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N-Nitrosodimethylamine in Drinking-water

Background document for development of
WHO *Guidelines for Drinking-water Quality*

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Preface

One of the primary goals of WHO and its Member States is that "all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water." A major WHO function to achieve such goals is the responsibility "to propose ... regulations, and to make recommendations with respect to international health matters …."

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International Standards for Drinking-water*. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO *Guidelines for Drinking-water Quality* (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published on selected chemicals in 1998 and on microbiological aspects in 2002. The third edition of the GDWQ was published in 2004, the first addendum to the third edition was published in 2005, and the second addendum to the third edition was published in 2008.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared and updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants of potential health concern in drinking-water. In the first and second editions, these constituted Volume 2 of the GDWQ. Since publication of the third edition, they comprise a series of free-standing monographs, including this one.

For each chemical contaminant or substance considered, a lead institution prepared a background document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America (USA) prepared the documents for the third edition and addenda.

Under the oversight of a group of coordinators, each of whom was responsible for a group of chemicals considered in the GDWQ, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors. The draft documents were also released to the public domain for comment and submitted for final evaluation by expert meetings.

During the preparation of background documents and at expert meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the Joint FAO/WHO Meeting on Pesticide Residues and the Joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite, in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO Internet site and in the current edition of the GDWQ.

Acknowledgements

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The work of the following working group coordinators was crucial in the development of this document and others contributing to the second addendum to the third edition:

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The draft text was discussed at the Working Group Meeting for the second addendum to the third edition of the GDWQ, held on 15–19 May 2006. The final version of the document takes into consideration comments from both peer reviewers and the public. The input of those who provided comments and of participants in the meeting is gratefully acknowledged.

The WHO coordinators were Dr J. Bartram and Mr B. Gordon, WHO Headquarters. Ms C. Vickers provided a liaison with the Programme on Chemical Safety, WHO Headquarters. Mr R. Bos, Assessing and Managing Environmental Risks to Health, WHO Headquarters, provided input on pesticides added to drinking-water for public health purposes.

Ms Penny Ward provided invaluable administrative support at the Working Group Meeting and throughout the review and publication process. Ms Marla Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comment are greatly appreciated.

Acronyms and abbreviations used in the text

2,4-D	2,4-dichlorophenoxyacetic acid
CAS	Chemical Abstracts Service
CYP	cytochrome P450
DMA	dimethylamine
DNA	deoxyribonucleic acid
Epi-DMA	epichlorohydrin-dimethylamine
FAO	Food and Agriculture Organization of the United Nations
GDWQ	*Guidelines for Drinking-water Quality*
IARC	International Agency for Research on Cancer
K_{ow}	octanol/water partition coefficient
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
MCPA	4-(2-methyl-4-chlorophenoxy)acetic acid
NDMA	*N*-nitrosodimethylamine
NDMA-*d6*	[6-^{2}H]*N*-nitrosodimethylamine
polyDADMAC	polydiallyldimethylammonium chloride
ppm	part per million
RNA	ribonucleic acid
TD_{05}	tumorigenic dose$_{05}$; the dose level that causes a 5% increase in tumour incidence over background
USA	United States of America
UV	ultraviolet
WHO	World Health Organization

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1. GENERAL DESCRIPTION

1.1 Identity

CAS No.: 62-75-9

Molecular formula: $C_2H_6N_2O$

N-Nitrosodimethylamine (NDMA) is also known as dimethylnitrosoamine, *N*,*N*-dimethylnitrosoamine, *N*-methyl-*N*-nitrosomethanamine, *N*-nitroso-*N*,*N*-dimethylamine, DMN and DMNA.

1.2 Physicochemical properties[1]

Property	*Value*[a]
Melting point	−50 °C
Boiling point	151–154 °C
Vapour pressure	1080 Pa at 25 °C
Water solubility	miscible
Log octanol/water partition coefficient	−0.57
Henry's law constant	3.34 Pa·m^3/mol at 25 °C

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

1.3 Major uses and sources in drinking-water

NDMA is produced as a by-product of industrial processes that use nitrates and/or nitrites and amines under a range of pH conditions (WHO, 2002). This is due to inadvertent formation when alkylamines, mainly 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 discharges of such industries as rubber manufacturing, leather tanning, pesticide manufacturing, food processing, foundries and dye manufacturing, as well as in sewage treatment plant effluent. Almost all of the releases are to water. NDMA can occur in drinking-water through the degradation of dimethylhydrazine (a component of rocket fuel) (Siddiqui & Atasi, 2001; Mitch et al., 2003b). NDMA has also been detected in emissions from diesel vehicle exhaust (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 & 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.

NDMA may also be formed during the treatment of drinking-water (OME, 1994). NDMA's precursor, DMA, may enter surface water streams from agricultural runoff, since it has been detected in the faeces of dairy cattle (van Rheenan, 1962). Water

[1] Conversion factor in air: 1 ppm = 3.08 mg/m^3.

treatment plants incorporating a chlorination process (e.g. sodium hypochlorite and/or chloramine) also form NDMA as a disinfection by-product (Richardson, 2003). NDMA can also be formed as a by-product of anion-exchange treatment of water (Kimoto et al., 1980). For further details on NDMA's formation during disinfection processes, see section 6.2.

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: bromacil, benazolin, 2,4-D, dicamba, MCPA and mecoprop (WHO, 2002).

Since 1990, 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, with a range from 1.02 to 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 (WHO, 2002). Based on the average concentration of NDMA mentioned above and percent estimate of detection, it was calculated that approximately 200 g of NDMA may have been released into the environment through the use of these herbicides.

There are no industrial or commercial uses of NDMA in Canada or the USA. 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).

1.4 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 range from 25.4 to 254 h in air (Atkinson, 1985). Modelling of environmental partitioning was done based on a half-life for NDMA in air of 5 h (DMER & AEL, 1996). The short half-lives for NDMA in air suggest that it is not persistent in this compartment. Since NDMA is miscible in water and has a low vapour pressure and a low 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 & 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 (Conestoga-Rovers & Associates, 1994; WHO, 2002). This observation is supported in the groundwater compartment, where, in the absence of light, NDMA has the potential to persist (OME, 1991). Modelling of environmental partitioning was done based on a mean half-life of 17 h for NDMA in surface water at 25 °C (DMER & AEL, 1996). Howard et al. (1991) reported a half-life range for NDMA in groundwater of 1008–8640 h, based on estimated unacclimated aqueous aerobic biodegradation.

2. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

2.1 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 $\mu g/m^3$).

In 1990 surveys of ambient air conducted in the vicinity of a chemical production facility in Elmira, Ontario, 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. 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 USA (Brunnemann & 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 & Hoffmann, 1978). Concentrations of NDMA in environmental tobacco smoke–contaminated indoor air in these countries were generally between 0.01 and 0.1 $\mu g/m^3$ (Health Canada, 1999).

2.2 Water

Releases of NDMA into water in Canada have been measured primarily in Ontario and vary considerably. As an example, in 1996, a chemical plant released wastewater containing NDMA into the St Clair River at a concentration of 0.266 $\mu g/l$ (Environment Canada, 1997). In April 1997, concentrations of NDMA in the wastewater at the point of release to surface water ranged from 0.096 to 0.224 $\mu g/l$ for this company. These

concentrations are expected to decrease, as the company installed a wastewater treatment plant in 1998.

In a survey of sewage treatment plant effluent in Ontario in 1990, NDMA was detected in 27 of 39 samples, with the maximum concentration being 0.22 µg/l (OME, 1991). Chlorination of secondary wastewater effluent typically results in the formation of between 0.02 and 0.10 µg of NDMA per litre (Mitch & Sedlak, 2002a).

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. The highest concentration of NDMA in raw water was 0.008 µg/l from two water treatment plants in 1996 (WHO, 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). Concentrations of NDMA in the municipal aquifer in Elmira ranged from 1.3 to 2.9 µg/l, 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 1994 and 1995, NDMA concentrations of up to 0.005 µg/l (detection limit 0.001 µg/l) in raw surface water and groundwater supplies in rural areas in southern Ontario were reported (OME, 1991).

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 plants using a specific pre-blended polyamine/alum water treatment coagulant (WHO, 2002). 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. A survey of NDMA concentrations in drinking-water systems 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. Drinking-water and source water samples were tested as part of the validation of the analytical methods developed in Charrois et al. (2004). One series of samples was from a city in Alberta, Canada, that used chloramination and UV disinfection. The source water had no detectable NDMA (detection limits ranged from 0.4 to 1.6 ng/l), but the levels measured were 0.067 µg/l in the finished water and 0.16 µg/l in the distribution system. Further investigation confirmed that distribution system samples had much higher levels of NDMA than the finished water at the treatment plant. Clearly, there is a need for more studies that measure NDMA levels in the distribution systems of water treatment facilities using chloramine.

2.2.1 Water reuse

Treatment studies on groundwater at a chemical plant in southern Ontario, Canada, indicated that activated sludge can accumulate NDMA, particularly when nitrification and denitrification are applied to increase the age of the sludge. Concentrations of NDMA sampled in activated sludge ranged from 5 to 10 mg/l (WHO, 2002). In the USA, NDMA has been reported to be a common constituent of sewage sludge. Concentrations ranged from 0.6 to 45 µg/g in the dried sludge from 14 of 15 cities (Mumma et al., 1984).

2.3 Food

NDMA can be formed during food processing, preservation and/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 (WHO, 2002):

- foods preserved by the addition of nitrate and/or nitrite, such as cured meat products (in particular, bacon) and cheeses (since these methods of preservation introduce nitrosating species into the food);
- foods preserved by smoking, such as fish and meat products (since 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 (since combustion gases can contain oxides of nitrogen);
- pickled and salt-preserved foods, particularly pickled vegetables (since 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, owing to the 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 or increased use of nitrosation inhibitors, such as ascorbate or erythorbate (Cassens, 1997; Sen & Baddoo, 1997).

Levels in Canadian foods in the late 1970s and early 1980s have been fully reviewed in WHO (2002). Concentrations of NDMA 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 µg/kg to 4.2 µg/kg. For cheese, the range was from <1 µg/kg to a maximum of 68 µg/kg. NDMA was not detected in milk products apart from skim milk powder at concentrations below 0.7 µg/kg. NDMA was also not detected in baby food, apple juice, ketchup, sauces, margarine or butter. 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. Malt beverages such as beer and whiskey contain NDMA, but again levels have been dropping. Canadian beer analysed in 1988–1989 had a mean concentration of only 0.10 µg/l. NDMA levels in imported beer averaged 0.71 µg/l in 1991–1992 and 0.15 µg/l in 1994 (Sen et al., 1996).

2.4 Estimated total exposure and relative contribution of drinking-water

Based on a worst-case estimation of exposure to NDMA in contaminated air, water and food, the daily NDMA intake of a 20- to 59-year-old would be 0.005–0.016 µg/kg of body weight per day (WHO, 2002). Daily intake of NDMA from ingestion of drinking-water was estimated at 0.0003–0.001 µg/kg of body weight per day, 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 (WHO, 2002). The low-end value is similar to those observed in some chloramine-treated drinking-water, which shows that human exposure to NDMA via drinking-water is likely to provide a relative contribution below 10% of total exposure. In a home not containing environmental tobacco smoke, the major source of exposure to NDMA is food (0.0043–0.011 µg/kg of body weight per day). If there is regular indoor exposure to environmental tobacco smoke, then this source would exceed all the other sources combined by almost an order of magnitude (0.05 µg/kg of body weight per day).

3. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

While 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 & 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 & 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).

Once absorbed, NDMA and its metabolites are distributed widely (Daugherty & 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 & 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.

Quantitative information from studies on the metabolism of NDMA in humans was not identified. However, based upon a few studies in which the metabolic conversion of NDMA in human liver preparations has been examined, there appear to be no 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 P450 [CYP2E1]–dependent mixed-function oxidase system (Haggerty & Holsapple, 1990; Lee et al., 1996). Along the α-hydroxylation pathway, the hydroxymethylnitrosamine

($HOCH_2CH_3NBN=O$) 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. Metabolic conversion of the intermediate radical via denitrosation may lead to the formation of methylamine (CH_3NH_2) and formaldehyde.

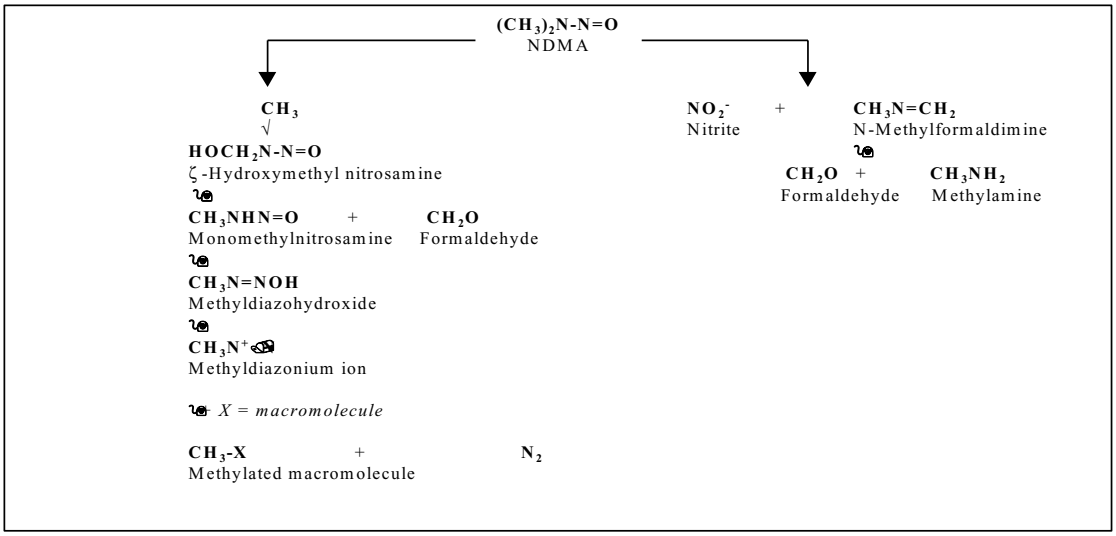

Figure 1: Pathways of NDMA metabolism (adapted from ATSDR, 1989; Haggerty & Holsapple, 1990; Lee et al., 1996)

4. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS

4.1 Acute exposure

NDMA is highly acutely toxic after oral administration to rats, with LD_{50}s ranging from 23 to 40 mg/kg of body weight. It is also highly acutely toxic via inhalation; 4-h LC_{50}s are 240 mg/m^3 for rats and 176 mg/m^3 for mice (WHO, 2002). One day after three dogs were exposed (via inhalation) to NDMA at 49 mg/m^3 for 4 h, one had died, and the others were moribund (ATSDR, 1989). In all three species, acute inhalation exposure produced haemorrhagic necrosis in the liver. An increased blood clotting time was additionally reported for the NDMA-exposed dogs (ATSDR, 1989). Following intraperitoneal exposure, LD_{50}s of 43 mg/kg of body weight in rats and 20 mg/kg of body weight in mice have been reported (IARC, 1978). In other laboratory species, acute exposure to NDMA produced effects in the liver (hepatotoxicity), kidney (tumours) and testes (necrosis of the seminiferous epithelium) (Magee & Barnes, 1962; Schmidt & Murphy, 1966; Hard & Butler, 1970a,b; McLean & Magee, 1970; OME, 1991).

4.2 Short-term exposure

Hepatic effects (i.e. hepatocyte vacuolization, portal venopathy and 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 of NDMA per kilogram of body

weight per day for 30, 7–28 or 5–11 days, respectively; in mice receiving 5 mg/kg of body weight per day in drinking-water for 7–28 days; in hamsters receiving 4 mg/kg of body weight per day in drinking-water for 1–28 days; in guinea-pigs, cats and monkeys receiving 1 mg/kg of body weight per day for 30 days or 5 mg/kg of body weight per day for 5–11 days; in dogs receiving 2.5 mg/kg of body weight per day, 2 days per week, for 3 weeks; and in mink receiving 0.32 mg/kg of body weight per day for 23–34 days) (summarized from 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 and myocardium) has been reported following examination of rats receiving 3.8 mg of NDMA per kilogram of body weight per day in the diet for 1–12 weeks (Khanna & Puri, 1966). Gastrointestinal haemorrhage has been observed in rats receiving dietary doses of 10 mg of NDMA per kilogram of body weight per day for 34–37 days (Barnes & Magee, 1954) and in mink receiving 0.3 or 0.6 mg of NDMA per kilogram of body weight 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 of NDMA per kilogram of body weight per day from the diet (period not specified) (Martino et al., 1988).

4.3 Long-term exposure

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.

4.4 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 of NDMA per litre 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 of NDMA per kilogram of body weight induced testicular damage (necrosis or degeneration of the seminiferous epithelium) (Hard & 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 of NDMA per litre for 75 days prior to mating and throughout pregnancy and lactation (estimated daily and total intakes of 0.02 mg/kg of body weight per day and 2 mg/kg of body weight, respectively). The proportion of deaths (based upon the total number of stillborn and neonatal deaths) was increased ($P < 0.05$) 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.

4.5 Genotoxicity and related end-points

In numerous studies conducted in vitro in bacterial and mammalian cells, there has been 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 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 (Hakura et al., 1999, 2003). The mutation rate was up to 8 times higher with some human S9 fractions.

Similarly, 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 & Ashby, 1988; Cliet et al., 1989; Neft & Conner, 1989; Sawada et al., 1991), bone marrow cells (Bauknecht et al., 1977; Wild, 1978; Neal & Probst, 1983; Collaborative Study Group for the Micronucleus Test, 1986; Neft & Conner, 1989; Krishna et al., 1990; Sato et al., 1992; Morrison & Ashby, 1994), spleen cells (Neft & 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 of body weight 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 of NDMA per kilogram of body weight 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 & Swenberg, 1978; Abanobi et al., 1979; Mirsalis & Butterworth, 1980; Brambilla et al., 1981, 1987; Bermudez et al., 1982; Cesarone et al., 1982; Barbin et al., 1983; Doolittle et al., 1984; Kornbrust & 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 & 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). Effects (i.e. increased unscheduled hepatic DNA synthesis) have been observed in rats at doses as low as 0.1 mg of NDMA per kilogram of body weight (Mirsalis & Butterworth, 1980).

4.6 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 a number of studies in which 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 & 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 & Toya, 1970; Anderson et al., 1979, 1986, 1992) or through inhalation (Moiseev & 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). An increased incidence of renal tumours has also been observed in rats administered either a single oral (Magee & Barnes, 1962) or intraperitoneal (Hard & Butler, 1970a; McLean & Magee, 1970) dose of NDMA (at levels of 30–60 mg/kg of body weight).

In a more recently conducted comprehensive 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 concentrations of NDMA[1] (Brantom, 1983; Peto et al., 1991a,b). The estimated daily intakes of NDMA ranged from 0.001 to 0.697 mg/kg of body weight in the males and from 0.002 to 1.224 mg/kg of body weight in the females. A control group of 120 males and 120 females received drinking-water without NDMA (Brantom, 1983; Peto et al., 1991a,b). 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. There were no significant differences in body weight between the exposed animals and the controls. Dose-related increases in tumour incidence were observed only in the liver of both males and females. The increase in tumour incidence was greatest for hepatocellular carcinoma and biliary cystadenoma. Non-neoplastic effects observed in the liver included hyperplastic nodules and the shrinkage of hepatocytes.

4.7 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

[1] The concentrations of NDMA were 33, 66, 132, 264, 528, 1056, 1584, 2112, 2640, 3168, 4224, 5280, 6336, 8448 and 16 896 µg/l.

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 transversions (Swenberg et al., 1991). O^6-Methylguanine and O^4-methylthymine (formed at about 1% of the amount of O^6-methylguanine) are strongly promutagenic by direct mispairing. O^6-Methylguanine causes guanine:cytosine to adenine:thymine (i.e. G:C to A:T) transitions, whereas O^4-methylthymine causes A:T to 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 (reviewed in Haggerty & 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 administered (orally) 0.1 mg of NDMA per kilogram of body weight, 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 (intragastrically) a single dose of 1 mg of NDMA per kilogram of body weight (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 dose of 20 mg of NDMA per kilogram of body weight 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 & Barnes, 1962; Schmidt & Murphy, 1966; Hard & Butler, 1970a; McLean & Magee, 1970). In contrast, the long-term oral administration of low doses of NDMA (i.e. <2 mg/kg of body weight per day) increased the incidence of liver but not kidney tumours in these animals (Brantom, 1983; Lijinsky & 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

(Lindamood et al., 1984) 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 to 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 of NDMA per kilogram of body weight (Mirsalis et al., 1993) and in the liver, kidney and lung of *lacI* transgenic mice administered five daily doses of 1 mg of NDMA per kilogram of body weight (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.

5. EFFECTS ON HUMANS

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

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 (Goodman et al., 1992; González et al., 1994; Pobel et al., 1995), 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. In the studies conducted by De Stefani et al. (1996) and Rogers et al. (1995), 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 rather 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; results were relatively consistent in this

regard, with there being an association with cancer most commonly with NDMA; results for nitrite were mixed, and there was an inverse association with nitrate.

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 & 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.

6. PRACTICAL ASPECTS

6.1 Analytical methods and analytical achievability

Owing to the potent carcinogenicity of NDMA, it is necessary to be able to detect it in drinking-water at nanogram per litre levels. In order to achieve this degree of sensitivity, concentration of the sample by extraction followed by separation and quantification on a gas chromatograph/mass spectrometer are a necessity.

A comprehensive review of the many published methods up to the mid-1990s is found in the WHO (2002) review. New methods that are specifically developed for use in monitoring drinking-water supplies have been published recently; these are somewhat more feasible and less expensive than earlier methods.

A method for nitrosamines in drinking-water using solid-phase extraction, capillary column gas chromatography and chemical ionization tandem mass spectrometry has been published by the USEPA (2004). Isotope dilution is used for NDMA analysis using NDMA-*d6* as the surrogate. Seven other nitrosamines can also be measured using the internal standard method. This method is intended for large-scale surveys and has a detection limit for NDMA of 0.28 ng/l and a lowest concentration minimum reporting level of 1.6 ng/l. The lowest concentration minimum reporting levels for the other seven nitrosamines range from 1.2 to 2.1 ng/l.

The Ontario Ministry of the Environment (in Canada) has published two new methods. One is specifically for NDMA (OME, 2004a) and uses solid-phase extraction onto Ambersorb 572 and elution with dichloromethane. Separation and quantification are achieved by capillary column gas chromatography and high-resolution mass spectrometry. NDMA-*d6* is used to quantify the NDMA by the isotope dilution method. The detection limit for NDMA was 0.4 ng/l, and the reporting detection limit was set at 1.0 ng/l. The other method is for *N*-nitrosamines in general (OME, 2004b). The same general approach is used, with NDMA-*d6* being used to quantify NDMA by the isotope

dilution method. The method detection limit (reporting detection limit) for NDMA was reported as 0.4 ng/l (1 ng/l).

A new method specifically designed to measure *N*-nitrosamines at nanogram per litre levels in drinking-water using bench-top equipment has been published (Charrois et al., 2004). The method uses a two-component solid-phase extraction followed by gas chromatography/mass spectrometry and ammonia positive chemical ionization detection for excellent selectivity and sensitivity. Using NDMA-*d6* as the isotope dilution/surrogate standard, the method detection limit for NDMA was 1.6 ng/l; with the internal standard method, it was 0.7 ng/l. The method was able to accurately quantify seven other *N*-nitrosamines in addition to NDMA. In the field trials, two new disinfection by-products were found for the first time (*N*-nitrosopyrrolidine and *N*-nitrosomorpholine), although they were quantitatively significantly less than NDMA.

6.2 Treatment and control methods and technical achievability

6.2.1 Formation during disinfection

Choi & Valentine (2002a) demonstrated that NDMA is formed by the reaction of monochloramine with DMA, a ubiquitous component of surface waters. Approximately 12 µg of NDMA per litre was produced by reaction of 4.5 mg of DMA per litre with 5 mg of pre-formed monochloramine per litre after 24-h contact at pH 7. Maximum formation of NDMA occurred when the ratio of DMA to monochloramine was approximately 1:1. No significant amount of NDMA was formed by reaction of hypochlorous acid and DMA in the absence of ammonia. A reaction mechanism and a kinetic model for NDMA formation were proposed. In other studies (Choi & Valentine, 2002b), reaction of 4.5 mg of DMA per litre with 5 mg of monochloramine per litre produced 12 µg of NDMA per litre; this increased to 60 µg/l when the monochloramine dose was raised to 100 mg/l.

It was demonstrated (Choi & Valentine, 2002b) that NDMA formation by reaction of DMA with monochloramine does not require the presence of nitrite. However, NDMA can also be formed by reaction of DMA with hypochlorous acid in the presence of nitrite, and increasing the hypochlorous acid concentration increases the concentration of NDMA formed (Choi & Valentine, 2003). In the absence of hypochlorous acid, the NDMA concentration increased from 0.34 to 0.65 mg/l as the nitrite concentration increased from 2.3 to 46 mg/l in the presence of 5 mg of DMA per litre. When 5 mg of hypochlorous acid per litre were added, the range of NDMA concentrations was 0.14–15 µg/l.

When deionized water spiked with DMA was treated with pre-formed monochloramine, the NDMA concentration increased with increasing dose, reaching a plateau of approximately 70 ng/l with 50 mg of monochloramine per litre. When the DMA concentration was varied with a fixed dose of 5 mg of monochloramine per litre, the maximum yield of NDMA (11 µg/l) was obtained with approximately 10 mg of DMA per litre (Choi et al., 2002).

Similar results were obtained by Mitch & Sedlak (2002b), who showed that NDMA could form during chloramination of DMA and other secondary amines. The concentration of NDMA formed (around 25 µg/l with DMA at 45 mg/l and monochloramine at 50 mg/l) was approximately an order of magnitude higher than with a

similar reaction between DMA and sodium hypochlorite. The formation rate was found to be pH dependent and most rapid in the range from pH 6 to pH 8 (the usual range for drinking-water disinfection). Increasing the monochloramine concentration (50–125 mg/l) increased the rate. An NDMA formation test (similar to a trihalomethane formation potential test) has been described (Mitch et al., 2003b).

NDMA can also be generated by reaction of dichloramine with DMA (dichloramine can be an undesired by-product formed during chloramination or breakpoint chlorination). When dichloramine (16 mg/l) was added to DMA (~100 µg/l), approximately 1.5 µg of NDMA per litre was present after 8 h compared with approximately 0.1 µg/l when monochloramine (10 mg/l) was added (Schreiber & Mitch, 2005).

Natural water was chloraminated (5 mg of chlorine per litre; Cl_2:N ratio 5:1) using chlorine followed by ammonia and ammonia followed by chlorine and using pre-formed monochloramine. The NDMA concentrations were all in the range 9–11 ng/l, suggesting that order of addition is not an important factor in NDMA formation (Najm & Trussell, 2001).

Although DMA acts as a precursor for NDMA formation, several studies have shown that the concentrations of DMA present in water sources cannot account for the quantities of NDMA formed during disinfection. In one study, it was reported that thiram was a more efficient precursor than DMA (Graham et al., 1996). Possible NDMA precursors have been discussed by Siddiqui & Atasi (2001) and Mitch et al. (2003b).

NDMA can be expected to form during chlorination of surface waters containing ammonia due to the inevitable formation of monochloramine. However, in a survey of disinfection by-products in groundwaters, NDMA concentrations were below 0.02 µg/l in waters containing 5–25 mg/l ammonium-nitrogen treated with up to 1.5 mg of chlorine per litre (Duong et al., 2003).

NDMA appears not to be formed during ozonation (Najm & Trussell, 2001).

Cationic polyelectrolytes (Epi-DMA and polyDADMAC products) can also act as precursors for the formation of NDMA by reaction with chloramines or hypochlorite. NDMA concentrations of 180–400 ng/l were produced when five commercial polyDADMACs were chlorinated, then ammoniated (Wilczak et al., 2003). NDMA concentrations could be reduced by chlorinating after filtration. Delaying the addition of ammonia following chlorination also decreased NDMA formation, but possibly at the expense of greater formation of chlorinated by-products such as trihalomethanes. Laboratory coagulation tests were used to examine any effect of the age (0–50 h) of polyelectrolyte solutions on the yield of NDMA (Kohut & Andrews, 2003). Tap water was spiked with nitrite at 500 µg/l, then treated with aluminium sulfate (4.7 mg of aluminium per litre), either polyDADMAC (10 mg/l) or Epi-DMA (20 mg/l), and sodium hypochlorite (4 mg/l). NDMA concentrations were found to increase with the age of Epi-DMA solutions, but this effect was not significant with polyDADMAC. The maximum yields of NDMA were approximately 20 ng/mg Epi-DMA (reached after 3 h) and 8 ng/mg polyDADMAC (reached after 50 h).

When a mixed ion-exchange resin was contacted with various waters, the following concentrations of NDMA were found (Kimoto et al., 1980): a) tap water with 0.5–1.5 mg of chlorine per litre, 920 ng/l; b) water a) treated with granular activated carbon, 8 ng/l; and c) water b) plus 0.8 mg of chlorine per litre, 133 ng/l. In another study (Najm & Trussell, 2001), NDMA was found at concentrations up to 130 ng/l when various resins were contacted with deionized water or groundwater (neither containing chlorine). Only resins containing trimethyl or dimethyl-ethanol quaternary amine functional groups produced NDMA.

Potential methods for reducing the formation of NDMA during disinfection are:

- avoiding the use of chloramination;
- use of breakpoint chlorination; or
- removal of ammonia prior to chlorination (although likely impractical and uneconomic).

6.2.2 Treatment

NDMA is not removable by air stripping, activated carbon adsorption, reverse osmosis or biodegradation (Siddiqui & Atasi, 2001; Mitch et al., 2003a). It is degraded extremely slowly by ozone (Hoigné & Bader, 1983). Potential treatment technologies are UV irradiation, UV plus hydrogen peroxide and resin (e.g. Ambersorb 572) adsorption.

Currently, the most common process for NDMA removal is UV irradiation. The principal by-products of UV photolysis of NDMA are DMA and nitrite (Bolton & Stefan, 2000; Mitch et al., 2003a). When UV/hydrogen peroxide is applied, nitrate is the major degradation product, and the concentration of DMA is significantly lower than with direct photolysis (Bolton & Stefan, 2000). Several medium-pressure UV installations are in place for the treatment of groundwaters contaminated by NDMA of industrial origin. Medium-pressure UV lamps are generally more economic for NDMA destruction than low-pressure lamps. The UV dose required for 90% removal of NDMA is about 1000 mJ/cm^2, approximately 10 times higher than that required for virus inactivation (Mitch et al., 2003a). Therefore, NDMA removal using UV irradiation is feasible but expensive.

A comparison was made of the ability of low- and medium-pressure mercury UV lamps to degrade NDMA spiked at 75 µg/l into "synthetic" drinking-water (Sharpless & Linden, 2003). Both lamps gave effective degradation with similar efficiencies; addition of 100 mg of hydrogen peroxide per litre gave a 30% increase in rate for the low-pressure lamp but did not affect degradation by the medium-pressure lamp.

Irradiation with a 13-W low-pressure mercury lamp required about 15 min for complete degradation from a 7.5 µg/l solution at pH 7; a 750 µg/l solution required 5 h. The degradation products were methylamine and DMA, the relative amounts depending upon the reaction conditions (Lee et al., 2005).

Pulsed UV could potentially be more effective in oxidizing NDMA, because higher UV intensities can be delivered compared with continuous-wave UV technology (Liang et al., 2003). Tests were conducted in deionized water, high-organics (total organic carbon 3 mg/l) surface water and low-organics high-alkalinity groundwater. The tests were

conducted using 40–50 m^3 of test water in a batch reactor equipped with a 5-kW xenon lamp. In deionized water spiked with NDMA at 2 µg/l, removals of approximately 70% and 90% required UV dosages of 0.35 and 0.7 kWh/m^3, respectively, at a pulse input of 2 Hz; increasing the pulse rate improved removal. Removal was poorer in groundwater and poorer still in surface water; 80% removal from surface water required 1.4 kWh/m^3 at 10 Hz. Addition of hydrogen peroxide did not improve removal, but did inhibit the reformation of NDMA when treated water was chlorinated.

Laboratory batch tests were conducted to compare the effectiveness of various adsorbents to remove NDMA spiked at 100 µg/l into groundwater (Fleming et al., 1996). The adsorbents tested were F400 (coal-based activated carbon), CSC (coconut-based activated carbon), Ambersorb 572 and 563 (carbonaceous adsorbents), XAD-7 (macroporous resin) and a range of zeolites with and without pretreatment with copper, iron and nickel. The zeolites and XAD-7 were ineffective (<20% removal). The order of best removal for the other adsorbents was A572 > CSC > A563 > F400.

In an analytical procedure, adsorption onto Ambersorb XE-340 carbonaceous adsorbent was found to be effective for concentration of NDMA from water spiked with 50 ng/l; recoveries of 64–89% were obtained (Kimoto et al., 1981).

Isotherm data have been published for adsorption of NDMA from an initial concentration of 1000 µg/l in distilled water onto various activated carbons (Kommineni et al., 2003). These have been used to calculate the carbon adsorption capacities for equilibrium NDMA concentrations of 100 and 500 µg/l, as shown in Table 1. These demonstrate that NDMA is very poorly adsorbed by activated carbon. The adsorption capacities were unchanged or reduced when the tests were repeated using NDMA spiked into groundwater.

Table 1: Carbon adsorption capacities for equilibrium NDMA concentrations[a]

		Adsorption capacity (mg/g) at equilibrium NDMA concentration	
Activated carbon	Type	100 µg/l	500 µg/l
F400	Coal-based	0.23	0.61
F300	Coal-based	0.19	1.18
BCP/MOD1	As F300/F400 but specially treated	0.24	0.82
Centaur	Catalytically enhanced	0.30	0.51
PCB	Coconut shell–based	0.30	1.28
Ambersorb 600	Hydrophobic carbonaceous resin	0.26	1.10
Ambersorb 572	Hydrophobic carbonaceous resin	0.22	0.65
Alltech 5776	Coconut shell–based	0.36	1.59

[a] From Kommineni et al. (2003).

In column tests using BCP/MOD1 carbon with empty bed contact times of 4.8 and 1.6 min, breakthrough of NDMA started to occur almost immediately and was effectively complete (900 µg/l) after treatment of 800 bed volumes. The calculated capacity was 0.8 mg/g granular activated carbon.

Three zeolites were tested for the removal of NDMA from solutions containing NDMA at 500–7500 mg/l. The adsorption capacities were relatively low (<10 mg/g). Silica and alumina were less effective than the zeolites (Zhu et al., 2001).

NDMA is poorly removed by reverse osmosis. Within wastewater recycling plants, NDMA was removed with approximately 50% efficiency by thin-film composite reverse osmosis membranes (Mitch et al., 2003a).

7. GUIDELINE VALUE

There is conclusive evidence that NDMA is a potent carcinogen in experimental animals by several routes of exposure, including through ingestion of drinking-water. NDMA has been classified by IARC in Group 2A, "probably carcinogenic to humans" (IARC, 1987), which was upgraded from its previous classification of Group 2B, "possibly carcinogenic to humans" (IARC, 1978). The mechanism by which NDMA produces cancer is well understood to involve biotransformation by liver microsomal enzymes, generating the methyldiazonium ion. This reactive metabolite forms DNA adducts, with most evidence pointing to O^6-methylguanine as the likely proximal carcinogenic agent.

As a consequence of the clear evidence of carcinogenicity, there have been few studies of other possible toxic end-points. It has therefore been decided that the 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 in promoting genotoxicity in the Ames test than rat S9 fractions suggests that humans may be especially sensitive to the carcinogenicity of NDMA.

Although there have been several case–control studies and one cohort study of NDMA in humans, none of them can be used to derive a quantitative risk of cancer. The results are supportive of the assumption that NDMA consumption is positively associated with either gastric or colorectal cancer. However, none of the studies focused on 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 owing 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 female Colworth-Wistar rats at each dose. This study was used in WHO (2002) 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, WHO (2002) calculated values of TD_{05} 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 of body weight per day, with 95% lower confidence limits on the TD_{05} ranging from 18 to 61 µg/kg of body weight per day. For males, TD_{05} values ranged from 35 to 78 µg/kg of body weight per day, with 95% lower confidence limits ranging from 29 to 48 µg/kg of body weight per day.

These TD_{05} values can be used to calculate unit risks for the current assessment. Since the unit risk represents the increase in risk per unit increase in dose and the TD_{05} is the dose at which risk is increased by 5%, the unit risk is found by dividing 0.05 by the TD_{05}. To be conservative, an upper 95% confidence limit on the unit risk can be determined by dividing 0.05 by the 95% lower confidence limit on the TD_{05}.

For both sexes of rats on test, the unit risks ranged from 6.07×10^{-4} to 1.48×10^{-3} per µg/kg of body weight per day, with 95% upper bounds ranging from 8.22×10^{-4} to 2.77×10^{-3} per µg/kg of body weight per day. The most sensitive end-point was for hepatic biliary cystadenoma in female rats, where the 95% lower confidence limit on the TD_{05} was 18 µg/kg of body weight per day, resulting in a unit risk of 2.77×10^{-3} per µg/kg of body weight per day (Health Canada, 2005). This translates into an increased risk of cancer of 1 in 360 for each microgram of NDMA per kilogram of body weight per day exposure over an entire lifetime. No animal-to-human kinetic adjustment was applied to the calculation of the base unit risk.

Taking a conservative approach to the cancer risk assessment, in view of the evidence that humans may be particularly at risk from NDMA, the guideline value (GV) for NDMA in drinking-water associated with an upper-bound excess lifetime cancer risk of 10^{-5} can be calculated as follows:

$$GV = \frac{60 \text{ kg} \times 10^{-5}}{2.77 \times 10^{-3} \text{ per µg/kg of body weight per day} \times 2 \text{ litres/day}}$$

$$\approx 0.1 \text{ µg/l (100 ng/l)}$$

where:

- 60 kg is the average weight of an adult
- 10^{-5} is the upper-bound limit risk of one additional cancer per 100 000 of the population ingesting drinking-water containing NDMA at the guideline value for 70 years
- 2.77×10^{-3} per µg/kg of body weight per day is the unit risk calculated from the 95% lower confidence limit of the TD_{05} for hepatic biliary cystadenoma in female rats (WHO, 2002)
- 2 litres/day is the daily volume of water consumed by an adult.

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