current standards (e.g., small group sizes, single dose levels, limited histopathological examination), there has been clear, consistent evidence of carcinogenicity in studies where rodents (i.e., rats, mice, hamsters) were exposed to NDMA orally, via inhalation or by intratracheal instillation. NDMA increased the incidence of liver and Leydig cell tumours in rats ingesting this nitrosamine from drinking water or the diet (Terao et al., 1978; Arai et al., 1979; Ito et al., 1982; Lijinsky and Reuber, 1984); increased tumour incidences were noted at concentrations of NDMA of about 5 mg/L in drinking water and 10 mg/kg in the diet. Hepatic, pulmonary and renal carcinogenicity was observed in mice administered NDMA via drinking water (Terracini et al., 1966; Clapp and Toya, 1970; Anderson et al., 1979, 1986, 1992) or through inhalation (Moiseev and Benemanskii, 1975); increases in tumour incidence were observed at concentrations of NDMA in drinking water ranging from 0.01 to 5 mg/L. Moreover, in some cases (e.g., Terracini et al., 1966), the period of exposure to NDMA was relatively short (i.e., 3 weeks). NDMA increased the incidence of liver tumours in hamsters exposed intratracheally (Tanaka et al., 1988). The administration of NDMA to pregnant rats (by intraperitoneal injection) or mice (by stomach tube) increased the frequency of hepatic and renal tumours in the offspring (Alexandrov, 1968; Anderson et al., 1989).

One study in particular stands out as the most comprehensive one to use for a quantitative risk assessment due to the exceptionally high power (2040 rats) and wide concentration range that was used. This carcinogenicity bioassay (designed to provide detailed information on exposure–response) involving lifetime exposure, 15 dose groups of 60 male and 60 female Colworth-Wistar rats were provided with drinking water containing a wide range of 15 concentrations (from 33 to 16 896 µg/L) of NDMA (Brantom, 1983; Peto et al., 1991a,b). The estimated daily intakes of NDMA ranged from 0.001 to 0.697 mg/kg bw in the males and from 0.002 to 1.224 mg/kg bw in the females. A control group of 120 males and 120 females received drinking water without NDMA. Groups of animals were taken for interim sacrifice after 12 and 18 months of study. Survival of the animals was reduced with increasing dose; animals in the highest dose group did not survive longer than 1 year. Survival in the low-dosed groups was good (up to 3.5 years). At low dose rates, it was found that the number of liver neoplasms induced was proportional to the dose rate, with no indication of a threshold. In addition, a variety of nonneoplastic abnormalities were seen in the liver at low doses; these included hyperplastic nodules and shrinkage of hepatocytes.

9.2.4 Genotoxicity and related end-points

There is overwhelming evidence that NDMA is mutagenic and clastogenic (reviewed in IARC, 1978; ATSDR, 1989). Increased frequencies of gene mutations, chromosomal damage, sister chromatid exchange and unscheduled DNA synthesis have been observed in a wide variety of cell types, in assays conducted in the presence or absence of metabolic activation. Positive results have been observed in human as well as rodent cells. Two studies by Hakura et al. (1999, 2003) found that S9 fractions from human sources were considerably more active than those from rats in stimulating the mutagenic response to NDMA in the Ames test: the mutation rate was up to 8 times higher with some human S9 fractions.

Clear evidence of genetic effects has also been observed in *in vivo* studies. Clastogenic effects (e.g., micronuclei, sister chromatid exchange, chromosomal aberrations) in hepatocytes (Tates et al., 1980, 1983, 1986; Mehta et al., 1987; Braithwaite and Ashby, 1988; Cliet et al., 1989; Neft and Conner, 1989; Sawada et al., 1991), bone marrow cells (Bauknecht et al., 1977; Wild, 1978; Neal and Probst, 1983; Collaborative Study Group for the Micronucleus Test, 1986; Neft and Conner, 1989; Krishna et al., 1990; Sato et al., 1992; Morrison and Ashby, 1994), spleen cells (Neft and Conner, 1989; Krishna et al., 1990) and peripheral blood lymphocytes (Tates et al., 1983; Sato et al., 1992), as well as in oesophageal (Mehta et al., 1987) and kidney cells (Robbiano et al., 1997), have been observed in rodents (rats, mice or hamsters) administered NDMA either orally or by intraperitoneal injection. Increased frequencies of micronucleated cells were observed at doses as low as 5 mg/kg bw in rats (Trzos et al., 1978; Mehta et al., 1987). Effects in germ cells (i.e., micronucleated spermatids) were observed in mice given 6 or 9 mg NDMA/kg bw via intraperitoneal injection (Cliet et al., 1993). The inhalation exposure of female mice to NDMA at 1030 mg/m^3 increased the frequency of micronucleated bone marrow cells (Odagiri et al., 1986). Evidence of genotoxicity (e.g., chromosomal aberrations, micronuclei, gene mutation, DNA strand breaks) has also been observed in the offspring of hamsters (Inui et al., 1979) and mice (Bolognesi et al., 1988) administered NDMA during gestation. In rodents (rats, mice or hamsters) administered NDMA either orally or by intraperitoneal injection, evidence of DNA damage has been observed in the liver, kidneys and lungs (Laishes et al., 1975; Petzold and Swenberg, 1978; Abanobi et al., 1979; Mirsalis and Butterworth, 1980; Brambilla et al., 1981, 1987; Bermudez et al., 1982; Cesarone et al., 1982; Barbin et al., 1983; Doolittle et al., 1984; Kornbrust and Dietz, 1985; Loury et al., 1987; Mirsalis et al., 1989; Pool et al., 1990; Brendler et al., 1992; Jorquera et al., 1993; Asakura et al., 1994; Tinwell et al., 1994; Webster et al., 1996). DNA damage in thymus (Petzold and Swenberg, 1978), sperm (Cesarone et al., 1979) and nasal and tracheal cells (Doolittle et al., 1984) has also been noted. NDMA was mutagenic at the *lacI* locus (in the liver) in *in vivo* assays involving transgenic mice (Mirsalis et al., 1993; Tinwell et al., 1994; Butterworth et al., 1998). In addition, increased unscheduled hepatic DNA synthesis has been observed in rats at doses as low as 0.1 mg/kg bw (Mirsalis and Butterworth, 1980).

9.2.5 Reproductive and developmental toxicity

Available data are inadequate as a basis for assessment of the reproductive or developmental toxicity of NDMA. Interpretation of the results of most identified investigations is complicated by the high doses administered, likely to have induced acute or repeated-dose organ toxicity. In a report by Anderson et al. (1978), time to conception in female mice provided with drinking water containing 0.1 mg NDMA/L for 75 days prior to mating was about 3 days longer than in unexposed controls; no other reproductive effects were assessed in this study. In a study conducted with male

rats, a single intraperitoneal injection of 30 or 60 mg NDMA/kg bw induced testicular damage (necrosis or degeneration of the seminiferous epithelium) (Hard and Butler, 1970b).

In a single-generation study (Anderson et al., 1978) in which the reproductive effects of a number of substances were examined, groups of 20 female mice were provided with drinking water containing 0 or 0.1 mg NDMA/L for 75 days prior to mating and throughout pregnancy and lactation (estimated daily and total intakes of 0.02 mg/kg bw per day and 2 mg/kg bw, respectively). The proportion of deaths (based upon the total number of stillborn and neonatal deaths) was increased 2-fold in the NDMA-exposed animals compared with controls (i.e., 20% and 9.9%, respectively), due in large part to an increase in the number of stillborn animals. Exposure to NDMA had no effect upon maternal fluid consumption, litter size or average body weight of the weanlings, and no consistent gross or histopathological abnormalities were observed in the stillborn fetuses or dead neonates to account for the increased mortality.

The effects of NDMA on pregnant rats were studied by Nishie (1983). Single oral doses of 15 and 20 mg NDMA/kg bw given on day 18 of pregnancy resulted in lethality of 9.4% and 35.3% of pregnant rats, respectively, whereas no lethality was observed in non-pregnant rats. NDMA also increased serum α-hydroxybutyric dehydrogenase in pregnant rats on day 20 and decreased fetal weights in rats treated on days 13 and 18.

9.2.6 Mode of action

There is strong evidence that the toxicological effects of NDMA are directly dependent upon the CYP2E1-dependent metabolic conversion of this nitrosamine to highly reactive species. Lee et al. (1996) attributed the hepatotoxicity of NDMA to the methyldiazonium ion formed via the α-hydroxylation pathway; denitrosation was considered to make little contribution to the overall hepatotoxic effect of this nitrosamine in rats. The principal DNA adduct formed following exposure to NDMA is N^7-methylguanine (representing about 65% of all adducts formed initially upon exposure); O^6-methylguanine is a secondary adduct (representing about 7% of all adducts formed initially). Other DNA adducts formed in smaller amounts include N^3-methyladenine and O^4-methylthymine.

N^7-Methylguanine may undergo depurination, yielding apurinic sites, which, if not repaired prior to DNA replication, can result in guanine to thymine (i.e., G → T) transversions (Swenberg et al., 1991). Two adducts formed in small amounts, O^6-methylguanine and O^4-methylthymine (formed at about 1% of the amount of O^6-methylguanine), are strongly promutagenic by direct base mispairing. O^6-Methylguanine causes guanine:cytosine to adenine:thymine (i.e., G:C → A:T) transitions, whereas O^4-methylthymine causes A:T → G:C transitions (Swenberg et al., 1991; Souliotis et al., 1995).

Available data are consistent with the formation and persistence of the secondary adduct, O^6-methylguanine, being associated with both the carcinogenicity and mutagenicity of NDMA (see Haggerty and Holsapple, 1990; Swenberg et al., 1991; Souliotis et al., 1995). The ability of cells to repair DNA adducts (by removing O^6-methylguanine through the action of a specific O^6-methylguanine DNA-methyltransferase) prior to cell division likely plays a critical role in determining the susceptibility of tissues to tumour development.

In monkeys orally dosed with 0.1 mg NDMA/kg bw, O^6-methylguanine was detected in 32 tissues examined (Anderson et al., 1996). The highest levels were in the gastric mucosa and liver, but elevated levels were also present in white blood cells, the oesophagus, ovaries, pancreas, bladder and uterus. O^6-Methylguanine DNA-methyltransferase activity varied over a 30-fold range; the highest activities were in the gastric mucosa, liver, kidneys and lungs. The formation of

O^6-methylguanine was detected in fetal liver, lung, kidney, spleen and brain in a study in which pregnant patas monkeys were administered a single gastric NDMA dose of 1 mg/kg bw (Chhabra et al., 1995).

The greater persistence of O^6-methylguanine DNA adducts in the kidney compared with the liver in rats administered a single oral NDMA dose of 20 mg/kg bw parallels earlier findings in which the acute oral or intraperitoneal administration of NDMA to rats at such dose levels increased the incidence of kidney but not liver tumours (Magee and Barnes, 1962; Schmidt and Murphy, 1966; Hard and Butler, 1970a; McLean and Magee, 1970). In contrast, the long-term oral administration of low doses of NDMA (i.e., <2 mg/kg bw per day) increased the incidence of liver but not kidney tumours in these animals (Brantom, 1983; Lijinsky and Reuber, 1984; Peto et al., 1991a,b), a finding attributed to the first-pass metabolism of NDMA in the liver (Swenberg et al., 1991).

There are quantitative age- and species-related differences in hepatic O^6-methylguanine, possibly associated with variations in the activity of the transferase, consistent with observed variations in the carcinogenicity of the compound among species and strains exposed under various conditions. These include greater hepatic activity in adults compared with newborn mice (Coccia et al., 1988), in rats compared with mice and between strains of mice (greater in C3H than in C57BL) (Lindamood et al., 1984).

Evidence supporting a role for O^6-methylguanine formation in tumour development following exposure to NDMA was recently reviewed by Souliotis et al. (1995). G:C → A:T transitions have been observed in the *ras* oncogene in mouse lung tumours induced by NDMA (Devereux et al., 1991), in the livers of *lacI* transgenic mice administered a single dose of 4 mg NDMA/kg bw (Mirsalis et al., 1993) and in the liver, kidney and lung of *lacI* transgenic mice administered five daily doses of 1 mg NDMA/kg bw (Wang et al., 1998). Moreover, transgenic mice expressing high levels of O^6-methylguanine DNA-methyltransferase in the liver were less susceptible than normal controls to NDMA-induced hepatocarcinogenesis (Nakatsuru et al., 1993). However, Souliotis et al. (1995) also reported that the dose–response relationship for the accumulation of O^6-methylguanine in hepatic DNA in rats administered drinking water (for 28 days) containing concentrations of NDMA similar to those used in the study conducted at BIBRA Toxicology International (Brantom, 1983; Peto et al., 1991a,b) did not strictly parallel the dose–response for the development of hepatic tumours in the carcinogenicity bioassay.

10.0 Classification and assessment

There is conclusive evidence that NDMA is a potent carcinogen in experimental animals. NDMA has been classified by the International Agency for Research on Cancer in Group 2A, "probably carcinogenic to humans", which means that there is sufficient evidence of carcinogenicity in animals, but human data is limited (IARC, 1987). Based on the current weight of evidence, which includes more recent aimal studies, ,NDMA is considered highly likely to be carcinogenic to humans as determined by Environment Canada and Health Canada (2001). The mechanism by which NDMA produces cancer is well understood to involve biotransformation by liver microsomal enzymes, generating the methyldiazonium ion.

As a consequence of the clear evidence of carcinogenicity, there have been few studies of other possible toxic end-points, and existing data are inadequate to quantify health risk for NDMA by any end-point other than carcinogenicity.

There is also ample evidence that NDMA is genotoxic both *in vivo* and *in vitro*. Activation by liver microsomal S9 fractions is necessary for a positive *in vitro* result. The recent observation that human S9 fractions are much more active than rat S9 fractions in promoting genotoxicity in the Ames test suggests that humans may be especially sensitive to the carcinogenicity of NDMA.

There have been several case–control studies and one cohort study of NDMA in humans. Although none of these studies can be used to derive a quantitative risk of cancer, the results are supportive of a positive association between NDMA exposure and gastric or colorectal cancer. However, it should be noted that these studies did not consider drinking water as the route of exposure; instead, they used estimations of total dietary intake of NDMA.

Although there are several cancer bioassays in rodents available, one study in particular stands out as the most obvious one to use for a quantitative risk assessment due to the exceptionally wide concentration range that was used (15 dose groups between 33 and 16 896 µg/L) (Brantom, 1983; Peto et al., 1991a,b). The dose groups were also large, with 60 male and 60 female Colworth-Wistar rats at each dose level. This study was used in the IPCS (2002) and Environment Canada and Health Canada (2001) risk assessments to calculate the TD_{05} (i.e., the dose level that causes a 5% increase in tumour incidence over background) for hepatic cancers of various types in the male and female rats.

After successively removing higher dose groups to eliminate downturn, TD_{05} values were calculated by fitting a multistage model to the data and then finding the dose at which the excess risk was increased by 5% over background. For female rats, TD_{05} values ranged from 34 to 82 µg/kg bw per day (95% lower confidence limits [LCLs] 18 to 61 µg/kg bw per day). For males, TD_{05}s ranged from 35 to 78 µg/kg bw per day (95% LCLs 29 to 48 µg/kg bw per day) (Health Canada, 2008).

These TD_{05} values were used to calculate unit risks for the current assessment. Unit risks were calculated by dividing 0.05 by the TD_{05} or 95% LCL on the TD_{05} (TDL_{05}). An animal to human allometric scaling factor of $(0.35/70)^{1/4}$ was applied to the resulting unit risks. Use of this scaling factor accounts for interspecies differences in susceptibility to NDMA. Although the mechanism of action in both animals and humans appears qualitatively similar, there exists a lack of quantitative data with which to conclude that no interspecies differences exist. Further, it is possible that humans are more sensitive than laboratory animals to carcinogenicity related to *N*-nitroso compounds (Lijinsky, 1999).

Unit risks ranged from 2.28×10^{-3} (µg/kg bw per day)$^{-1}$ (95% upper bound of 3.09×10^{-3} (µg/kg bw per day)$^{-1}$, based on the TDL_{05}) for biliary cistadenomas to 5.57×10^{-3} (µg/kg bw per day)$^{-1}$ (95% upper bound of 1.04×10^{-2} (µg/kg bw per day)$^{-1}$) for carcinomas.

These unit risks can be used to determine a range of concentrations yielding risks of 10^{-4}, 10^{-5} and 10^{-6}. Doses in µg/kg bw per day were converted to concentrations in drinking water assuming an average human exposure via drinking water of 1.9 L/day (as indicated by the multi-route exposure assessment) and an average human adult body weight of 70 kg. The formula to convert from dose to concentration is:

$$\text{MAC (µg/L)} = \frac{\text{Dose (µg/kg bw per day)} \times 70 \text{ kg}}{1.9 \text{ L-eq/d}}$$

Based on the calculated unit risks, the estimated concentrations corresponding to lifetime human cancer risks of 10^{-4}, 10^{-5}, and 10^{-6} for these carcinomas are as follows:

Risk	Concentration in drinking water (µg/L)
10^{-4}	0.4–1.0 µg/L
10^{-5}	0.04–0.1 µg/L
10^{-6}	0.004–0.01 µg/L

The maximum acceptable concentration (MAC) for NDMA in drinking water associated with an excess lifetime cancer risk of 10^{-5} is 0.000 04 mg/L (0.04 µg/L).

10.1 International considerations

Other organizations have set guidelines or regulations pertaining to the concentration of NDMA in drinking water. For all cases, risk estimates have been based on a carcinogenic end-point and have used the same key study to derive acceptable levels for NDMA in drinking water.

WHO has established a guideline value of 0.1 µg/L for NDMA in drinking water. This concentration corresponds to a lifetime carcinogenicity risk of 10^{-5} and is based on a 60-kg average weight for an adult consuming 2 L of water per day. The major difference between the WHO guideline and Health Canada's drinking water guideline in that WHO did not use an allometric scaling factor in deriving the guideline value.

The California Environmental Protection Agency (EPA) has also used the Peto et al. (1991a,b) studies to derive a public health goal of 0.003 µg/L (3 ng/L) for NDMA in drinking water, corresponding to a lifetime theoretical extra cancer risk of 10^{-6}, assuming an average weight of 70 kg and drinking water consumption of 2 L/day. "Lifetime theoretical extra cancer risks" of 10^{-4} and 10^{-5} were calculated as 0.3 and 0.03 µg/L, respectively (OEHHA, 2006). The California EPA has set a notification level of 0.01 µg/L for NDMA in drinking water.

Most recently, the Peto et al. (1991a,b) studies on rat liver tumours were used by Australian investigators to determine a tolerable intake for NDMA using a modified benchmark dose approach (Fitzgerald and Robinson, 2007). A number of mathematical models were used to evaluate the incidence data and generate a tolerable daily intake (TDI) range of 4.0–9.3 ng/kg bw per day.

The potential for NDMA-induced carcinogenicity has also been assessed in the Priority Substances List Assessment Report on NDMA by Environment Canada and Health Canada (2001), which describes several potential sources of exposure to NDMA. Although drinking water was not identified as the most significant source of exposure to NDMA, they recommended monitoring of exposure from this source.

11.0 Rationale

Although there are no longer any industrial uses for NDMA in Canada, NDMA is produced as a by-product of industrial processes that use nitrates or nitrites and amines under a range of pH conditions. NDMA can be found in both surface water and groundwater sources, but it is found in drinking water primarily from its formation during treatment, in particular by chloramination. In Canada, the daily intake of NDMA from drinking water represents a relatively low contribution compared with other sources, such as foods. A multi-route exposure assessment determined that although the inhalation route of exposure to NDMA from drinking water is insignificant, exposure through dermal absorption is significant, and it has therefore been incorporated in the calculation of the MAC.

NDMA has consistently shown potent carcinogenicity in all laboratory animal studies. As a result, there has been little attempt to study other toxic end-points, and there are inadequate data available to make a meaningful assessment of end-points other than carcinogenicity. An animal to human allometric scaling factor was incorporated into the assessment to account for interspecies differences in susceptibility to NDMA.

The estimated lifetime cancer risk from exposure to NDMA in drinking water at levels ranging from 0.004 to 0.04 μg/L (4–40 ng/L) is considered to be "essentially negligible." The guideline for a carcinogen is normally established at a level at which the increased cancer risk is "essentially negligible" when a person is exposed to that level in drinking water over a lifetime. In the context of drinking water guidelines, Health Canada has defined this term as a range from one new cancer above background per 100 000 people to one new cancer above background per 1 million people (i.e., 10^{-5} to 10^{-6}) exposed to a contaminant at the MAC over a lifetime. In the case of NDMA, the MAC is established at a concentration that would present an "essentially negligible" risk of one new cancer above background per 100 000 people (i.e., 10^{-5}) exposed to NDMA at the MAC over a lifetime, which takes into consideration treatment limitations.

NDMA can be detected and measured at very low concentrations in drinking water. The presence of NDMA in drinking water is usually associated with its formation during water treatment rather than with its presence in the source water. Consequently, it is suggested that the organic nitrogen precursors be removed or the disinfection strategy used be modified in order to minimize the formation of NDMA without compromising the efficacy of the disinfection process. Once NDMA is present in drinking water, its reduction using UV irradiation is technically feasible, but it is expensive and may be difficult for smaller utilities.

Levels of NDMA in drinking water in Canada are generally estimated to be less than or equal to 5 ng/L (0.005 μg/L), although higher levels have been reported in some communities.

In summary, a MAC of 0.000 04 mg/L (0.04 μg/L) for NDMA is proposed based on the following considerations:

- It falls within the range considered to present an "essentially negligible" risk.
- It is detectable and measurable, with a method detection limit well below the MAC.
- It is achievable at reasonable cost, by implementing strategies to minimize its formation.

As part of its ongoing guideline review process, Health Canada will continue to monitor new research in this area and recommend any change(s) to the proposed guideline that it deems necessary.

12.0 References

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Appendix A: List of acronyms

2,4-D	2,4-dichlorophenoxyacetic acid
A	adenine
ANSI	American National Standards Institute
AOP	advanced oxidation processes
bw	body weight
C	cytosine
CYP	cytochrome P450
DMA	dimethylamine
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
$F_{air:water}$	air to water NDMA concentration
G	guanine
K_{aw}	Henry's law constant
K_{ow}	*n*-octanol/water partition coefficient
K_p	skin permeability coefficient
LC_{50}	median lethal concentration
LCL	lower confidence limit
LD_{50}	median lethal dose
L-eq	litre-equivalent
LOEC	lowest-observed-effect concentration
MAC	maximum acceptable concentration
MCPA	4-(2-methyl-4-chlorophenoxy)acetic acid
NDMA	*N*-nitrosodimethylamine
NOM	natural organic matter
NSF	NSF International
ppm	part per million
RNA	ribonucleic acid
RO	reverse osmosis
S9	liver homogenate prepared by 9000 × *g* centrifugation
SCC	Standards Council of Canada
T	thymine
TD_{05}	tumorigenic dose$_{05}$; the dose level that causes a 5% increase in tumour incidence over background
TDI	tolerable daily intake
TDL_{05}	95% lower confidence limit on the TD_{05}
U.S. EPA	United States Environmental Protection Agency
UV	ultraviolet
WHO	World Health Organization