INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com ISSN 2230 – 8407

Review Article

N-NITROSODIMETHYLAMINE AS A HAZARDOUS CHEMICAL TOXICANT IN DRINKING WATER

Sharma Veena*, Singh Manu
Department of Bioscience and Biotechnology, Banasthali University, Banasthali 304022, Rajasthan, India

Article Received on: 18/01/12 Revised on: 10/02/12 Approved for publication: 14/03/12

*Email: manu.singh418@gmail.com

ABSTRACT
Nitrosamines is a family of potent carcinogens, have been of concern for many decades due to their occurrence in foods, industrial workplace environments, and as groundwater contaminants. Human exposure to nitrosamines can result from formation of N-nitroso compounds either in food during storage or preparation or *in vivo*, usually in the stomach. N-Nitrosodimethylamine is one of the main N-nitroso compound which is commonly found in drinking water and is a potent hepatotoxin, carcinogen and mutagen and it induces fibrosis and cirrhosis in liver. All identified health risks associated with N-Nitrosodimethylamine in drinking water incorporates all relevant routes of exposure from drinking water—namely, ingestion as well as skin absorption from showering and bathing. The toxicity produced by N-Nitrosodimethylamine is mediated by its reactive metabolites and not by the parent compound. Decontamination of N-Nitrosodimethylamine relies mostly on UV irradiation, but these methods are rather impractical and expensive when applied to municipal and wastewater treatment. N-Nitrosodimethylamine is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals. When administered orally, N-nitrosodimethylamine induced liver hemangiosarcomas, hepatocellular carcinomas, and kidney and lung tumors in mice. Reactive oxygen species have been implicated as causative agents in many degenerative diseases, and also in the promotion phase in carcinogenesis. Toxic effects of N-nitrosodimethylamine, a potent carcinogenic and mutagenic substance, were also proposed to be due to reactive oxygen species formed by its metabolic activation. The mechanism by which N-Nitrosodimethylamine produces cancer is well understood to involve biotransformation by liver microsomal enzymes, generating the methyldiazonium ion.
KEYWORDS: N-Nitrosodimethylamine, Carcinogenic, Nitrosamines, Liver

INTRODUCTION

N-Nitrosodimethylamine (NDMA) is a member of a family of extremely potent carcinogens, the *N*-nitrosamines. Nitrosamines are compounds having the general structure as shown in,where $R_1$and R_2 are alkyl or aryl groups. **Figure 1**

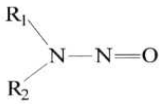


Figure 1 General structure of Nitrosamines

N-nitrosamines are formed in the reaction of an electrophilic substitution of organic nitrogen with a nitrosating compound. Nitrosamines are present in water, soil and air[1]. They can be found contaminating food, feeding stuff (where they create the highest risk for health), drugs, cosmetics, and pesticides[2,3]. About 5% of ingested nitrates are reduced to nitrites in saliva. These nitrites can subsequently react in solution with secondary and tertiary amines, as well as N-substituted amides, carbamates, and other related compounds, to form N-nitroso compounds within the gastrointestinal tract.[4] This internal formation is a major source of human exposure to N-nitrosamines. The formation of nitrosamines depends on the pH environment, alkalinity of amine, and temperature. Nitrosamines are comparatively stable under conditions present in organisms, before being subjected to degradation to biologicallly active derivatives[5]. N-nitrosodimethylamine (NDMA) is the most frequently detected member of this family.

N-Nitrosodimethylamine (NDMA) has received considerable attention as a disinfection byproduct because reaction of chloramines with amine moieties present in drinking water leads to the formation of this carcinogen.[6] Secondary and tertiary amines of natural and anthropogenic origin are important precursors for NDMA formation during chloramination. When administered orally, N-nitrosodimethylamine induced hepatocellular carcinomas and bile duct tumors in rats, when administered by intramuscular injection, it induced hemangiosarcomas in the liver and bile duct and nasal cavity tumors in mice.[7] NDMA is an emerging drinking water contaminant that is of interest to the environmental community because of its miscibility with water, as well as its carcinogenicity and toxicity.

Concerns about human exposure to NDMA from industrial sources also were voiced previously. During the 1970s, NDMA was detected in the air and water adjacent to a factory near Baltimore that produced UDMH from NDMA.[8] More alarming was the detection of NDMA in the air upwind of the plant in downtown Baltimore (0.1 mg/m^3), and at other sites in Belle, WV (0.1 mg/m^3), and New York City (0.8 mg/m^3), areas with no known industrial sources of NDMA. On the basis of those observations, some researchers suggested that NDMA formed in the polluted atmosphere could be responsible for elevated urban cancer rates.[8]

Properties

N-Nitrosodimethylamine is a nitrosamine which is a volatile, yellow, oily liquid of low viscosity. It is soluble in water, alcohol, ether, other organic solvents, and lipids. The compound is sensitive to light, especially ultraviolet light, and undergoes relatively rapid photolytic degradation. N-Nitrosodimethylamine is combustible, and when heated to decomposition, it emits toxic fumes of nitrogen oxides.

Table 1 Physical properties of NDMA

Property	Information
Molecular weight	74.1a
Specific gravity	1.0048 at 20°C/4°Ca
Melting point	< 25°Cb
Boiling point	151°C to 153°Ca
Log *Kow*	–0.57a
Water solubility	1,000 g/L at 24°Cb
Vapor pressure	2.7 mm Hg at 20°Cb
Vapor density relative to air	2.56a

Sources: aHSDB 2009, bChemIDplus 2009.[9]

Synonyms

N-methyl-N-nitrosomethanamine; N-nitrosodimethylamine; DMN; DMNA; dimethylnitrosoamine; nitrosodimethylamine; methanamine, N-methyl-N-nitroso ; dimethylamine

Sources And Occurrence

Many of the studies on the atmospheric occurrence of NDMA have focused on occupational exposure in certain industries for example, tire manufacturing or rocket fuel synthesis.[10] However, NDMA was not thought to build up in the atmosphere during day time since it is readily photolyzed by sunlight and as such has not been considered a concern for ambient air exposure. Its formation was considered to only occur in the night time and in the presence of water vapour.[11] 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.[12] NDMA present in the environmental discharges of industries such as rubber manufacturing, leather tanning, pesticide manufacturing, food processing, foundries and dye

Sources of NDMA in water

There are at least 4 known sources of nitrosamines and NDMA in particular. These are as follows:

- Direct industrial or human-derived contamination
- Microbial action
- Disinfection by-product formation
- 'Natural' degradation of precursors

NDMA may also be formed during the treatment of drinking water. Water treatment plants incorporating a chlorination or chloramination process in the presence of nitrogen-containing organic matter form NDMA as a disinfection by-product.[13] NDMA precursors such as DMA and trimethylamine may be present after drinking water treatment with nitrogen-based cationic polyelectrolytes or ion exchange resins.

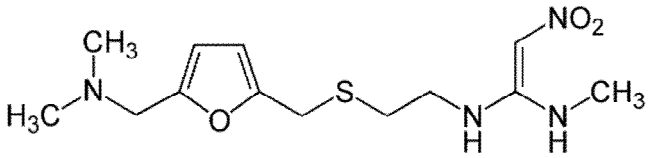
Atmospheric NDMA can be of primary origin, directly emitted by industrial processes, or of secondary origin, generated through atmospheric processes. In the 1970s, NDMA was detected in urban air (<1 μg m-3) near factories that either utilized NDMA or produced NDMA in their processes. The source of NDMA in these factories was related to the production of unsymmetrical dimethylhydrazine (UDMH) from NDMA.

Formation of NDMA by nitrosation

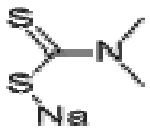
Nitrosation involves the formation of nitrosyl cation or similar nitrogen-containing species, such as dinitrogen trioxide (N_2O_3), during acidification of nitrite. The nitrosyl cation then reacts with an amine, such as dimethylamine, to form NDMA. This reaction occurs most rapidly at pH 3.4.[14] *In vivo* nitrosation occurs when nitrite enters the acidic environment of the stomach. Nucleophilic anions, particularly thiocyanate (a constituent of saliva), enhance the rate of nitrosation through catalytic NDMA formation from nitrite.

NDMA formation from chlorine and other oxidants

Monochloramine can react with DMA (dimethylamine) to produce NDMA. However, DMA is a potentially important precursor if it is present at high enough levels. The presence of bromide can also accelerate the formation of NDMA presumably through the formation of bromamines produced as a consequence of its oxidation by either free chlorine or monochloramine. However, this is not expected to be an important process unless bromide concentrations are exceptionally high. Although dimethylamine is a precursor to 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 ultimately to water. NDMA can also occur in drinking water through the degradation of dimethylhydrazine (a component of rocket fuel). **Figure 2**



Ranitidine



Dimethyldithiocarbamate

Figure 2 Structure of industrial precursors of NDMA

NDMA formation[15], its yield in laboratory-controlled studies is low. NDMA forms as a result of chlorine dioxide, ozone, hydrogen peroxide or permanganate reactions with dimethylamine both in the presence as well as in the absence of ammonia ions. The pharmaceutical ranitidine, which is often used to prevent gastritis, had the highest conversion efficiency to NDMA among selected tertiary amines during chloramination in laboratory-scale studies.[16] Mitch, Sedlak, Choi and Valentine demonstrated that NDMA formation during chlorination could occur through UDMH as an intermediate. The reaction between monochloramine and dimethylamine to form UDMH and the reaction of monochloramine with trimethylamine to form a 1,1,1-trimethyl hydrazinium salt have been known for formation of NDMA.

Exposure

The primary routes of potential human exposure to N-nitrosodimethylamine are ingestion, inhalation, and dermal contact. The general population may be exposed to unknown quantities of N-nitrosodimethylamine present in foods and beverages, tobacco smoke, herbicides, pesticides, drinking water, and industrial pollution .

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. Factors affecting this formation include the nature and amount of precursor compounds and the disinfection strategy used.[17]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.

Air

NDMA may occasionally be emitted into the atmosphere from sites of manufacture/use of dimethylamine and other sites at which NDMA is inadvertently formed, i.e. tanneries, pesticide manufacturing plants, rubber and tire industries, etc. NDMA may also form in night time air as the result of the atmospheric reaction of dimethylamine with NOx. N-Nitrosodimethylamine was measured in mainstream cigarette smoke at 13 to 65 ng per cigarette for nonfiltered cigarettes and 5.7 to 43 ng for filtered cigarettes and in sidestream smoke at 680 to 823 ng for nonfiltered cigarettes and 1,040 to 1,770 ng for filtered cigarettes. It was found at

concentrations of 90 to 240 ng/m^3 in smoke-filled rooms, such as bars, but at less than 5 ng/m^3 in residences.[18]

Soil

NDMA may be released into the environment as the result of land application of sewage sludge containing this compound or as the result of land application of certain pesticides contaminated with this compound. NDMA may also form in soils under conditions which favor nitrosation of nitrosamine precursors.[18]

Food

N-Nitrosodimethylamine is present in a variety of foods, including cheese, soybean oil, various meat products, bacon, various cured meats, frankfurters, cooked ham, fish and fish products, spices used for meat curing, apple brandy, other alcoholic beverages, and beer. Concentrations in these foodstuffs have been measured at up to 850 µg/kg (in spices used in curing).[19]

Drugs

N-Nitrosodimethylamine has been detected in numerous drugs formulated with aminopyrene, including tablets, suppositories, injections, drops, and syrups, at concentrations ranging from less than 10 to 371 µg/kg.[18]

CARCINOGNECITY

N-Nitrosodimethylamine is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals**.** NDMA has been tested in rats by oral administration via drinking water, gavage and diet. The main target organ upon long-term oral administration is the liver, although also tumours in lungs and kidneys have been reported. A comprehensive oral long-term carcinogenicity study has been conducted by Peto *et al*. who examined in detail the dose-response relationship for the effects of NDMA and NDEA on oesophageal cancer or on various types of liver cancer. *N*-Nitrosodimethylamine caused tumors in numerous species of experimental animals, at several different tissue sites, and by several different routes of exposure.[20] N-Nitrosodimethylamine caused kidney tumors in rats and mice exposed orally or by inhalation or intraperitoneal injection and in rats exposed prenatally or by subcutaneous injection.

Urinary N-nitrosamines has been reported for populations from widely separate regions of the world and support a link between exposures to this group of chemical carcinogens and the incidence of different types of cancer. Indeed, subjects with high-risks of developing stomach, oesophageal, colon and urinary bladder cancers were found to excrete higher levels of N-nitrosamines in their urine compared to their relevant low-risk control groups[21]. Their role as causative agents in the carcinogenesis of some human neoplastic diseases has been extensively reviewed .Numerous oral studies in which NDMA was administered for intermediate durations (15-365 days) have been conducted.

Deaths resulting from intermediate duration exposure to NDMA were usually attributed to liver toxicity or carcinogenicity. There is increasing evidence, derived from *in vitro* and *in vivo* metabolic studies, indicating that the carcinogenic effects of NDMA are due to a metabolite rather than the compound itself.[22] NDMA is converted into an alkylating (methylating) agent after metabolism by microsomal mixed-function oxidases. This process occurs principally in the liver and to a lesser extent in kidney and lungs, and results in the methylation of cellular macromolecules such as DNA, RNA and other proteins.

HEALTH EFFECTS

Respiratory Effects. Freund (1937) observed small hemorrhages in the bronchi and trachea of a person who died from accidental exposure to vapors of NDMA.[23]

Cardiovascular Effects. Subpericardial hemorrhage was observed in a person who died from accidental exposure to vapors of NDMA.

Gastrointestinal Effects. Gastrointestinal hemorrhage was observed in a person who died from accidental exposure to vapors of NDMA .

Hepatic effects. Hepatotoxicity is a predominant effect of high concentrations of inhaled NDMA in animals. Pathologic examination of dogs following exposure to 16-144 ppm NDMA for 4 hours showed marked necrosis and varying degrees of hemorrhage in the liver.

Cancer. Rats and mice that were continuously exposed to 0.07 ppm NDMA for 25 and 17 months respectively, developed significantly increased incidences of lung, liver and kidney tumors. Tumor types included various adenomas, carcinomas, and sarcomas in the lung, liver and kidneys, and hemangiomas in the liver.

USES

N-Nitrosodimethylamine is used primarily as a research chemical. Prior to April 1, 1976, the compound was used as an intermediate in the electrolytic production of 1,1 dimethylhydrazine , a storable liquid rocket fuel containing approximately 0.1% *N*-nitrosodimethylamine as an impurity.[24] Other uses of N-nitrosodimethylamine include the control of nematodes, inhibition of nitrification in soil, plasticizer for rubber and acrylonitrile polymers, in active metal anode-electrolyte systems (high-energy batteries), in the preparation of thiocarbonyl fluoride polymers, and as a solvent in the fiber and plastics industry, an antioxidant, a softener of copolymers, and an additive to lubricants.

TREATMENT

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.[25]

Municipal scale

The most commonly used treatment method for the reduction of already formed NDMA is photolysis by ultraviolet radiation (UV).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),[26]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.

UV irradiation and advanced oxidation

The most common process currently used for NDMA reduction is UV irradiation The principal by-products of UV photolysis of NDMA are DMA and nitrite. When UV/ H2O2 is applied, nitrate is the major degradation product, and the concentration of DMA is significantly lower than with direct photolysis.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.[27]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.

Removal of NDMA from water by sorbents (AC and zeolites) and reverse osmosis

In water, however, the high miscibility (NDMA has a very low Henry's constant of 2.6 x 10–4 atm.M–1 at 20ºC) and low vapour pressure results in long residence times. This means that volatilisation from water is unlikely to occur to any great extent. The small and polar nature of NDMA means that it is poorly sorbed onto particles and ACs, but at least one recent study has shown that some zeolites or alumina-modified amorphous silica gels could be effective in its removal.Its small size also leads to significant amounts of NDMA leaching through reverse-osmosis membranes and therefore only about 50% is removed by this means.[28] Also increasing membrane fouling and other effects tend to lead to less NDMA being removed.

Preventing NDMA formation

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,chlorine dioxide or ozone,[29] upstream of chloramination can deactivate organic precursors.

Biodegradation of NDMA

The results of investigation of the metabolism of dialkylnitrosamines (i.e. N-nitrosodimethylamine) suggest the formation of monoalkylnitrosoamine in the first phase of biotransformation as a transition product with simultaneous degradation to alkylating compounds (i.e. diazoalkane or carbonium ion).[30] A scheme of biodegradation of nitrosamines using the example of N-nitrosodimethylamine is shown in **Figure 3** .

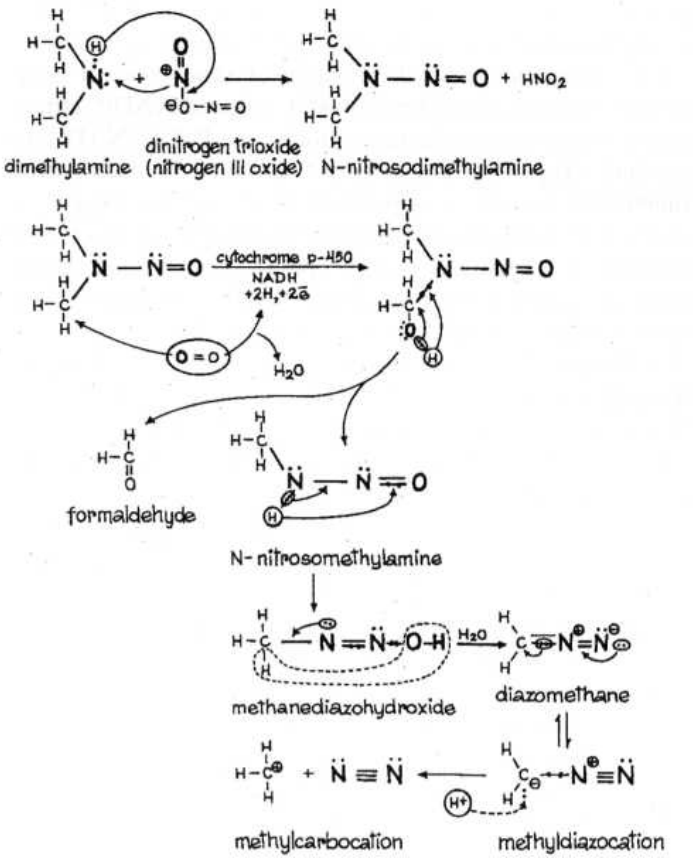


Figure 3 Biodegradation of NDMA

MECHANISM OF ACTION

High oral doses lead to tumours of the kidney and nasal cavity, If the compound is given continuously in drinking water, liver is additional target. Both compounds are hydroxylated, NDMA to formaldehyde and the ultimate carcinogen methyldiazonium ion, and NTDMA is oxidized to HCHO and N-nitromethylamine.The latter compound, on further activation, probably reduction, leads to tumours of the spinal cord. NDMA is metabolized by CYP2E1, an enzyme that is inducible by ethanol, which stabilizes the protein, and by fasting, which increases CYP2E1 mRNA levels.[31] Because NTDMA is structurally so similar to NDMA our working hypothesis is that both compounds are hydroxylated by the same enzyme. Since the product of NTDMA hydroxylation, N-nitromethylamine, is not an ultimate carcinogen and the tumour site is different for the two compounds, we postulated a reduction of NTDMA to NDMA as the first step in NTDMA activation to the ultimate carcinogen, **Figure 4.**

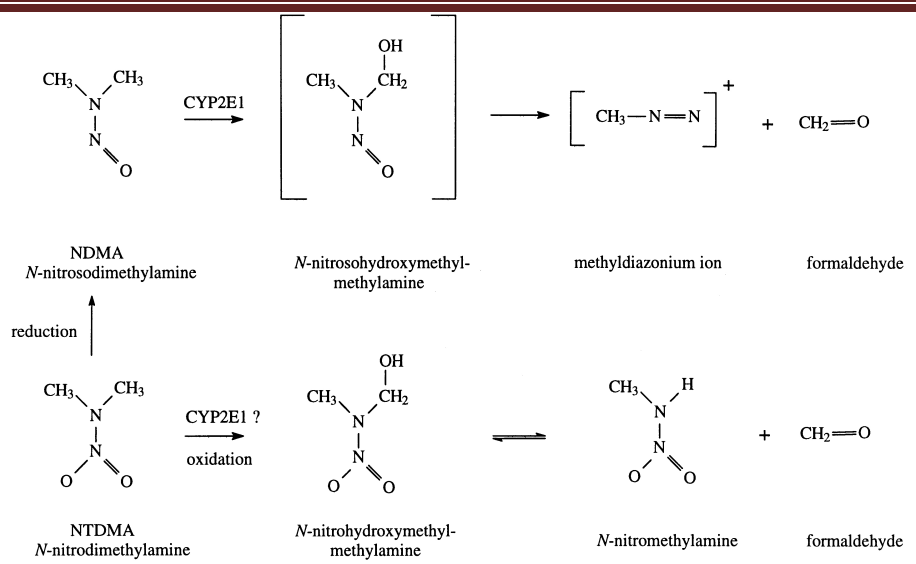


Figure 4 Mechanism of action of NDMA

KINETICS

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%), primarily from the lower intestinal tract.

Distribution and excretion

Once absorbed, NDMA and its metabolites are distributed widely and likely passed to offspring through mothers' milk. 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.

Metabolism

The metabolism of NDMA involves either the α-hydroxylation or denitrosation of the nitrosamine.[32] 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. 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.[32] It is the α-hydroxylation pathway that is believed to form the active metabolites responsible for NDMA's genotoxicity and carcinogenicity. **Figure 5**

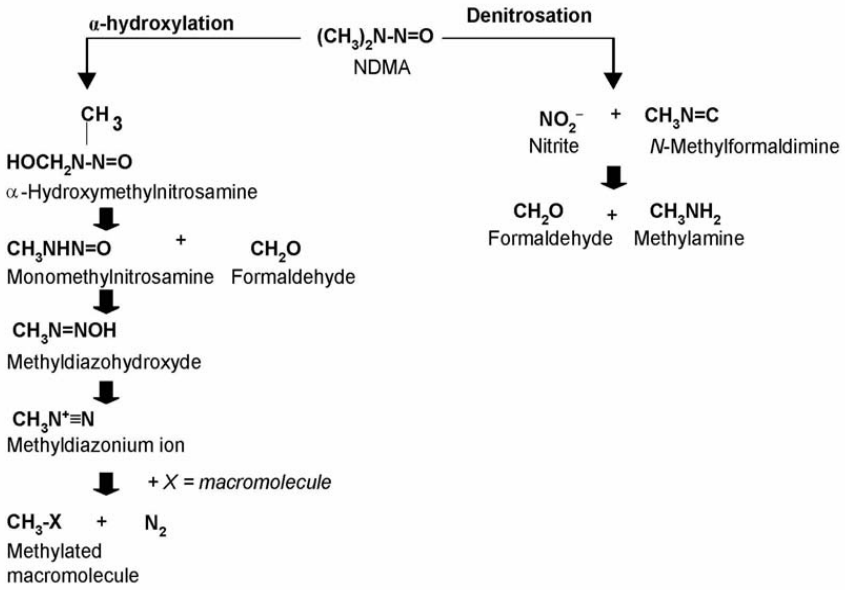


Figure 5 Pathways of NDMA metabolism (adapted from ATSDR, 1989; IPCS 2002)

DISCUSSION

Nitrosodimethylamine (NDMA) belongs to a group of extremely toxic and mostly carcinogenic substances, the N-nitrosamines. Nitrosamines are not new contaminants; their potential carcinogenic effects have been studied for over 40 years. NDMA is not an industrially or commercially important chemical; nevertheless, it can be released into the environment from a wide variety of manmade sources. NDMA has been detected in ambient air, water and soil, low levels of NDMA (measurable in terms of ppm) are commonly found in the air of car interiors, food, malt beverages (beer, whiskey), toiletry and cosmetic products, rubber baby bottle nipples and pacifiers, tobacco products and tobacco smoke, pesticides used in agriculture, hospitals, and homes, and sewage sludge. It is due to the inadvertent formation of NDMA in industrial situations when alkylamines, mainly dimethylamine and trimethylamine, come in contact and react with nitrogen oxides, nitrous acid, or nitrite salts, or when trans-nitrosation via nitro or nitroso compounds occurs. Thus, potential exists for release into the environment from industries such as tanneries, pesticide manufacturing plants, rubber and tire manufacturers, alkylamine manufacture/use sites, fish processing industries and dye manufacturers. In the ambient atmosphere, NDMA should be rapidly degraded upon exposure to sunlight. The half-life for direct photolysis of NDMA vapor is on the order of 5 to 30 minutes. In surface water exposed to sunlight, NDMA would also be subject to photolysis. On soil surfaces, NDMA would be subject to removal by photolysis and volatilization.

REFERENCES

1. Hecht S.S.,Hoffman D. Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke. Carcinogenesis, 9, 875, 1988.
2. Osterdahl B.G. The migration of tobacco-specific nitrosamines into the saliva of chewers of nicotine-containing chewing gum. Food Chem. Toxicol, 28, 619, 1990.
3. Low H. N-nitrosocompouds. Arch. Environ. Health, 29, 5, 1974.
4. Brendler S.Y., Tompa A., Hutter K.F., Preussmann R., Pool-zobel B.L. *In vivo* and *in vitro* genotoxicity of several N-nitrosamines in extrahepatic tissues of the rat. Carcinogenesis, 13, 2435, 1992.
5. Hinuma K., Matsuda J., Tanidan, Hori S., Tamura K., Ohno T., Kano M., Shimoyama T. N-nitrosamines in the stomach with special reference to *in vitro* formation, and kinetics after intragastric or intravenous administration in rats. Gastroenterol. Jpn., 25, 417, 1990.
6. Mitch,W.A.; Sharp, J. O.; Trussell, R. R.; Valentine, R. L.; Alvarenz-Cohen, L.; Sedlak, D. L. N-Nitrosodimethylamine (NDMA) as a drinking water contaminant: A review. *Environ. Eng. Sci. 20*, 389–404. 2003
7. Klein RG, Janowsky I, Pool-Zobel BL, *et al*. Effects of long-term inhalation of *N*-nitrosodimethylamine in rats. In: O'Neill IK, Chen J., Batsch H, eds. Relevance to human cancer of *N*-nitroso compounds, tobacco and mycotoxins. Lyon, France: IARC: 322-8 (IARC Sci Publ). 1991
8. Shapley D. Nitrosamines: scientists on the trail of prime suspect in urban cancer. Science 191:268-270. 1976.
9. HSDB.. *Hazardous Substances Data Bank.* National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB and search on CAS number. Last accessed: 10/7/09. 2009
10. IARC.. Chemicals, Industrial Processes and Industries Associated with Cancer in Humans. IARC, Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, Supplement 4. Lyon,France: International Agency for Research on Cancer. 292, 1982
11. Stefan, M. I.; Bolton, J. R. UV direct photolysis of N-nitrosodimethylamine (NDMA): Kinetic and product study. *Helv. Chim. Acta*, *85*, 1416–1426. 2002
12. Toxicological profile for *N*-nitrosodimethylamine. Agency for Toxic Substances and Disease Registry (ATSDR), U.S. Public Health Service in collaboration with the U.S. Environmental Protection Agency, December. 1989.
13. Kimoto, W.I., Dooley, C.J., Carre, J., and Fiddler,W. Nitrosamines in tap water after concentration by a carbonaceous adsorbent. *Water Res*. 15, 1099–1106.1981
14. Mirvish, S.S. Formation of *N*-nitroso compounds: Chemistry, kinetics and *in vivo* occurrence. *Toxicol. Appl. Pharmacol*. 31, 325–351,1975.
15. Mitch, W.A., and Sedlak, D.L. Formation of *N*nitrosodimethylamine (NDMA) from dimethylamine during chlorination. *Environ. Sci. Technol*. 36**,** 588–595. 2002
16. Omietanski, G.M., and Sisler, H.H. The reaction of chloramine with tertiary amines. 1,1,1-trisubstituted hydrazinium salts. *J. Am. Chem. Soc*. 78**,** 1211–1213. 1956
17. Andrzejewski, P.; Kasprzyk-Hordern, B.; Nawrocki, J. N-nitrosodimethylamine (NDMA) formation during ozonation of dimethylamine-containing waters. *Water Res*, *42* (4-5), 863–870. 2008
18. Fine, D.H., Rounbehler, D.P., Rounbehler, A., Silvergeld, A., Sawicki, E., Krost, K., and Demarrais, G.A. Determination of dimethylnitrosamine in air, water, and soil by thermal energy analysis: Measurements in Baltimore, MD. *Environ. Sci. Technol*. 11, 581–584. 1977
19. Hotchkiss JH. Preformed N-nitroso compounds in foods and beverages. *Cancer Surv*; 8: 295-321, 1989
20. Anderson LM, Hagiwara A, Kovatch RM, et al. 1989. Transplacental initiation of liver, lung, neurogenic, and connective tissue tumors by N-nitroso compounds in mice. Fund Appl Toxicol 12:604-620.
21. Preussmann, R. Occurrence and exposure to *N*-nitroso compounds and precursors. In J.K. O'Neill, R.C. von Borstel, C.T. Miller, J. Long, and H. Bortsch, Eds., N-Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer: Proceedings of the VIIIth International Symposium on N-Nitroso Compounds held in Banff, Canada, 5–9 September, 1983, Switzerland: International Agency for Research on Cancer, 3–15. 1984
22. Peto R, Gray R, Brantom P, et al. Dose and time relationships for tumor induction in the liver and oesophagus of 4080 inbred rats by chronic ingestion of *N*-nitrosodiethylamine or *N*-nitrosodimethylamine. Cancer Res; 51: 6452-69. 1991
23. Freund HA. Clinical manifestations and studies in parenchymatous hepatitis. Ann Int Med 10:1144-1155. 1937
24. HSDB. *Hazardous Substances Data Bank.* National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB and search on CAS number. Last accessed: 10/1/12 2012
25.Sacher, F., Lenz, S., and Brauch, H.-J. Analysis of primary and secondary aliphatic amines in waste water and surface water by gas-chromatography-mass spectrometry after derivatization with 2,4-dinitrofluorobenzene or benzenesulfonyl chloride. *J. Chromatogr.* 764**,** 85–93. 1997
26. Mitch, W.A., and Sedlak, D.L. Prevention of NDMA formation during chlorination. Presentation at the 4th Symposium in the Series on Groundwater Contaminants: Perchlorate and NDMA in Groundwater: Occurrence, Analysis and Treatment: Groundwater Resources Association of California, April 17, Baldwin Park, CA.2002
27. Stefan, M.I., and Bolton, J.R. UV direct photolysis of *N*-nitrosodimethylamine (NDMA): Kinetic and product study. *Helvetica Chim. Acta* 85, 1416–1426.2002
28. Von Gunten, U. Ozonation of drinking water: Part II. Disinfection and by-product formation in presence of bromide, iodide or chlorine. *Water Res.*, *37*, 1469–1487. 2003
29. Lee, C.; Yoon, J.; von Gunten, U. Oxidative degradation of N-nitrosodimethylamine by conventional ozonation and the advanced oxidation process ozone/hydrogen peroxide. *Water Res.*, *41* (3), 581–590.2007
30. Haradak K. Microbial degradation of nitrosamines. Bull. Japan. Soc. Sci. Fisheries, 46, 723, 1980.
31. Hu,Y., Ingelmann-Sundberg,M. and Lindros,K. Induction mechanisms of cytochrome $P_4$50 2E1 in liver: interplay between ethanol treatment and starvation. *Biochem. Pharmacol*., 50, 155–161.1995
32 Phillips, J.C., Lake, B.G., Heading, C.E., Gangolli, S.D. and Lloyd, A.G. Studies on the metabolism of dimethylnitrosamine in the rat. I. Effects of dose, route of administration and sex. Food Cosmet. Toxicol., 13:203–209.197