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Summary Review of Health Effects Associated with Dimethylamine

Health Issue Assessment

Environmental Criteria and Assessment Office
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Preface

The Office of Health and Environmental Assessment has prepared this summary health assessment to serve as a source document for EPA use. The summary health assessment was developed for use by the Office of Air Quality Planning and Standards to support decision making regarding possible regulations of dimethylamine as a hazardous air pollutant.

In the development of the summary health assessment document, the scientific literature has been inventoried through December 1989, key studies have been evaluated, and summary/conclusions have been prepared so that the chemical's toxicity and related characteristics are qualitatively identified. Observed effect levels and other measures of dose-response relationships are discussed, where appropriate, so that the nature of the adverse health responses is placed in perspective with observed environmental levels.

Any information regarding sources, emissions, ambient air concentrations, and public exposure has been included only to give the reader a preliminary indication of the potential presence of this substance in the ambient air. While the available information is presented as accurately as possible, it is acknowledged to be limited and dependent in many instances on assumption rather than specific data. This information is not intended, nor should it be used, to support any conclusions regarding risk to public health.

Abstract

Chemical properties, sources, environmental fate, biodistribution, biometabolism and toxicity studies for dimethylamine (DMA) are reviewed. At 25°C, DMA is a colorless, alkaline, flammable gas which is readily soluble in water. Sources of DMA are both natural and anthropogenic. Atmospheric concentrations near plants emitting DMA range from 0 to 0.13 ppm (0 to 242 $\mu g/m^3$). In the atmosphere, this amine reacts in daylight with hydroxyl radicals, and in darkness with nitric acid or nitrate. Estimates of half-life of DMA in the lower troposphere are 3 to 6 hrs. Additional hydroxyl-related reactions form dimethylnitrosamine, N-nitrodimethylamine (NNDA), amides, and formaldehyde. Inhalation, ingestion, and endogenous production account for the body burden of DMA. DMA is readily absorbed when ingested or inhaled with 80 to 90 percent excreted unmetabolized in urine. Nasal and liver microsomes convert some DMA to formaldehyde. In the presence of nitrite and acidic conditions (e.g., stomach), DMA can be converted to nitrosamines; although it appears that the amounts required exceed reasonable dietary conditions. Acute toxicity in animals is due to ocular and sensory irritation. The inhalation LC_{50} in mice has been estimated to be 7,650 ppm and in rats 4,540 ppm. The slope of the dose/percent mortality curve for both species is steep; for rats, the lowest level for mortality is 3,983 ppm. The oral LD_{50} in animals (250 to 700 mg/kg b.wt.) is dependent on its alkalinity. Inhalation studies of up to 2 yrs in 2 or more species indicate concentration-dependent toxicity, primarily in nasal mucosa, with no other tissues affected except for a 10 percent decrease in body weight at 175 ppm. There is no evidence for carcinogenicity or mutagenicity. No data were found on teratogenic or reproductive effects. Human data related to DMA exposure were not located except for secondary reports of eye irritation at low concentrations, with nose, throat, and lung irritation at 100 ppm DMA. Skin or eye contact produces severe, sometimes permanent burns. Further data are needed on ambient levels and human health effects.

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1. Summary and Conclusions

Dimethylamine (DMA) is a flammable, alkaline, colorless gas at room temperature and atmospheric pressure. It is volatile due to its high vapor pressure (at 25°C, vapor pressure is 1,500 Torr). It is a somewhat stronger base than ammonia and dissolves rapidly in water to yield alkaline solutions. DMA has a characteristic fishy odor at lower concentrations, whereas at higher concentrations (100 to 500 ppm), its odor is more like that of ammonia. Odor detection thresholds for DMA in air and water are approximately 0.3 and 0.7 ppm, respectively.

DMA enters the atmosphere from both natural and anthropogenic sources. It has been found in the excreta of humans, pigs, cattle, and poultry. DMA also occurs naturally in fruit, vegetables, grains, and especially seafood. Anthropogenic sources of DMA include production losses, losses from dispersive uses, automobile emissions, and emissions from garbage dumps and waste treatment facilities. Data on atmospheric levels of DMA in the United States were not found. However, DMA levels ranging from 0 to 0.13 ppm (0 to 242 $\mu g/m^3$) have been measured in an industrial area with plants that emit DMA.

From several studies of the atmospheric reactions of DMA, it can be estimated that the reaction with the hydroxyl radical is the most important process that degrades this amine during daylight, while reactions with nitric acid or nitrate (NO_3) are significant in the dark, according to some researchers. Based on reaction rate measurements, the half-life of DMA in the lower troposphere was estimated to be 3 to 6 hours in daylight. No rate data were found for the suggested dark processes. The hydroxyl radical ($HO^{\bullet}$) is reported to form dimethylamino radicals that react further with nitrogen oxides (NO_x) and oxygen to form dimethylnitrosamine (DMNA), N-nitrodimethylamine (NNDA), amides, and formaldehyde. The highly carcinogenic DMNA is destroyed by sunlight with a half-life of approximately one hour, while the carcinogenic NNDA is relatively stable to this radiation. Reactions of DMA with ozone (O_3) and nitrogen tetroxide (N_2O_4) have also been studied; based on the typical concentrations of these pollutants in ambient air, such reactions are not important to the degradation of DMA.

DMA can be introduced into the body via ingestion or inhalation. Additionally, studies have shown that DMA can be synthesized within the body from other dietary constituents by microorganisms in the gut and by unidentified endogenous pathways. It has been suggested that DMA is an important nutrient, acting as a stimulator of postprandial gastrin secretion and directly as a stimulator of gastrointestinal mucosal growth.

Quantitative absorption studies with single doses of labeled DMA have not been performed; however, data from other studies indicated that DMA is readily absorbed following inhalation or ingestion. The major site of absorption in adult male rats following inhalation of [^{14}C]DMA at 10 or 175 ppm for 6

hours was the nasal mucosa. Very little, if any, of the inhaled [^{14}C]DMA reached the lung directly. Following ingestion, the major site of DMA absorption appears to be the upper small intestine; absorption from the stomach is barely detectable, as expected for an ionized substance.

After absorption, DMA travels via the blood to the various internal organs and tissues. Tissue distribution studies performed in adult male rats and guinea pigs indicate that 4 hours following an intravenous dose of 10 mg/kg [^{14}C]DMA, concentrations of radioactivity are highest in the kidneys. Levels of [^{14}C] in most other tissues were less than half the kidney levels. A similar distribution pattern was observed in adult male rats immediately following a 6-hour inhalation exposure to [^{14}C]DMA at 10 or 175 ppm.

DMA is excreted mainly via the urine. After inhalation of [^{14}C]DMA at 10 ppm for 6 hours, male rats excreted mean levels of 78, 12.5, and 1.5 percent of the recovered [^{14}C] in the 0- to 72-hour urine, feces, and expired air, respectively. After 6-hour exposures to 175 ppm [^{14}C]DMA, mean levels of 86.7, 5.1, and 1.5 percent of the recovered [^{14}C] were found in the 0- to 72-hour urine, feces, and expired air, respectively . After intravenous injection of 60 µmol of [^{14}C]DMA, adult male rats excreted 85 to 90 percent of the dose into the 0- to 24-hour urine as unmetabolized DMA. Less than 0.1 percent of the dose was expired as [^{14}C]DMA and 0.5 percent as radiolabeled carbon dioxide.

Balance studies indicate that urinary excretion accounts for 95 percent of the DMA excreted in combined urine and feces. DMA excretion can range from 1.5 to 14.7 times intake, depending on the amount of DMA ingested. The excess DMA is considered to arise from *in vivo* synthesis by the host and/or gastrointestinal flora. DMA can be absorbed from the gut into the bloodstream; from there, it can be secreted into the bile, gastric juice, and saliva. Therefore, DMA does undergo a certain amount of enterohepatic circulation.

It has previously been suggested that DMA is an end metabolite, i.e., that it is not metabolized. However, it has been shown that DMA can be metabolized *in vitro* to formaldehyde, albeit slowly, by rat hepatic and nasal microsomes. Perhaps as much as 8 percent of inhaled DMA may be converted to formaldehyde by rats *in vivo*. No information was found in the available literature on potential DMA metabolites other than formaldehyde nor on DMA metabolites in urine or feces. However, 98.7 percent of the radioactivity in the 0- to 24-hour urine of male rats injected intravenously with DMA was shown to be unmetabolized parent compound, indicating that little, if any, DMA metabolites are excreted in the urine. There is evidence to show that DMA can be chemically converted to DMNA in the presence of nitrite and acidic conditions and that this conversion can take place in the mammalian stomach when the compounds are administered by gastric intubation. However, it has not been demonstrated that significant levels of DMNA are formed in the stomach under reasonable dietary conditions or that absorption of DMNA from the gastrointestinal tract occurs under these conditions. The experimental doses used in these studies are relatively high when compared to air exposure routes.

The high water solubility and alkalinity of DMA contribute greatly to the compound's toxicity. Acute inhalation exposures in rats and mice produce immediate signs of ocular and sensory irritation. Under experimental

conditions, the decrease in respiratory rate at particular air concentrations is determined. The air concentration for 50% depression is the RD_{50}. The RD_{50} values for rats and mice, 573 and 511 ppm, respectively, are much lower than the LC_{50} values (4,540 and 7,650 ppm for rats and mice, respectively). Although no LOEL was actually determined, a TLV for sensory irritation for humans was estimated to be between 0.01 RD_{50} and 0.1 RD_{50}, with 0.1 RD_{50} the ceiling value. This range is between 5 and 51 ppm DMA. In rats exposed to DMA concentrations of 600 ppm for 6 hours, pathological lesions were limited mainly to the eyes and nasal mucosa. As the DMA concentration approached lethal levels, greater toxicity to the lung and liver were observed. For all doses tested, however, the tissues of the nasal cavity were most severely affected, and a distinct anterior-to-posterior severity gradient was observed; the lung was minimally affected.

The irritant properties of aqueous DMA also appear to be mainly responsible for its acute oral toxicity. The oral LD_{50} values for aqueous DMA in mice, rats, guinea pigs, and rabbits are 5 to 11 times lower than for neutralized DMA. DMA is also highly irritating to the eyes of rabbits.

The results from studies on subchronic and chronic inhalation toxicity of DMA in rodents show the same basic trends as those found with acute exposures. In mice and rats exposed to DMA at 0, 10, 50, or 175 ppm for 6 hours/day, 5 days/week for up to 12 months, the most sensitive tissue was the nasal mucosa. No other tissue, including liver and lung, was affected. Body weights, however, were approximately 10 percent lower in the 175-ppm group than in controls. Slight pathological lesions were observed in the olfactory sensory cells of animals in the 10-ppm groups; this concentration, however is considered to be the NOAEL, with 50 ppm, the LOAEL concentration. The NOAEL data at 10 ppm from this chronic study were used to calculate a RfDi for DMA for humans of 2 µg DMA/m^3 (1.0 ppb) of air. This value has been verified by the RfD work-group in 11/89. Reports of hepatic, testicular, pulmonary, immunological, and central nervous system effects from long-term, low-level exposure of animals to DMA have been made, but are questionable because they are from studies that would be considered inadequate by today's standards.

No evidence for carcinogenicity resulting from exposure to DMA has been found. A 2-year toxicity/oncogenicity study in rats and mice has been completed, but the results have not been published in full; there was no evidence of increased tumors in these animals. The available genetic toxicology studies are mostly inadequate and tend to show that DMA is nonmutagenic. Several studies indicate that combined administration of DMA and nitrite produces signs of toxicity similar to those observed after DMNA administration. These include liver damage, mutagenicity, and carcinogenicity. However, the doses of nitrite and DMA required to produce these effects are extremely high, making the theory of DMA conversion to the carcinogenic DMNA under normal dietary or inhalation exposure conditions questionable.

No information was found in the available literature on teratogenic and reproductive effects of DMA.

A search of the primary literature failed to produce any reports on the human health effects associated with exposure to DMA. However, several secondary sources have reported a variety of acute toxic effects associated

with DMA exposure. All reported effects of DMA in humans are related to the compound's irritancy. Exposure to DMA vapors produces irritation of the eyes with conjunctivitis and corneal edema. Inhalation of concentrations higher than 100 ppm can cause irritation of the nose and throat and lung irritation with dyspnea and cough. The vapors may also produce primary skin irritation and dermatitis. Direct contact with the liquid can produce severe and sometimes permanent eye damage or skin burns. The effects of long-term, low-level exposure to DMA are not known.

In conclusion, adequate data on practically all aspects of the environmental levels and fate and the toxicity of DMA are lacking. Atmospheric levels of DMA in the United States are not known. The percentage of atmospheric DMA arising from natural or anthropogenic pathways has not been fully characterized. Although a sustained level of DMNA does not apparently result from the degradation of DMA in normal atmospheres, the concentrations of NNDA that result have not been determined. No 2-year chronic toxicity/oncogenicity, teratology, or reproductive studies in animals were found although a 2-year study has been completed, but not published. Additionally, no epidemiology studies or case histories of DMA exposure to humans were found. Finally, evidence for the chemical conversion of DMA to DMNA in the atmosphere, *in vitro*, and *in vivo* has been found, but the potential health effects associated with combined exposure to DMA and nitrites after ingestion has not been adequately demonstrated.

2. Background Information

2.1 Physical and Chemical Properties

DMA (CAS No. 124-40-3) is a flammable, alkaline, colorless gas at room temperature and atmospheric pressure. At relatively high concentrations (i.e., over 2 percent), the vapors are heavier than air and can travel a considerable distance to reach an ignition source and flashback (Air Products and Chemicals, Inc., 1983). Concentrated DMA vapors are also corrosive and have been reported to damage the boots, gloves, and face shields of firefighters attempting to plug a leaking tank car (Howard, 1984). Contact of DMA vapors with strong oxidizers, chlorine, or mercury can cause fires and explosions (Mackinson et al., 1981). DMA can be compressed into a clear, water-white liquid (E. I. du Pont de Nemours & Company, 1984).

DMA is a somewhat stronger base than ammonia. It dissolves rapidly in water to yield alkaline solutions ranging from water-white to pale straw in color (E. I. du Pont de Nemours & Company, 1984). Several physical and chemical properties of DMA are presented in Table 2-1.

2.2 Organoleptic Properties

DMA has a characteristic fishy odor at lower concentrations. However, at higher concentrations (100 to 500 ppm), the fishy odor is no longer detectable and the odor is more like that of ammonia (Braker and Mossman, 1980). Following a review of the literature, Amoore and Hautala (1983) reported the odor detection threshold of DMA in air to be 0.34 ppm. The original data sources were not referenced. Based on a TLV of 10 ppm for DMA, an odor safety factor (TLV/detection threshold) of 29 was calculated. According to the authors, this means that 50 to 90 percent of distracted persons can smell DMA at its TLV level. However, Braker and Mossman (1980) stated that prolonged exposure to DMA may result in a loss of odor detection.

The organoleptic properties of DMA in water were studied by Dzhanashvili (1967). Threshold concentrations for odor and aftertaste were investigated on a group of 11 subjects in 14 series of experiments. DMA was found to impart an ammoniacal odor to water with a detection threshold concentration of 0.67 mg/L. However, the taste and color of water were not affected by DMA concentrations 10-fold higher. Water became undrinkable at DMA concentrations as low as 20 mg/L due to its strong ammoniacal odor. Amoore and Hautala (1983) reported an odor detection threshold of 0.29 mg/L for DMA in water.

2.3 Natural Sources of Dimethylamine

DMA is a naturally occurring chemical that is abundant and widespread in our ecosystem. It has been found in the manure of beef cattle and in the air surrounding piggeries, poultry houses, and dairy cattle barns (Zimnal, 1979; Kliche et al., 1978; Mosier and Torbit, 1976). DMA is also found at relatively high concentrations in seafood. Lin et al. (1984) purchased samples of 25

Table 2-1. Physical and Chemical Properties of Dimethylamine

Parameter	*Value*	*Reference*
Molecular formula	C_2H_7N	Braker and Mossman (1980)
Molecular weight	45.085	Braker and Mossman (1980)
Vapor pressure at:		
20°C	24.7 psi (1,280 Torr)	Air Products and Chemicals Incorporated (1983)
21.1°C	26.0 psi (1,344 Torr)	Braker and Mossman (1980)
25°C	29.0 psi (1,500 Torr)	E. I. du Pont de Nemours & Company (1984)
52°C	66.7 psi (3,448 Torr)	Air Products and Chemicals Incorporated (1983)
Boiling point	6.9°C	Braker and Mossman (1980)
Melting point	-93°C	Air Products and Chemicals Incorporated (1983)
Freezing point	-92.2°C	U.S. Coast Guard (1984)
Vapor density (air = 1)	1.55	Air Products and Chemicals Incorporated (1983)
	1.6	E. I. du Pont de Nemours & Company (1985)
Solubility in water at 60°C	23.7 percent (by weight)	Braker and Mossman (1980)
Base equilibrium constant, k_b; in water	6.03×10^{-4}	Schweizer et al. (1982)
Specific gravity at:		
6.9°C	0.671	U.S. Coast Guard (1984)
25°C	0.65	E. I. du Pont de Nemours & Company (1985)
Flash point	20°F (-6.7°)	U.S. Coast Guard (1984)

different dried seafoods from local (Taipei, Taiwan) markets and 25 different fresh seafoods from local fisheries. DMA ranging from 3 to 2,043 ppm was found in 48 of the 50 samples. Highest DMA levels were found in dried squid (956 to 2,043 ppm), dried cod (1,105 ppm), and dried octopus (972 ppm). Because of the high levels of DMA in seafood diets common to the Orient and because DMA is known to be converted to DMNA, concerns have been raised that the high incidence of stomach cancer in Orientals may be related to high dietary DMA (Lin et al., 1984). In addition to being present in seafood, measurable quantities of DMA have been found in fresh fruit, vegetables, and grains obtained at retail stores (Neurath et al., 1977). This natural occurrence is not due to pesticide use, but natural synthesis and degradation of the chemicals in the material.

2.4 Production, Use, and Occupational Exposure

2.4.1 Production

2.4.1.1 Manufacturing Process

DMA is produced by the interaction of methanol and ammonia over a catalyst at high temperature (Schweizer et al., 1982).

2.4.1.2 Production Volume

The public portion of the Toxic Substances Control Act (TSCA) Chemical Substance Inventory (TSCA Inventory) reported the production of between 71 and 210 million pounds (32 to 95 million kilograms) of DMA in 1977. This volume was the output of five manufacturers (CICIS, 1987).

The U.S. International Trade Commission (1986, 1985, 1984, 1983, 1982) reported that 28 to 35 million kilograms of DMA were produced annually during 1981 through 1985 and approximately 0.01 to 0.50 million kilograms were imported annually during 1980 through 1983 (Table 2-2). Export volumes have been reported for all methylamines (mono-, di-, tri-) combined, and these volumes have steadily decreased since 1980 (SRI International, 1985a; Table 2-2).

Table 2-2. Production Volume, Imports, and Exports of Dimethylamine (million kilograms) for 1980-1985

Year	Production[a] volume	Imports[a]	Exports[a,b]
1980	--	0.50	7.47
1981	32.97	0.29	6.46
1982	30.45	0.01	5.62
1983	27.75	0.01	3.73
1984	32.22	--	--
1985	29.89	--	--

[a]*U.S. International Trade Commission (1986, 1985, 1984, 1983, 1982).*

[b]*These values represent export volumes for all methylamines (mono-, di-, and tri-) combined (SRI International, 1985a).*

SRI International (1985b) listed four domestic producers of all three methylamines (mono-, di-, tri-). Producers and the combined annual production capacity of the methylamines they manufacture are as shown at the top of the next page:

Producer	Annual Production Capacity (million kilograms)
E. I. du Pont de Nemours and Co., Inc. Belle, WV	75
Air Products and Chemicals, Inc. Pensacola, FL	68
International Minerals and Chemicals Corp. Terre Haute, IN	10
GAF Corp. Calvert City, KY	5

2.4.1.3 Producers and Importers

2.4.1.3.1 Producers. The following companies were listed in the public portion of the TSCA Inventory as manufacturers of DMA (CICIS, 1987):

Air Products and Chemicals, Inc.
Pace, FL

American Bio-Synthetics Corporation
Milwaukee, WI

American Cyanamid Company
Bound Brook, NJ

E. I. du Pont de Nemours and Co., Inc.
Belle, WA and La Porte, TX

GAF Corporation
Calvert City, KY

IMC Chemical Corporation
Terre Haute, IN

2.4.1.3.2 Importers. The following importers of DMA were identified in the public portion of the TSCA Inventory (CICIS, 1987)

BASF Wyandotte Corporation
Parsippany, NJ

ICI Americas, Inc.
Wilmington, DE

2.4.1.4 Technical Product Composition.

Grades of DMA available are technical anhydrous, a 99 percent grade, and technical aqueous (25 and 40 percent) (Hawley, 1981). DMA solutions are

available in glass bottles, drums, tank cars, and trucks while liquefied gas is available in steel cylinders, tank cars, and tank trucks (National Fire Protection Association, 1986; Hawley, 1981).

2.4.1.5 Storage, Handling, and Disposal

It is recommended that DMA should be stored in a cool dry place; containers should be protected against physical damage. Outside or detached storage is preferable. Inside storage of liquid solutions should be in a standard storage room or cabinet for flammable liquids. Inside storage of gas cylinders should be in cool, well-ventilated areas away from oxidizing agents, heat, sparks, or open flames. Accidental contact with mercury must be avoided (Genium Publishing Corporation, 1986; National Fire Protection Association, 1986).

Protective clothing such as impervious gloves, face shields, aprons, boots, and plastic coveralls should be worn to prevent possible skin contact; splash-proof safety glasses should be worn to prevent any possibility of eye contact (Genium Publishing Corporation, 1986; Mackison, et al., 1981). Eyewash stations and safety showers should be readily available in use and handling areas (Genium Publishing Corporation, 1986).

Bulk quantities of DMA may be disposed of by burning at a safe location or by incineration in incinerators equipped with a scrubber or thermal unit to reduce NO_x emissions (Mackison et al., 1981; Sittig, 1981). Small quantities should be allowed to evaporate if local, state, and Federal regulations permit doing so (Genium Publishing Corporation, 1986).

2.4.2 Use

DMA is used as a chemical intermediate for producing dimethylformamide and dimethylacetamide. It is also used in the production of pesticides such as Pestox and ziram (Schweizer et al., 1982). Other miscellaneous uses include the production of an anesthetic (Pontocaine), an antihistamine (Benadryl), rubber accelerators (Monex, Thionex), a propellant for rockets (UDMH), a catalyst (DMP-30), water treatment chemicals and a surfactant (Triton X-400) (Schweizer et al., 1982). It also has potential applications as an acid gas absorbent, an antioxidant, in dyes and other textile chemicals, in pharmaceutical prescriptions, in textile chemicals, as a dehairing agent for leather, and as a reagent for magnesium determination (Hawley, 1981).

2.4.3 Occupational Exposure

Estimates of occupational exposure to DMA have been reported in industrial hygiene surveys performed by the National Institute for Occupational Safety and Health (NIOSH). According to the National Occupational Hazard Survey (NOHS), conducted by NIOSH from 1972 to 1974, 27,364 workers in 1,914 plants were potentially exposed to DMA in the domestic workplace environment (Stanford Research Institute, 1976). The largest number of exposed workers were involved in general building, chemicals and allied products, heavy construction, rubber and plastic products, primary metals, and medical and other health services industries.

Preliminary data from the National Occupational Exposure Survey (NOES), conducted by NIOSH from 1980 to 1983, indicated that 8,700 workers including 952 women at 183 sites were potentially exposed to DMA in the workplace in 1980 (NOES, 1984). The largest number of exposed workers were involved in chemicals and allied products, business services, health

services, and primary metals industries. Unlike NOHS, the NOES estimates were based only on direct observation by the surveyor of the actual use of the compound.

The current time-weighted average (TWA) TLV for DMA exposure in the workplace is 10 ppm (18 mg/m^3) (American Conference of Governmental Industrial Hygienists, 1986). This same level, 10 ppm, has also been adopted by the National Institute for Occupational Safety and Health (NIOSH) as an 8-hour TWA permissible exposure limit for DMA (Mackison et al., 1981).

No data were available on DMA concentrations in U.S. plants. In two studies from Germany, DMA has been found in two workplaces at concentrations in the air of 0.61 to 1 ppm (Bretschneider and Matz, 1973) and at 0.65 to 18 ppm (Bittersohl and Heberer, 1980).

2.5 Quantitation and Analysis

DMA can be detected and analyzed in air, water, and soil by several methods, but because of its chemical properties, careful attention to assay technique is necessary to obtain accurate, quantitative results. Because of DMA's low acute toxicity (see Sections 4.1.1 and 4.2.1) and its easily detectable odor, few sensitive methods for its analysis in air were developed until it was recognized that carcinogenic DMNA could be formed from DMA in the environment. NIOSH (in a report prepared for NIOSH by Stanford Research Institute, 1976) does recommend a method of analysis for DMA in air. In this method, air is sampled by drawing a known volume through a tube that contains silica gel to trap the organic vapors present. The silica gel is then extracted with an acid-methanol solution and the solution is neutralized with potassium hydroxide. The DMA is quantified by gas chromatography (GC). The method has been validated with the use of a 48-L air sample for the range of 3.8 to 16 ppm. Specific methods for DMA are not included in U.S. Environmental Protection Agency's methods for the analysis of municipal and industrial wastewater (Longbottom and Lichtenberg, 1982) or in test methods for the evaluation of solid waste (SW-846) (U.S. Environmental Protection Agency, 1982), although methods for the determination of DMNA appear in both of these publications.

Some of the recently developed methods of analysis are described in Table 2-3. DMA's volatility allows it to be analyzed by GC, but its reactive nature causes it to adsorb on many column-packing materials. To overcome adsorption and the consequent peak broadening, specially treated column materials must be used or the amines must be chemically converted to derivatives that may be more easily chromatographed. Although the common flame ionization detector (FID) can be used to measure DMA or its derivatives, a greater sensitivity can be attained by the use of a nitrogen-phosphorus FID (NP-FID, the alkali salt bead type) (Kuwata et al., 1980). Since Boehm et al. (1983) have been able to detect as little as 1 ppb with the use of an FID, it may be possible to detect DMA at 1 ppb in air with the use of the more sensitive NP-FID. Fuselli et al. (1982) adsorbed amines from ambient air on charcoal and analyzed them by an NP-FID detector following desorption using heat. However, they were unable to detect levels of DMA below 5 ppb, because they could not completely desorb the amines.

Several other methods use a derivatization procedure before the measurement technique is applied. Derivatization usually forms a material that highly absorbs ultraviolet (UV) radiation or that fluoresces. These methods have been used for the analysis of DMA in air, biological fluids, water, and foodstuffs. As shown in Table 2-3, DMA can be quantitated at levels in the

Table 2-3. Analytical Methods for Dimethylamine

Method Outline[a]	Application	Detection Limit	Comments	Reference
Direct GC:				
Inject air sample, FID	air	ca. 180 µg/m³ (100 ppb)	--	Bretschneider and Matz (1973)
Absorb in acid, neutralize, inject, NP-FID	water	10,000 µg/L	applied to industrial wastewater and sewage	Onuska (1973)
Ultrafiltration, inject, FID	biological fluids	470 µg/L [sic] [b]	found 320 µg/L in normal human serum	Dunn et al. (1976)
Inject, FID	water water	ca. 1,000 µg/kg ca 10 µg/kg	limit based on detector	Kubelka et al. (1976)
Absorb on silica gel, extract, inject, FID	workplace air	3,600 µg/m³ (1.9 ppm)	requires a 48-L sample of air	Stanford Research Institute (1976)
Absorb in acid, neutralize, inject, NP-FID	air	ca. 1 µg/m³ (0.5 ppb)	--	Kuwata et al. (1980)
Absorb on activated charcoal, desorb by heat, inject into GC, NP-FID	air	9 µg/m³ (4.9 ppb)	DMA found at 52-241 ppb in 30-L samples from industrial areas	Fuselli et al., (1982)
Absorb amines in acid, seal in septum bottle with NaOH, inject head space vapor, FID	air	2 µg/m³ (1.1 ppb)	sensitivity could be increased with use of NP-FID	Boehm et al., (1983)
Absorb on Sep-PAK C_{18} extract with H_2O-MeOH	air	0.18 µg/m³ 0.1 ppb	analyzed air in farm areas; no DMA found, only monoethylamine (MMA) and trimethylamine (TMA)	Kuwata et al., (1983)

(continued)

Table 2-3 Continued

Method Outline[a]	Application	Detection Limit	Comments	Reference
Direct GC (continued):				
Extract with acid, neutralize and extract with benzene, inject, NP-FID	fish and seafood	6,400 µg/kg	--	Lundstrom and Racicot (1983)
Direct injection, NP-FID	aqueous solutions	ca. 10 µg/m^3	can be used on liquid from impingers	Audunsson and Mathiasson (1984)
Derivatization and GC:				
Distill from KOH, extract, derivatize as $CF_3CON(CH_3)_2$, inject, FID	water and foodstuffs	100 µg/m^3	procedure will find chemically bound DMA	Neurath et al. (1977)
Distill from NaOH, derivatize with C_6F_5COCl, inject, NP-FID or MS	foodstuffs and beer	ca. 100 µg/kg	procedure will find chemically bound DMA	Ripley et al. (1982)
Direct liquid chromatography (LC):				
Absorb on silica gel, extract with MeOH/H_2O measure with ion chromatograpy	air	3,600 µg/m^3 (1.9 ppm)	a method for occupational air sampling	Bouyoucos and Melcher (1983)
Derivatization and LC:				
Derivatize, TLC, quantitate with polarography	air	2 µg/m^3, (1.1 ppb)	--	Bittersohl and Heberer (1980)
	urine	50 µg/L		
Derivatize, HPLC, UV detector	serum	<200 µg/L	--	Baba et al. (1984)
Absorb and derivatize on a resin, extract, HPLC, with UV or fluorescence detector	air	ca. 40 µg/m^3 (22 ppb)	used a 10-L air sample	Elskamp and Schultz (1986)
Derivatization, TLC, quantitate with fluorescence	water or foodstuffs	ca. 0.001 µg/kg	--	Gracheva et al. (1986)

(continued)

Table 2-3. Continued

Method Outline[a]	Application	Detection Limit	Comments	Reference
Nonchromatographic methods:				
Fourier transform infrared spectroscopy (FT-IR) of vapors	confined air/gases (smog-chamber)	1.8 µg/m³ (1 ppb)	used a 720-m path length in the gas	Tuazon et al. (1978)
Infrared spectroscopy	confined air/gases	ca. 1500 µg/m³ (0.8 ppm)	--	Glasson (1979)
React with CS_2, acidify, determine color photometrically	urine	450 µg/L	--	Beal and Bryan (1978)
Form dithiocarbamate derivative and assay	air	not reported in abstract	--	Yakimova et al. (1985)

[a]A brief outline of the method is provided.
[b]The author stated that the method's detection limit was 470 µg/L, but he reported detecting DMA at 320 µg/L in serum. This discrepancy may be the result of a concentration process caused by the ultrafiltration step used.

parts-per-million (mg/kg) to parts-per-trillion (ng/kg) range. Many of the methods use concentration techniques such as absorption in solid or liquid matrices, then a distillation step, followed sometimes by extraction. If distillation of a material with an alkali solution is used, DMA may be spuriously generated by hydrolysis of a chemical precursor such as dimethylacetamide (Ripley et al., 1982; Neurath et al., 1977).

Infrared (IR) spectroscopic methods for analyzing vapors, usually with the use of the Fourier transform technique, requires such complex, expensive equipment that they have been applied only in smog chamber research studies of reactions of DMA in air (Glasson, 1979; Pitts, 1978; and Tuazon et al., 1978). This method does allow simultaneous detection of N- nitro- and N-nitrosodimethylamines, but such mixtures cannot be quantitated because their spectra overlap. No reports of the use of FT-IR to measure DMA concentrations in ambient air were found. The very different properties of these substances do not normally allow their combined determination by chromatography or derivatization by the same reagents.

2.6 Environmental Levels and Fate

2.6.1 Sources of Dimethylamine in the Environment

Total environmental releases from manufacturing processes have been estimated at approximately 630,000 kg in 1975 (1.4 million lb/year) (Brown et al., 1975). The fraction that enters the atmosphere was not estimated, but from the manufacturing process (Schweizer et al., 1982) we expect that most of the release will be into waste water. Since methylamine plants have generated strong odors during operation (Keko, 1975), some gas emissions are known to have occurred. Losses from the dispersive uses will be considerably less than this quantity because less than 15 percent of the DMA produced is used dispersively. DMA from herbicides such as diuron, monuron, and fenuron and fungicides such as thiram and ziram may also enter the environment due to hydrolytic or microbial degradation after agricultural use. However, no estimates of the amounts of DMA released from pesticides have been found. DMA is also generated by catalyst-equipped automobiles at approximately 0.11 mg/mile in the exhaust gases (Cadle and Mulawa, 1980). As much as 95,000 kg/year of DMA may enter the atmosphere from this source, if we assume that 50 percent of the miles driven by motor vehicles are equipped with catalytic converters (1/2 of 1.77×10^{12} miles/yr in 1985; Motor Vehicles Manufacturers Association, 1987).

Several biogenic sources of DMA have also been reported. DMA has been reported to be present at 1 to 7 ppm in some fresh vegetables such as corn, kale, lettuce, and peas (Ripley et al., 1982; Neurath et al., 1977). DMA may enter the environment from these materials as they are used or degraded. Since human and animal metabolism apparently produces small concentrations of DMA in the urine (10 to 25 mg/L) (Zeisel et al., 1985; Bittersohl and Heberer, 1980; Beal and Bryan, 1978), some of the DMA in the environment may be from this source. Humans and animals excrete creatinine, and it has been reported that this material is partially transformed to DMA in sewage treatment plants (Thomas and Alexander, 1981). DMA has been detected in the effluent air from garbage units in Russia (Sidorenko et al., 1978), and from air over cattle manure in barns (Kliche et al., 1978; Zimnal, 1979), or feed lots (Mosier and Torbit, 1976; Mosier et al., 1973).

2.6.2 Environmental Levels

Although there are apparently a wide variety of sources of DMA in the environment and there is concern that DMA may be converted into DMNA in the atmosphere, very few published reports of studies were found that measured concentrations of the DMA in general urban or rural areas. All of the reports found in recent literature are from outside the United States. In contrast, several studies of the concentration of DMNA in urban areas have been reported (Pellizzari et al., 1986; Chuong et al., 1978; Fine et al., 1977; U.S. Environmental Protection Agency, 1977; Fine et al., 1976). As shown in Table 2-4, atmospheric levels of DMA as high as 0.13 ppm (242 $\mu g/m^3$) were found at industrial sites in Italy (Fuselli et al., 1982), and DMA has been detected at levels at 0.0004 ppm (0.65 $\mu g/m^3$) near office buildings in Russia (Sidorenko et al., 1978). DMA has been measured at 0.09 ppm (17 $\mu g/m^3$) in air outside a rendering plant in Japan (Kuwata et al., 1983).

Table 2-4. Reported Atmospheric Concentrations of Dimethylamine

	DMA Concentration		
Location	*$\mu g/m^3$*	*ppm*	*References*
Air from residences, Russia	51-57	0.028-0.031	Sidorenko, et al., (1978)
Air from garbage chutes, Russia	667	0.370	
Air from office buildings, Russia	8,73	0.00484	
Air outside office buildings, Russia	0,65	0.00035	
Ambient air around rendering plant, Japan	17	0.0094	Kuwata et al., (1983)
Industrial area[a], site A, Italy	120-148	0.065-0.080	Fusselli et al., (1982)
Industrial area[a], site B, Italy	212-242	0.115-0.131	
Industrial area[a], site C, Italy	0-52	0-0.030	
Air in cow shed, Japan	ND (<0.24)[b]	<0.00013	Kuwata et al., (1983)
Air around poultry waste unit, Japan	ND (<0.45)[b]	<0.00025	
Air in large dairy cattle barn (1,000-2,000 cattle)	ND-1,500[c]	ND-810[c]	Kliche et al., (1978)

[a]An area with industrial plants that emit DMA and other methylamines.
[b]ND :none detected. Air was sampled in the farm areas shown and assayed for low molecular weight amines. TMA at 0.5 to 11 $\mu g/m^3$ and MMA at 0 to 1.8 $\mu g/m^3$ were found. However, DMA (at the detection limits shown) was not found.
[c]From 126 air samples taken over a 12-month period (3 samples per day) DMA was selected on four days (85 samples). The detection limit varied from 0.1 to 0.7 ppm.

Because DMA is highly soluble in water and easily absorbed by acidic materials, one would expect that releases of the amine into the environment would disperse into air, water, and soil easily. Its concentration in the environment is often rapidly reduced by further reactions (see Section 2.6.3).

2.6.3 Environmental Chemistry

Studies of the reactions of DMA with other constituents in air and water, and by microbial systems have been performed in the last several years to

determine the fate of DMA in the environment. Since DMNA has been shown to be carcinogenic in animals, many of these studies have measured the reactions of DMA with environmental levels of nitrogen oxides (NO_x) or nitrites to form DMNA. Reactions that have been studied are shown below:

2.6.3.1 Reaction of DMA With Hydroxyl Radicals (HO•) in Air.

The first step is formation of two types of DMA radicals:

i) $HO\bullet + CH_3NHCH_3 \rightarrow \bullet CH_2NHCH_3 + H_2O$ (2-1) [Atkinson, 1985]

ii) $HO\bullet + CH_3NHCH_3 \rightarrow CH_3\overset{\bullet}{N}CH_3 + H_2O$ (2-2) [Atkinson, 1985]

Both processes are important and competitive. The DMA radicals formed above can react further with O_2, NO, and $\bullet NO_2$ to form formaldehyde and methylformamide (Atkinson, 1985). The $CH_3\overset{\bullet}{N}CH_3$ radical subsequently reacts with NO, NO_2, and O_2, with reactions with NO_2 and NO predominating:

$$CH_3\overset{\bullet}{N}CH_3 + O_2 \rightarrow CH_3(NOO)CH_3 \xrightarrow{h\upsilon} CH_3N{=}CH_2 + HO_2$$ (2-3) [Atkinson, 1985]

$$CH_3\overset{\bullet}{N}CH_3 + NO \xrightarrow{h\upsilon} CH_3(NNO)CH_3$$ (2-4) [Atkinson, 1985]

$$CH_3\overset{\bullet}{N}CH_3 + NO_2 \rightarrow CH_3(NNO_2)CH_3 \xrightarrow{h\upsilon} CH_3N{=}CH_2 + HONO$$ (2-5) [Atkinson, 1985]

The $\bullet CH_2NHCH_3$ radical reacts with O_2:

$$\bullet CH_2NHCH_3 + O_2 \rightarrow CH_2{=}N\text{-}CH_3 + HO_2$$ (2-6) [Atkinson and Carter, 1984]

2.6.3.2 Reactions of DMA With Ozone

DMA reacts with ozone in the gas phase; the general form of the reaction is:

$$(CH_3)_2NH + O_3 \rightarrow H\text{-}\overset{\overset{O}{\|}}{C}\text{-}H + N_2 + H_2O$$ (2-7) [Dushutin and Sopach, 1976]

This reaction which is discussed below indicates that formaldehyde is produced with no observed N-nitroso, nitrate or nitrite compounds.

$$(CH_3)_2NH + O_3 \rightarrow CH_3N{=}CH_2 + O_2 + H_2O \qquad (2\text{-}8)$$

[Atkinson and Carter, 1984]

DMA also reacts with ozone in aqueous solutions:

$$(CH_3)_2NH + O_3 \rightarrow CH_3\text{-}NH\text{-}\overset{\overset{O}{\|}}{C}\text{-}H + H\text{-}\overset{\overset{O}{\|}}{C}\text{-}H + CH_3NHOH + \text{other products} \qquad (2\text{-}9)$$

[Elmghari-Tabib et al., 1982]

2.6.3.3 *Aqueous Reaction of DMA* with Nitrite.

Reactions with nitrite (NO_2^-) ion in aqueous solution:

$$(CH_3)_2NH + H^+ + NO_2^- \rightarrow (CH_3)_2N\text{-}NO + H_2O \qquad (2\text{-}10)$$

[Blatt, 1943]

2.6.3.4 *DMA Reactions with Nitrogenous Compounds*

DMA reacts with nitrogen oxides and nitrogen acids in the gas phase, with and/or without light:

$$(CH_3)_2NH + ON\text{-}NO_3 \rightarrow (CH_3)_2N\text{-}NO + HNO_3 \qquad (2\text{-}11)$$

$$(CH_3)_2NH + HONO \rightarrow (CH_3)_2N\text{-}NO + H_2O \qquad (2\text{-}12)$$

$$(CH_3)_2NH + NO_x \rightarrow (CH_3)_2N\text{-}NO_2 \qquad (2\text{-}13)$$

$$(CH_3)_2NH + NO_x \rightarrow (CH_3)_2NNO + (CH_3)_2\,N\text{-}NO_2 \rightarrow \qquad (2\text{-}14)$$

$$(CH_3)_2N\text{-}NO_2 + (CH_3)_2N\overset{\overset{O}{\|}}{C}\text{-}H + H\overset{\overset{O}{\|}}{C}\text{-}H + (CH_3)_2NN(CH_3)_2 + \text{Others}$$

[Grosjean, 1980; Glasson, 1979; Pitts, 1978; Tuazon et al., 1978;Dushutin and Sopach, 1976; Hanst et al., 1977]

Reactions with nitrogen acids as aqueous solutions of nitrogen oxides:

$$NO + NO_2 + H_2O \rightarrow 2HONO \qquad (2\text{-}15)$$

$$CH_3NHCH_3 + HONO \rightarrow CH_3N(NO)CH_3 + H_2O \qquad (2\text{-}16)$$

[Blatt, 1943; Glasson, 1979]

Reaction with atmospheric HNO_3 in air:

$CH_3NHCH_3 + HNO_3 \rightarrow$ products not specified (2-17) [Atkinson, 1985)

All of these reactions may contribute to the degradation of DMA in the environment. The importance of these reactions in the various compartments of the environment has not been completely defined; pertinent reported studies are discussed below.

Atkinson (1985) proposed that the reaction with HO is the primary mechanism for degradation of most atmospheric organic pollutants, but notes that for certain amines, reaction with gas phase HNO_3 "may be the dominant loss process in urban environment." No rate data are reported for this reaction.

The reactive HO• is formed in the atmosphere by the action of sunlight (estimated concentration is given below). Because of its high reactivity, it does not accumulate, but reaches a very low equilibrium concentration during daylight. From Atkinson's (Atkinson et al., 1979) measured rate of the reaction of DMA with HO• (6.5×10^{-11} cm^3/molecules-sec) and estimates of boundary layer (the atmosphere nearest the planet extending from the surface to a few thousand meters altitude) HO• concentrations, one can calculate the half-life of DMA removal from the lower atmosphere by reaction 1. Values of 3 to 6 hours are obtained with the use of the HO• concentrations of 1×10^6 to 0.5×10^6 molecules/cm^3 suggested for the tropospheric boundary layer. (see Cupitt, 1987). Other processes of DMA removal from the atmosphere (reactions Nos. 2-7, 2-8, 2-11 through 2-14, and 2-17, or absorption in rain; see Brimblecombe and Dawson, 1984) are probably negligible (as discussed in the following paragraph) since they are much slower than the reaction with HO•.

Pitts and his co-wòrkers (Pitts, 1978; Tuazon et al., 1978) studied the reactions of 0.1 to 5 ppm levels of nitrogen oxides in air with equal concentrations of methyl and ethyl amines, including DMA and diethylamine (DEA). Their experiments were performed in "smog chambers" of 16 to 50 m^3 volume to minimize reactions on the surfaces. Using the larger chambers, the reaction was observed for a 4-hour period, 2 hours in the dark and then 2 hours in sunlight. A small yield of N-nitrosoamine is rapidly formed from the dialkylamine during the dark period (2.8 percent yield with diethylamine), while only 20 percent of the amine was consumed. During exposure to sunlight, 90 to 95 percent of the dialkylamine was degraded (half-life, 30 to 65 minutes) and a mixture of products was formed. The major product found was the diakylamine-nitramine (R_2N-NO_2, R = CH_3 in the DMA case). Aldehydes, amides, peroxyacetylnitrate, and carbon monoxide were also found in significant yields. The N-nitrosoamine formed initially in the dark was destroyed by the sunlight with a half-life of approximately 1 hour. In the larger chamber, in which 0.1 ppm of amine was introduced, the mixture was analyzed by GC-MS after absorption on Tenax, while FT-IR spectrometry was used to determine concentrations in the smaller chamber. In the latter case the initial concentrations of the amines were 3 to 5 ppm. The FT-IR procedure does not allow the quantitative differentiation of N-nitramines from N-nitrosoamines in air mixtures. Pitts concludes that N-nitrosoamines may form from a rapid reaction of nitrous acid (HONO) and the amine in air, but at the typical ppb levels of NO_2 and nitrous oxide (NO) present in the air the

conversion will be very low. The nitrous acid is formed in the equilibrium reaction below,

$$NO_2 + NO + H_2O \leftrightarrows 2HONO \qquad (2\text{-}18)$$

but since the rate of the forward reaction does not become significant until the NO concentrations equal 1 to 20 ppm the direct reaction of HONO with dialkylamines does not normally occur to any extent. Therefore, reactions (2-1) and (2-2) describe the primary reaction in sunlight; reactions (2-3) through (2-5) then occur to form a series of products, but the N-nitrosoamine so formed is destroyed in the sunlight.

Other groups have also studied the gas phase reaction of DMA at ppm concentrations (Hanst et al., 1977; Dushutin and Sopach, 1976; Glasson, 1979). Such gas phase reactions are very difficult to study because reactions on surfaces of reaction chambers used or reactions on aerosol particles may occur that make it difficult to evaluate properly the gas phase processes. Glasson (1979) reported such problems when studying the reaction of 3.7 to 13.5 ppm DMA with 2 ppm of NO and 2 ppm of NO_2 in a 614-liter stainless steel chamber. With no light introduced, 6 to 7 percent of the DMA was converted to DMNA after 6.7 hours, while the DMA concentration decreased by approximately 80 percent. The results were similar with or without excess water vapor added. Since 80 percent of the DMA is also lost when the experiment was performed without NO_x present, Glasson suggested that adsorption of DMA on the chamber surface accounted for the loss and furthermore, that the DMNA formation occurred primarily by reaction 2-5.

Hanst et al. (1977) also found low yields of DMNA in a similar study, but they did not consider surface reactions that may have degraded DMA.

In studies of the gas phase reaction of 6 to 3,600 ppm of DMA with ppm levels of nitrogen tetroxide in a 120-liter chamber, DMNA, dimethylnitramine, and dimethylammonium nitrate were found as products (Dushutin and Sopach, 1976). Absorption of the gases followed by wet-chemical methods was used to follow quantitatively the course of the reactions. At 5 ppm concentrations of each reactant the reaction was found to exhibit a half-life of less than ten minutes. Even though an aerosol formed in the chamber, the authors did not consider the importance of heterogenous reactions.

The reaction of O_3 with DMA was also studied by Dushutin and Sopach (1976). They were able to detect formaldehyde as a product of the reaction and found that the reaction was quite fast at the concentrations studied (5 ppm). Tuazon and co-workers (1978) (reported by Atkinson and Carter, 1984) determined the rate of the reaction of DMA with O_3 in air. They found a second order rate constant of 2.61×10^{-18} cm^3/molecules-sec that is consistent with Dushutin and Sopach's result. Tuazon's group found that the major product was N-methylmethyleneamine, $CH_3N=CH_2$. Because of the typical low concentration of O_3 in the atmosphere, this reaction is too slow (half-life = 4.4 days at ca. 30 ppb of ozone) to be a significant process that would consume DMA under normal conditions.

From the above results one can suggest that ppb levels of DMA are destroyed within hours with formation of negligible levels of DMNA in the daytime, while removal of DMA by reaction with nitric acid or NO_3 radicals

may predominate at night (Atkinson, 1985; Atkinson and Carter, 1984). Pitts (1978) summarizes the results of these studies as follows: "Thus, even though ambient NO_x and HONO concentrations from mobile and stationary sources may be quite high under certain meteorological conditions (and high primary emission levels), the risk of forming significant amounts of nitrosoamines or nitramines in the urban or suburban atmosphere seems correspondingly low. However, in specialized industrial cases, where sub-ppm concentrations of amines may be released into ambient polluted air, within and immediately downwind from the facility, the possibility of formation of nitrosoamines and, in sunlight, of nitramines and amides, seems real." A study of the levels of DMNA in the air of Paris, France (Chuong et al., 1978) is consistent with this suggestion. In 25 percent of the air samples taken, DMNA was found at 0.005 to 0.11 ppb, and the concentrations were lower after periods of sunshine.

Reactions of DMA with other substances in the atmosphere are apparently not the only possible source of DMNA in the atmosphere. Two specific sources from industry have been found (see Fine et al., 1976); these were from a chemical factory manufacturing unsymmetrical dimethylhydrazine which affected air and salt water concentrations of DMNA. Nitrosoamines can also be formed from NO_x and trialkylamine in the atmosphere (Pitts, 1978).

The carcinogens, DMNA and dimethylnitramine, are physically and chemically quite different from DMA; these compounds are neutral rather than alkaline, and since they have boiling points of 154°C and 187°C, respectively (Weast, 1986), they are much less volatile than DMA, which is a gas at standard temperature. DMNA is easily synthesized by treating DMA, as its hydrochloride, with sodium nitrite in water at 70 to 75°C at slightly acid pH. Under these conditions, over 88 percent yields of DMNA can be obtained (Blatt, 1943). From a kinetics study of this reaction (Mirvish, 1975), it has been found that the rate of formation of DMNA would be slow at environmental concentrations of DMA and nitrite ion. First, Mirvish reports that the reaction rate is dependent on pH, with the maximum rate occurring at 3.4, the rate became very slow at pH less than 1.5, and too slow to measure at pH's above 7. At any particular pH, the rate of the reactions was found to depend on the first power of the DMA concentration and the second power of the NO_2^- concentration, as shown:

$$\text{Rate} = k \times [\text{DMA}] \times [NO_2^-]^2 \qquad (2\text{-}19)$$

This dependence is the result of the following series of reactions that occur:

$$NO_2^- + H^+ \rightarrow HONO \qquad (2\text{-}20)$$

$$2\,HONO \rightarrow N_2O_3 + H_2O \qquad (2\text{-}21)$$

$$(CH_3)_2NH + N_2O_3 \rightarrow (CH_3)_2N\text{-}NO + HONO \qquad (2\text{-}22)$$

Certain other materials such as the thiocyanate (NCS^-), chloride, or bromide ions can modify this mechanism at pH's below 2.5 (Mirvish, 1975), by the following reactions:

$$HONO + H^+ + NCS^- \rightarrow ON\text{-}NCS + H_2O \qquad (2\text{-}23)$$

$$ON\text{-}NCS + (CH_3)_2NH \rightarrow (CH_3)_2N\text{-}NO + H^+ + NCS^- \qquad (2\text{-}24)$$

From these data it can be calculated that 0.125 percent of the DMA in an aqueous solution of equal concentrations of DMA and sodium nitrite at 1.0 mg/L would be nitrosated within one hour at 25°C if the pH is 3.4. Further, estimates of the DMNA formation at other concentrations change considerably with pH or reactant concentrations because of the effects of pH and the third order of the reaction, as shown:

Table 2-5. Conditions for DMA Conversion to DMNA

Concentration			
DMA, gm/L	*$NaNO_2$, gm/L*	*pH*	*Conversion to DMNA in 1 hour, %*
1.0	*1.0*	*3.4*	*0.125*
0.1	*1.0*	*3.4*	*0.012*
0.1	*1.0*	*6.0*	*0.0001*
0.1	*0.1*	*3.4*	*0.0001*
0.1	*0.1*	*6.0*	*0.000001*

Keefer and Roller (1973) found that this nitrosation is catalyzed by formaldehyde or chloral at pH's above 6, but yields do not exceed 1 percent after 17 hours when 0.05 M amine is allowed to react with 0.2 M sodium nitrite in the presence of 0.05 M formaldehyde. In the absence of one of these aldehydes, no nitrosation was detected. In other work at similar concentrations (900 mg/L of DMA, with excess NO^-_2), the yield of DMNA was found to be less than 15 percent after 6 hours at 37°C and a pH of 3 (Ziebarth, 1974). Others report that no nitrosamines are formed at pH values above 6, at environmental concentration, unless microbial materials are present (Tate and Alexander, 1976; Ayanaba and Alexander, 1973) or actinic light is used as a catalyst (Ohta et al., 1982).

3. Metabolism

3.1 Inhalation Exposure

McNulty and Heck (1983) and McNulty et al. (1983) studied the metabolism of inhaled [^{14}C]DMA in rats. McNulty and Heck (1983) exposed groups of four male Fischer 344 rats for 6 hours to either 10 or 175 ppm [^{14}C]DMA. The [^{14}C]DMA (Amersham Corp.) had a specific activity of 57 mCi/mmol and a radiochemical purity of 98 to 99 percent. Immediately after exposure, the rats were placed in individual metabolism cages for the separate collection of urine, feces, and expired air. Seventy-two hours after termination of exposure, the disposition of the recovered radioactivity was similar for each airborne concentration, with more than 90 percent in the urine and feces, 7 to 8 percent in the tissues and carcass, and 1.5 percent in the exhaled air (Table 3-1).

Table 3-1. Disposition of Radioactivity in Rats Exposed to [^{14}C] Dimethylamine[a]

	Percent Disposition at Exposure Concentrations of	
[^{14}C] Distribution	*10 ppm*	*175 ppm*
Urine	*78.0 ± 1.0*	*86.7 ± 2.8*
Feces	*12.5 ± 0.8*	*5.1 ± 1.5*
Expired air	*1.5 ± 0.1*	*1.5 ± 0.3*
Tissues and carcass	*8.0 ± 0.9*	*6.7 ± 1.1*

[a] *Disposition is expressed as a percentage of the total recovered radioactivity. Percentages represent the mean ± standard error (±SE) for four rats.*
Source: McNulty and Heck (1983).

When groups of rats were similarly exposed and killed immediately after exposure, the highest concentration of radioactivity was in the respiratory and olfactory mucosa, whereas concentrations of [^{14}C] in liver, lung, kidney, brain, and testes were approximately 2 orders of magnitude less than in the nasal mucosal tissues (Table 3-2). When tissues were radioassayed 72 hours after being exposed to 10 or 175 ppm [^{14}C]DMA, appreciable concentrations of radioactivity remained only in the nasal mucosa, where respiratory tissue contained 73.0 ± 8.3 and 336.2 ± 96.6 nmol equivalents of DMA per gram of tissue, respectively (olfactory concentrations were not determined). Following exposure to 175 ppm [^{14}C]DMA, radioactivity in plasma was eliminated in a biphasic manner. The relatively long half-life for the slow phase (44.6 and 63.6 hours for two rats) was similar to the half-lives of some plasma proteins and

was postulated to be due to incorporation of [^{14}C] into protein subsequent to metabolism of [^{14}C]DMA.

Table 3-2. Tissue Distribution of Inhaled [^{14}C]Dimethylamine Immediately Postexposure

Tissue	*nmol Equivalents of DMA/g Tissue[a] at Exposure Levels of*	
	10 ppm	*175 ppm*
Respiratory mucosa	19,500 ± 3,200	72,200 ± 6,100
Olfactory mucosa	6,200 ± 1,400	29,000 ± 4,900
Liver	43.1 ± 9.7	758.0 ± 21.1
Lung	32.3 ± 7.8	689.8 ± 72.7
Kidney	96.1 ± 19.2	1,708.5 ± 120.9
Brain	24.4 ± 7.1	465.8 ± 2.3
Testes	27.6 ± 6.8	542.8 ± 27.8

[a]The values represent the mean ± SE for four rates.
Source: McNulty and Heck (1983.

DMA can be introduced into the body via ingestion or inhalation. Additionally, studies have shown that DMA can be synthesized within the body from other dietary constituents by microorganisms in the gut and by unidentified endogenous pathways. It has been suggested that DMA is an important nutrient, acting as a stimulator of postprandial gastrin secretion and directly as a stimulator of gastrointestinal mucosal growth.

Several studies were conducted to determine the identity of the DMA metabolites. Groups of three rats were injected intravenously (iv) with 20 μCi of the commercial [^{14}C]DMA or commercial [^{14}C]DMA further purified by ion chromatography to remove any $^{14}CO_2$ prior to injection. Rates of [^{14}C] exhalation were identical for both groups, indicating that the expired radioactivity was due to metabolic breakdown of [^{14}C]DMA to $^{14}CO_2$ and not from the injection of radiolabeled contaminants. Analysis of 0- to 24-hour urine samples from these animals indicated that 98.7 ± 0.2 percent of the radioactivity was the parent compound as determined by chromatography. The remaining radioactivity (< 2%) was unidentified and eluted at two separate chromatographic positions.

McNulty et al. (1983) performed additional experiments to identify the metabolites of DMA in the nasal mucosa of rats (see Section 3.2.5 for details). Experiments were performed *in vitro* using microsomes prepared from liver and from respiratory and olfactory nasal mucosa. All microsomal preparations metabolized DMA to formaldehyde, although DMA was a poor substrate for the N-demethylation reaction. The data also showed that DMA is metabolized *in vitro* to formaldehyde by both cytochrome P-450 and flavin adenine dinucleotide (FAD)-containing mono-oxygenases. *In vivo,* unextractable radioactivity was observed in DNA, RNA, and protein isolated from respiratory and olfactory mucosa of rats exposed to either 10 or 175 ppm of [^{14}C]DMA.

The authors concluded that as much as 8 percent of the absorbed DMA may be converted to formaldehyde *in vivo* and, subsequently, may be incorporated into tissue macromolecules or further metabolized to carbon dioxide and exhaled (McNulty and Heck, 1983; McNulty et al., 1983).

3.2 Oral Administration

3.2.1 Dimethylamine Biochemistry

DMA can be introduced into the mammalian gastrointestinal tract in several ways. In the diet, DMA is present in substantial amounts in a number of foods, especially certain seafoods (see Section 2.3). In addition, DMA is produced from other dietary components, such as creatinine, lecithin, and choline, by bacterial metabolism in the lower gut (Asatoor and Simenhoff, 1965). A general scheme for the formation of aliphatic amines in the mammalian gut has been proposed by Lowis et al. (1985) (Figure 3-1).

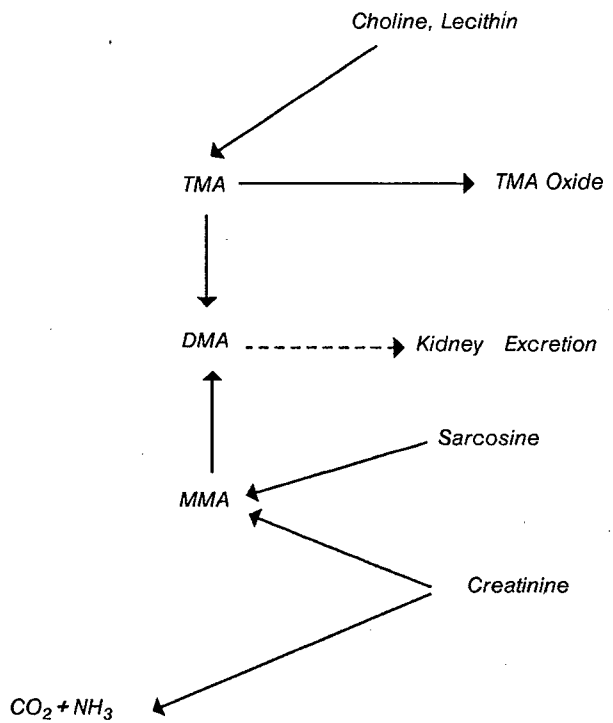

Figure 3-1. Proposed scheme for the formation of methylamine (MMA), dimethylamine (DMA), and trimethylamine (TMA) in the mammalian gut.
Source: Lowis et al. (1985).

Experiments using germ-free rats and control rats consuming the same methylamine-free diet indicated that gut bacteria were not essential for the formation of DMA (Zeisel et al., 1985). Consequently, the authors concluded that endogenous pathways that are capable of forming DMA must exist, but these endogenous mechanisms remain unidentified.

It has been suggested that DMA is an important nutrient, acting as a stimulator of postprandial gastrin secretion (Lichtenberger et al., 1982) and to stimulate growth of the gastrointestinal mucosa (Dembinski et al., 1984).

3.2.2 Absorption

The gastrointestinal absorption of DMA has been studied in 15- to 20-week-old male Wistar rats by Ishiwata et al. (1984a,b) using ligated gut sections *in situ*. Additionally, blood samples were taken via heart puncture from rats which had been injected with DMA into the ligated upper intestine.

The rates of disappearance of DMA from the ligated sections of gut were monoexponential over 30 minutes. Disappearance half-lives were 8.3, 11.6, 31.5, and 11.0 minutes for the upper small intestine, lower small intestine, cecum, and large intestine, respectively. Absorption of DMA from the stomach was scarcely detectable (disappearance half-life, 198 minutes). Following injection of DMA into the ligated upper small intestine, DMA levels in the blood increased from 0.28 ± 0.06 to 3.0 ± 1.0 ppm within 5 minutes and then decreased to 1.2 ± 0.21 ppm by 30 minutes.

Similar experiments have been performed with guinea pigs (Ishiwata et al., 1977). As with the rats (Ishiwata et al., 1984a,b), no loss of DMA from the stomach of the guinea pigs was detected after 20 minutes. However, only 15.4 ± 6.1 percent of the injected DMA remained in the upper small intestine after 20 minutes. The rate of DMA disappearance from the small intestine was monoexponential over the sampling period. These data may not be as conclusive as those for the rat because blood levels of DMA were not monitored, and, according to the authors, the injection solution contained DMA, DMNA, nitrite, and nitrate, and not DMA alone.

A weak organic base, such as DMA, is present in ionized form in the stomach. In such an ionized state, it is unlikely to be absorbed. However, in the small intestine, the opposite is true.

3.2.3 Distribution

The gastrointestinal distribution of DMA in rats fed diets containing normal (23.6 ppm) or low (1 ppm) levels of DMA was studied by Ishiwata et al. (1984a,b; 1982). Groups of five adult male Wistar rats were killed after 1 week on the appropriate diet. Their gastrointestinal tracts were excised and the contents of the stomach, small intestine (divided into four equal lengths), cecum, and large intestine were removed and assayed for DMA content by GC. For rats fed diets containing 23.6 ppm DMA, DMA levels were highest in the contents of the stomach, and tended to decrease in the more distal sections of the gastrointestinal tract. The authors attributed the relatively higher DMA concentrations in the contents of the large intestine to the absorption of water from the gut. Gastrointestinal levels of DMA in this group of rats were higher than DMA levels in the diet. In rats fed diets low in DMA,

the distribution pattern was different. The stomach contained the lowest DMA levels, approximately 1 ppm, whereas the other sections of the gut contained DMA concentrations higher than were in the diet. The authors attributed this distribution pattern to the synthesis of DMA in the lower gut with subsequent absorption into the blood followed by secretion into the small intestine via the bile.

Chaudhari and Dutta (1981) studied the tissue distribution of DMA in male Hartley guinea pigs and male Sprague-Dawley rats weighing between 300 and 400 g. Animals were anesthetized and a cannula was inserted into each external jugular vein. [^{14}C]DMA, 10 mg (20 μCi)/kg, was injected into one cannula, and blood samples were removed from the other cannula at 0.5, 1, 2, 3, and 4 hours postinjection. At the end of 4 hours, the animals were killed and samples of heart, liver, spleen, adrenal, kidney, brain, lung, pituitary, and abdominal fat were radioanalyzed. The biological half-life and apparent volume of distribution were calculated from a plot of blood concentration of DMA against time based on the assumption that the rate of DMA disappearance from the blood was first order.

The biological half-life and volume of distribution of [^{14}C]DMA in the rat were 3.92 ± 0.59 hours and 1.76 ± 0.17 L/kg, respectively. The corresponding values in the guinea pig were 4.62 ± 0.48 hours and 1.58 ± 0.26 L/kg, respectively. There was no statistically significant difference between corresponding rat and guinea pig values, indicating that there were no species differences for these parameters. The volume of distribution values are not especially high, and the binding was nonspecific rather than covalent.

The results of the tissue distribution studies are presented in Figure 3-2. No species differences were apparent except that mean [^{14}C] concentrations in the abdominal fat of the guinea pigs were significantly higher than those in the rats. The authors could not explain the biological significance of this difference. Levels of DMA equivalents were highest in the kidneys of both species, and tissue-to-blood ratios were greater than 1 for kidney, spleen, adrenal, and pituitary. The concentration of [^{14}C]DMA equivalents in the blood was not reported.

3.2.4 Excretion and Secretion

Beal and Bryan (1978) studied the excretion of [^{14}C]DMA in male Sprague-Dawley rats weighing 200 to 250 g. Each of eight rats was injected intraperitoneally (ip) with 60 μmol (6.2 μCi) of [^{14}C]DMA and immediately placed in metabolism cages. Urine, but not feces, was analyzed for [^{14}C]DMA content. The authors reported that 85 to 90 percent of the dose was excreted in the 0- to 24-hour urine as unmetabolized DMA. They apparently did not analyze the urinary radioactivity for DMA metabolites. Less than 0.1 percent of the dose was excreted as expired DMA, and only 0.5 percent was excreted as expired carbon dioxide. No other data on this experiment were provided.

DMA excretion by adult male Wistar rats maintained on a normal diet containing 7.4 ppm DMA was studied by Lowis et al. (1985). Eight rats weighing 300 to 400 g each were placed in individual metabolism cages. Urine and feces were collected and analyzed for amine content. Over the course of the 14-day experimental period, the rats consumed approximately 12 g of food/day (88.8 μg DMA/day). DMA excretion showed a large variation, ranging

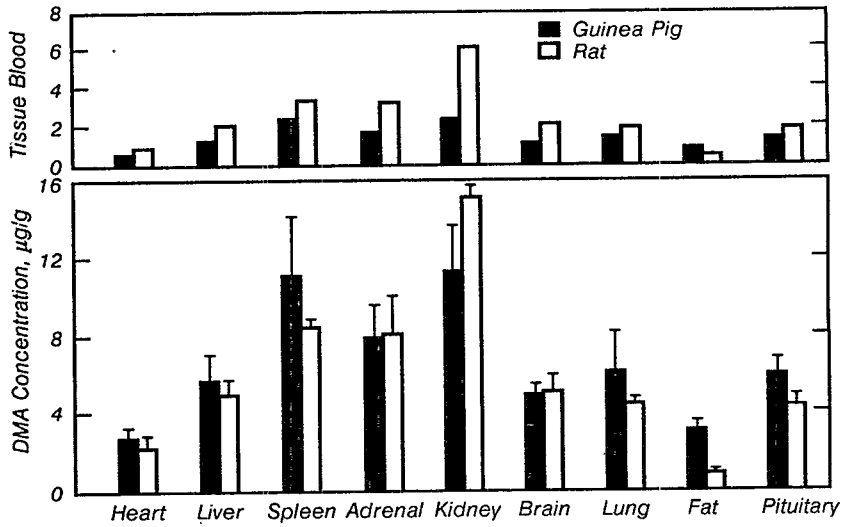

Figure 3-2. ***Tissue distribution of [^{14}C]dimethylamine 4 hours after intravenous administration at 10 mg (20 µCi)/kg. Concentrations are expressed in terms of micrograms of dimethylamine equivalents per gram set weight, and each value given is the mean ±SE for at least four animals.***

Source: Chaudari and Dutta (1981)

from 120 to 1,840 µg/day in urine and 3 to 95 µg/day in feces. Mean excretion values were approximately 506 µg/day in urine and 21 µg/day in feces.

Similar results were reported by Ishiwata et al. (1982). Groups of five adult male Wistar rats were maintained for 1 week on diets containing DMA at 23.6 or 1.0 ppm. The rats were then placed in individual metabolism cages and fed the appropriate diet for an additional week. Urine and feces were collected daily and analyzed for DMA content by GC.

The rats on the normal and low-DMA diets consumed an average of 12.7 ± 2.1 and 19.2 ± 4.6 g of food per day, respectively. Daily DMA excretion was relatively constant over the 7 days and was observed mainly in the urine. Fecal DMA excretion was less than 5 percent of total DMA excretion for both groups of rats. In rats fed diets containing 23.6 ppm DMA, excretion of DMA was 1.5 times higher than that ingested. In rats fed the low-DMA diets, DMA excretion was 14.7 times higher than DMA ingestion. The excess excretion of DMA was considered to be a result of *in vivo* DMA formation. Balance data for DMA ingestion in rats are summarized in Table 3-3.

Urinary excretion and balance of DMA in humans appear to be similar to that observed in rats. Simenhoff et al. (1963) reported that 85 percent of an oral dose of DMA·HCl (100 mg) was excreted in the urine of a normal volunteer within 12 hours after ingestion. Only unmetabolized urinary DMA was analyzed; therefore, the amounts of the dose metabolized and/or excreted in the feces are not known. Analyses of daily diets and 24-hour urine samples of four men and five women indicated that means ±SD of 10.4 ± 6.9 and

Table 3-3. Dimethylamine Balance in Rats

	Ingestion and Excretion of DMA (µg/day) by Rats Fed Diets Containing DMA at		
	23.6 ppm[a]	*7.4 ppm[b]*	*1.0 ppm[a]*
Ingestion	*300.1 ± 49.4*	*88.8*	*19.2 ± 4.6*
Excretion			
Urine	*432.6 ± 49.3*	*506.4*	*272.5 ± 12.5*
Feces	*21.7 ± 7.4*	*20.6*	*10.3 ± 2.2*
Total	*453.9 ± 47.9*	*527.0*	*282.8 ± 12.5*

[a]Mean ± SD for five rats over 7 days (Ishiwata et al., 1982).
[b]Means are estimated from data reported by Lowis et al. (1985).

21.1 ± 9.3 mg of nitrosatable compounds, primarily DMA, are ingested and excreted in the daily urine, respectively (Ishiwata et al., 1978).

Ishiwata et al. (1984a,b) have also reported data that indicate that DMA undergoes enterohepatic circulation. Five adult male Wistar rats were fasted overnight and anesthetized, and their bile ducts were cannulated. After recovering from the anesthetic, each animal was administered 250 µg of DMA intravenously (iv). Bile was collected at various times postinjection and analyzed for DMA content. Before the injection, the biliary DMA concentration was 0.59 ± 0.050 ppm. After injection, biliary DMA increased to a maximum of 3.7 ± 1.9 ppm at 30 minutes postinjection. A second, smaller peak was observed 3 hours postinjection. Thereafter, levels remained relatively constant between 0.3 and 0.6 ppm. The cumulative 24-hour biliary excretion was 6.2 ± 2.2 µg. Thus, biliary excretion, uncorrected for background excretion, accounted for less than 2.5 percent of the dose.

DMA may enter the gut via secretion from blood into the upper small intestine, gastric juice, and/or saliva. The secretion of DMA into the upper small intestine was studied by Ishiwata et al. (1984a,b). Groups of five adult male Wistar rats were fasted overnight and then anesthetized. Their abdomens were opened, and a 5-cm section of the small intestine was ligated 10 cm below the pylorus. Each rat was then administered 250 µg of DMA iv. At various times postinjection, the animals were killed and several samples were taken: blood samples were taken via heart puncture; urine samples were taken from the bladder; and the ligated section of intestine was excised, and its contents removed. All samples were analyzed for DMA by GC.

According to the authors, the data indicate that following an intravenous injection, DMA in blood is excreted into the urine and secreted into the upper small intestine. The initial half-life of DMA in blood was 12.5 minutes, followed by a rise in DMA levels between 15 and 20 minutes, and then a second phase of monoexponential disappearance with a half-life of 15.2 minutes. The temporary second rise in blood DMA was attributed to absorption of the DMA secreted into the gut.

The half-lives reported here for the disappearance of DMA from the blood, 12.5 to 15.2 minutes, are considerably shorter than those reported by Chaudhari and Dutta (1981) of 3.92 to 4.62 hours. However, the values reported by Chaudhari and Dutta were based on the disappearance of [^{14}C] from the blood following intravenous injection of [^{14}C]DMA, and their calculations were based on measurements taken over 4 hours instead of 30 minutes, with the assumption that the rate of DMA disappearance from the blood was first order. Therefore, these data would not account for the rise in blood DMA that Ishiwata et al. (1984b) attributed to reabsorption from the small intestine and would incorporate the slow-phase disappearance of [^{14}C]DMA metabolites bound to plasma proteins (see Section 3.1).

Ishiwata et al. (1978) have demonstrated that DMA can also be secreted into human saliva. A 32-year-old male volunteer ingested 100 mg of DMA·HCl dissolved in water or in wafer form. Total nitrosatable compounds, primarily DMA, were then measured at various times in samples of saliva. A definite increase in salivary DMA was observed (Figure 3-3); the initial rise in DMA after drinking the solution was due to traces of DMA remaining in the mouth. Levels of nitrosatable compounds in the saliva of 11 untreated people (controls) were extremely low 0.3 ± 0.2 ppm (mean ± SD) of DMA equivalent; range, < 0.1 to 0.6 ppm.

DMA has been observed in the gastric juices of adult male Sprague-Dawley rats at 33.5 ± 10.5 nmol/mL (Zeisel et al., 1985). Experiments performed in ferrets and dogs demonstrated that DMA enters the gastric juice via the blood (Zeisel et al., 1986).

3.2.5 Metabolism

Concerns have been raised over the possibility of DMA being a procarcinogen because it can be converted to DMNA under a variety of conditions. Mirvish (1970) demonstrated that DMA nitrosation by nitrite can occur in buffered aqueous solutions. DMNA formation was maximal at pH 3.4 and was proportional to the DMA concentration and to the square of nitrite concentration. The formation of DMNA from DMA and nitrites has been demonstrated *in vitro* in human saliva (Tannenbaum et al., 1978; Ishiwata et al., 1975); both nitrite and DMA occur naturally in saliva (Ishiwata et al., 1978). Furthermore, nitrosation has been shown to occur in the stomach of dogs (Lintas et al., 1982), rats (Frank et al., 1985), and monkeys (Hayashi et al., 1980) given large oral doses of DMA and nitrite. Krull et al. (1979) also reported that 0.04 percent of a 250-μg oral dose of DMA was converted to DMNA in the stomachs of mice; the nitrite dose, however, was not reported.

With the exception of the abstract by Krull et al. (1979), most reports of DMNA formation *in vivo* have involved relatively massive doses of DMA and nitrite. Therefore, the production of DMNA at normal dietary levels of DMA and nitrite has not been clearly demonstrated. Furthermore, the effects of other dietary factors such as food, ascorbic acid, and phenolic and sulfhydryl groups, which tend to reduce the nitrosation reaction, have not been fully investigated (Lintas et al., 1982; Cantoni et al., 1974).

Some investigators believe that formation of DMNA from DMA *in vivo* under normal conditions may be negligible because of a low rate of reaction or

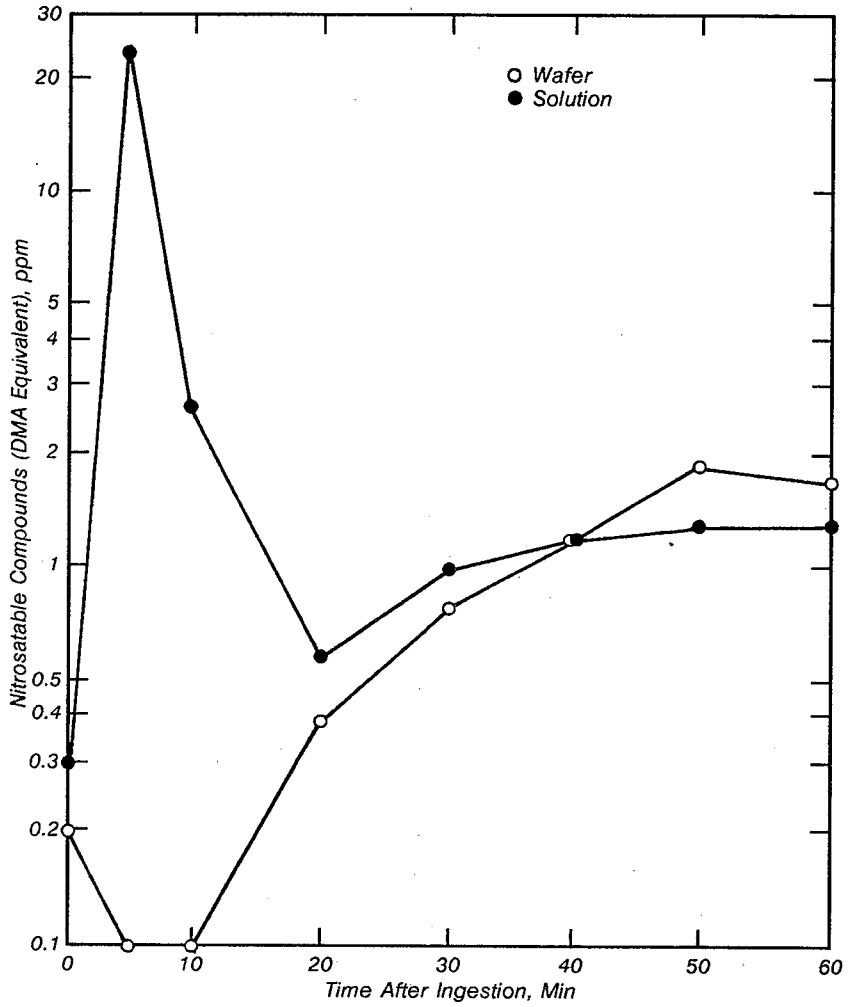

Figure 3-3. Concentrations of nitrosatable compounds in human saliva after ingestion of dimethylamine-hydrogen chloride (100 mg) in solution or wafter form.

Source: Ishiwata wt al. (1978)

because of interferences from other dietary components (Meier-Bratschi et al., 1983; Cantoni et al., 1974; Mirvish, 1970).

Although the metabolism of DMA, as opposed to its chemical reactions, has not been extensively investigated, McNulty et al. (1983) have performed several experiments *in vitro* to study the metabolism of DMA to formaldehyde. In one set of experiments, DMA or benzphetamine (a cytochrome P-450

substrate used as a positive control) was incubated with hepatic microsomes from untreated rats. The N-demethylation of DMA to yield formaldehyde did occur, but at a slow rate, 0.80 ± 0.04 nmol of formaldehyde/minute/mg protein, as compared to the N-demethylation of benzphetamine, 9.80 ± 0.37 nmol formaldehyde/minute/mg protein. When hepatic microsomes from rats induced with phenobarbital were used as the enzyme source, the rate of N-demethylation of DMA was reduced 40 percent whereas that of benzphetamine was nearly doubled. The reasons for this finding were not discussed. Boiling the microsomes or omitting reduced nicotinamide adenine dinucleotide phosphate (NADPH) prevented the N-demethylation of both substrates. The metabolism of N,N-dimethylaniline, a substrate for FAD-containing mono-oxygenases, was similar to that of DMA in the above experiments. These results suggested that DMA could be metabolized by both cytochrome P-450 and FAD-containing mono-oxygenases.

Additional experiments using hepatic microsomes from untreated rats were carried out. When n-octylamine, a cytochrome P-450 inhibitor, was added to the incubation mix, the N-demethylation of DMA and benzphetamine was significantly reduced ($p < 0.01$) when compared to controls. When the pH of the system was raised to 8.4, maximal for FAD-containing mono-oxygenase activity, the metabolism of DMA was not reduced whereas that of benzphetamine was. Finally, heat inactivation of FAD-containing mono-oxygenases decreased, but did not eliminate N-demethylation of DMA (data were not shown); this treatment had no effect on benzphetamine metabolism. These studies also show that DMA is metabolized *in vitro* to some extent by both cytochrome P-450 and FAD-containing mono-oxygenases in rat hepatic microsomes with the subsequent release of formaldehyde.

Metabolism of DMA to formaldehyde was also studied *in vitro* using microsomes isolated from the respiratory or olfactory mucosa of untreated rats. Turnover rates were very low, 0.20 ± 0.02 and 0.48 ± 0.04 nmol formaldehyde/ minute/mg protein (mean ± SE) for respiratory and olfactory mucosal microsomes, respectively. Indirect evidence was reported that indicated that this metabolism is also a combination of cytochrome P-450 and FAD- containing mono-oxygenase activities.

In vivo studies were conducted in male Fischer 344 rats exposed to [^{14}C]DMA at a level of 10 or 175 ppm for 6 hours. Immediately after exposure, the rats were killed, the nasal and olfactory mucosae were removed, and both tissues were fractionated. Bound radioactivity was found in RNA, protein, and DNA of both tissues after exposure at both levels. However, [^{14}C] bound to DNA was so low that it could not be accurately quantitated. The authors concluded that these results show that oxidative metabolism of inhaled DMA does occur *in vivo* in the nasal mucosa. They further suggested that DMA is N-demethylated *in vivo* by cytochrome P-450 to yield formaldehyde and, possibly, converted to N,N-dimethylhydroxylamine by FAD-containing mono-oxygenases. The N,N-dimethylhydroxylamine, being an unstable intermediate, would be further oxidized to formaldehyde; formaldehyde derived from both pathways could be covalently bound or otherwise incorporated into tissue macromolecules. Formaldehyde could also undergo further oxidation to carbon dioxide and be exhaled.

The binding of [^{14}C] to tissue macromolecules *in vivo* after administration of [^{14}C]DMA (10 mg (80 µCi)/kg, iv) to rats and guinea pigs was studied by

Chaudhari and Dutta (1981). They found radioactivity bound to DNA isolated from lung and liver of both species. The amounts bound 4 hours postinjection were extremely low, averaging 32 to 109 pmol DMA equivalents/mg DNA. These levels were much less than those observed after [^{14}C]DMNA administration, 529 to 4,196 pmol DMNA equivalents/mg DNA. Experiments performed *in vitro* indicated that the *in vivo* binding of [^{14}C] to DNA after [^{14}C]DMA injection could have been due to nonspecific binding or to binding of a radiolabeled contaminant. The *in vivo* binding of [^{14}C] to DNA in liver was not increased above control when guinea pigs were administered 80 μCi [^{14}C]DMA, iv, and were exposed to 50 ppm nitrogen dioxide for 4 hours postinjection, indicating that DMNA was not formed *in vivo* under those conditions.

3.3 Summary of Dimethylamine Metabolism

DMA introduced into the body via ingestion or inhalation can be distributed and/or metabolized in various tissues. Additionally, studies have shown that DMA can be synthesized within the body from other dietary constituents by microorganisms in the gut (Asatoor and Simenhoff, 1965) and by unidentified endogenous pathways (Zeisel et al., 1985). It has been suggested that DMA is an important nutrient, acting as a stimulator of postprandial gastrin secretion (Lichtenberger et al., 1982) and to stimulate growth of the gastrointestinal mucosa (Dembinski et al., 1984).

Quantitative absorption studies with single doses of labeled DMA have not been performed; however, data from other studies indicate that DMA is readily absorbed following inhalation or ingestion. The major site of absorption in adult male rats following inhalation of [^{14}C]DMA at 10 or 175 ppm for 6 hours was the nasal mucosa (McNulty and Heck, 1983). Very little, if any, of the inhaled [^{14}C]DMA reached the lung directly. Following ingestion, the major site of DMA absorption is apparently the upper small intestine. Ishiwata et al. (1984a,b; 1977) injected DMA into ligated sections of the gastrointestinal tracts of anesthetized adult male guinea pigs and rats, respectively, and followed the disappearance of the compound from those sections. In both species, the rate of disappearance occurred in the upper small intestine; absorption from the stomach was barely detected, as expected for an ionized substance.

After absorption, DMA travels via the blood to the various internal organs and tissues. Tissue distribution studies performed in adult male rats and guinea pigs indicate that 4 hours following an intravenous dose of [^{14}C]DMA at 10 mg/kg, concentrations of radioactivity are highest in the kidneys (Chaudhari and Dutta, 1981). Levels of [^{14}C] in most other tissues were less than half the kidney levels. A similar distribution pattern was observed in adult male rats immediately following a 6-hour inhalation exposure to [^{14}C]DMA at 10 or 175 ppm (McNulty and Heck, 1983).

DMA is excreted mainly via the urine. After inhalation of [^{14}C]DMA at 10 ppm for 6 hours, male rats excreted mean levels of 78, 12.5, and 1.5 percent of the recovered [^{14}C] in the 0- to 72-hour urine, feces, and expired air, respectively. After 6-hour exposures to 175 ppm [^{14}C]DMA, mean levels of 86.7, 5.1, and 1.5 percent of the recovered [^{14}C] were found in the 0- to 72-hour urine, feces, and expired air, respectively (McNulty and Heck, 1983). After intravenous injection of 60 μmol of [^{14}C]DMA, adult male rats excreted 85 to 90 percent of the dose into the 0- to 24-hour urine as unmetabolized

DMA. Less than 0.1 percent of the dose was expired as [^{14}C]DMA and approximately 0.5 percent as radiolabeled carbon dioxide (Beal and Bryan, 1978).

Balance studies indicate that urinary excretion accounts for 95 percent of the DMA excreted in combined urine and feces. DMA excretion can range from 1.5 to 14.7 times intake, depending on the amount of DMA ingested. The excess DMA is considered to arise from *in vivo* synthesis by the host and/or gastrointestinal flora. DMA can be absorbed from the gut into the bloodstream; from there, it can be secreted into the bile, gastric juice, and saliva. Therefore, DMA does undergo a certain amount of enterohepatic circulation.

It has previously been suggested that DMA is an end metabolite, i.e., that it is not metabolized (Asatoor and Simenhoff, 1965). However, McNulty et al. (1983) have shown that DMA can be metabolized *in vitro* to formaldehyde, albeit slowly, by rat hepatic and nasal microsomes containing P-450 and FAD monooxygenase enzyme activities. McNulty and Heck (1983) have suggested that as much as 8 percent of inhaled DMA may be converted to formaldehyde by rats *in vivo*. No information was found in the available literature on potential DMA metabolites other than formaldehyde or on DMA metabolites in urine or feces. However, 98.7 percent of the radioactivity in the 0- to 24-hour urine of male rats injected with DMA, iv, was shown to be unmetabolized parent compound, indicating that little, if any, DMA metabolites are excreted in the urine (McNulty and Heck, 1983). There is evidence to show that DMA can be chemically converted to DMNA in the presence of nitrite (large doses of both DMA and nitrite were used) and acidic conditions and that this conversion can take place in the mammalian stomach. However, it has not been demonstrated that significant levels of DMNA are formed in the stomach under reasonable dietary conditions or that absorption of DMNA from the gastrointestinal tract occurs under these conditions.

4. Animal Toxicology

4.1 Inhalation Toxicity

4.1.1 Acute Toxicity

The acute inhalation toxicity of DMA has recently been studied by scientists at the Chemical Industry Institute of Toxicology. Steinhagen et al. (1982) determined the RD_{50} of DMA (the DMA concentration that causes a 50 percent decrease in respiratory rate) in groups of male Fischer 344 rats and male Swiss-Webster mice. Animals were exposed in a head-only exposure chamber for 10 minutes to DMA concentrations ranging from 49 to 1,575 ppm. Maximal decreases in respiratory rate were reached after 2 to 7 minutes of exposure The RD_{50} values were similar for rats and mice, 573 and 511 ppm, respectively (Table 4-1), and were comparable to the RD_{50} value for ammonia in Swiss-Webster mice. The authors stated that their RD_{50} values for rats and mice support the current TLV of 10 ppm as being protective of DMA-induced sensory irritation.

It should be noted, however, that the RD_{50} technique is a screening tool for comparing the sensory irritation of various chemicals. It has been useful in predicting unacceptable occupational exposure concentrations due to intolerable sensory irritation and possible respiratory tract injury in humans.

Steinhagen et al. (1982) also determined the LC_{50} of DMA in groups of male Fischer 344 rats weighing 158 to 218 g each. Rats were exposed for 6 hours (whole-body) to DMA concentrations ranging from 600 to 6,119 ppm and mortality was observed for 48 hours postexposure. An LC_{50} value of 4,540 ppm was calculated (Table 4-1). The authors stated that, based on the pathology observed in the lungs of the survivors, the LC_{50} value would have been lower if mortality had been monitored for 14 days postexposure. The lowest concentration at which mortality occurred in rats was 3,983 ppm. The concentration versus percent mortality curve has a very steep slope, indicating a narrow range of response rates at all concentration studies. An estimate of LC_1 was derived from this graph; for rats, LC_1 is estimated at 2,800 ppm.

Clinical signs observed in the Steinhagen et al. (1982) study included eye irritation, gasping, and secretion of bloody mucus from the nose. Exposure at the levels tested resulted in severe nasal congestion, ulcerative rhinitis, and necrosis of the turbinates. In the lungs, ulcerative lesions of primary and secondary bronchioles occurred at 4,000 ppm and higher, while emphysema, bronchial hyperplasia, and pneumonitis occurred at 1,000 ppm and higher. Mild emphysema in peripheral areas of the lung was noted at 600 ppm. Other organs affected were the eyes and liver. Corneal edema was noted at 1,000 ppm. Fatty degeneration and focal necrosis of the liver and corneal ulceration,

Table 4-1. Acute Toxicity Values for Dimethylamine in Laboratory Animals

Species/ Sex	Route of Administration	Acute Toxicity Value	Reference
Mouse(M)	Inhalation	LC_{50}: 7,650 ppm (6,687-8,752 ppm)[b]	Mezentseva (1956)[a]
Mouse (M)	Inhalation	RD_{50}:511 ppm (414-654 ppm)	Steinhagen et al. (1982)
Rat (M)	Inhalation	LC_{50}: 4,540 ppm (4,208-4,899)	Steinhagen et al. (1982)
Rat (M)	Inhalation	RD_{50}: 573 ppm (460-747 ppm)	Steinhagen et al. (1982)
Mouse	Oral	LD_{50}: 316 mg/kg b. wt.	Dzhanashvili (1967)
Rat	Oral	LD_{50}: 698 mg/kg b. wt 8,100 mg/kg b. wt.[c]	Dzhanashvili (1967)
Guinea pig	Oral	LD_{50}: 240 mg/kg b. wt. 1,070 mg/kg b. wt. [c]	Dzhanashvili (1967)
Rabbit	Oral	LD_{50}: 240 mg/kg 1,600 mg/kg b. wt. [c]	Dzhanashvili (1967)

[a]*This LC_{50} value was calculated from the raw data reported by Mezentseva (1956). Mice were exposed for 2 hours.*
[b]*Values in parentheses are 95 percent confidence limits.*
[c]*These oral LD_{50} values are for DMA solutions titrated with hydrochloric acid to pH8.*

keratitis, edema, and loss of Descemet's membrane occurred at 2,500 to 6,000 ppm.

Buckley et al. (1984) exposed male Swiss-Webster mice (weighing approximately 30 to 40 g) 6 hours/day for 5 days to RD_{50} concentrations of DMA (511 ppm) to evaluate the extent of damage to the respiratory tract. Twenty-four mice were exposed in glass aquarium chambers (102-L capacity) with airflow ranging from 25 to 38 L/minute. DMA concentrations were achieved by direct metering into the chamber and were analyzed at least once an hour by IR spectrometry. Half of the mice were killed by exsanguination and necropsied immediately after the last exposure; the others were killed and necropsied 72 hours postexposure.

Body weights for all mice were decreased from 10 to 25 percent of control values and three mice died during exposure. In mice killed immediately post-exposure, severe exfoliation, erosion, ulceration, and necrosis of the respiratory epithelium in the nasal area were noted. In addition, severe ulceration and necrosis of olfactory epithelium and moderate degeneration of olfactory nerves in the lamina propria were noted. No lung lesions were observed. Mice killed 72 hours postexposure exhibited a reduction in nasal inflammation. However, there was little change in ulceration or degeneration of tissues. The 72-hour period was insufficient for recovery from the observed lesions.

Morgan et al. (1985) studied the effects of inhaled DMA on the nasal mucociliary apparatus in rats as examined in rapidly excised tissue by video analysis. Rats were exposed to 175 ppm DMA 6 hours/day for 9 days. Results indicated that DMA inhibited mucociliary function in the dorsal half of the maxilloturbinate, with normal ciliary activity persisting in the ventral meatus. Mucus flow patterns on the lateral wall were altered by DMA. This may explain in part the mechanism responsible for the nasal toxicity of DMA.

Gross et al. (1987) have recently reported additional histologic and video analysis of effects on the mucociliary apparatus at additional time points after 175 ppm DMA exposure (1, 2, 4, or 9 days and at 2 years). Acute and chronic DMA exposure produced erosion of anterior margins and fenestrations of the adjacent septum. Ciliastasis and mucostasis were observed only on the anteromedial aspect of the maxilloturbinate (see Figure 4-1). In the 2-year-old

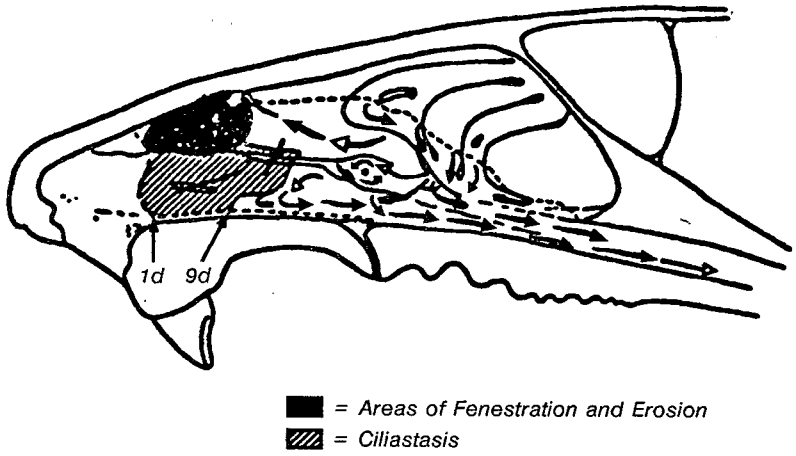

Figure 4-1. ***Anatomical diagram of the nasal cavity of a 10-wk-old rat exposed to 175 ppm DMA for 1 or 9 days. Arrows indicate direction of mucous flow. The asterisk indicates rotational flow over the posterior wall. The solid arrow indicates a region in which mucus flowed from the naso- to the maxilloturbinate over areas of ciliastasis following 9 days of exposure to DMA.***

Source: Gross et al. (1987).

chronically DMA-exposed rats (study described in detail in Section 4.1.3), mucociliary activity was present in areas adjacent to erosions of the turbinates and septum (see Figure 4-2). Abnormal mucus flow patterns, including altered or reversed direction of flow and "whirlpool-like" formation were observed in all treated rats, but were more severe following chronic exposure. The authors concluded that the mucociliary apparatus continues to function in nasal passages of rats having localized destruction of nasal epithelium induced by DMA exposure; this clearance system responds to alterations of nasal structure by modification of mucus flow patterns. Additional note was made of the dissimilar toxic cellular response to DMA when compared to formaldehyde

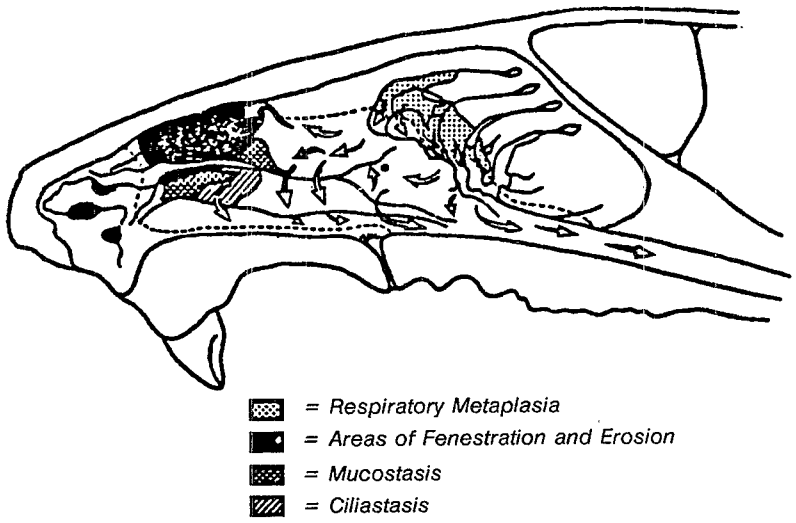

Figure 4-2. ***Anatomical diagram of the nasal cavity of an old rat following 2 years of exposure to 175 ppm DMA. Areas of ciliastasis and mucus flow patterns are similar to those seen from acute exposure. The asterisk marks an area of altered mucus flow on the lateral wall. There are areas of respiratory metaplasia on the ethmoid turbinates. The areas of fenestration and erosion are slightly larger than those observed after acute exposure.***

Source: Gross et al. (1987).

(which had been proposed as a metabolite of DMA in the nasal mucosa). The epithelial vacuolation and severe subepithelial destruction observed with DMA suggest that an alternative mechanism may be responsible for DMA toxicity, which appears to be related to DMA directly rather than formaldehyde *per se*.

4.1.2 Subchronic Toxicity

Hollingsworth et al. (1959) exposed groups of 10 rats, 6 guinea pigs, and 1 rabbit of each sex and 5 female mice (age, weight, and strain were not reported) to 97 or 183 ppm of DMA vapor for 7 hours/day, 5 days/week, for 18 to 20 weeks. Additionally, one male monkey was exposed to 97 ppm DMA and one female monkey was exposed to 183 ppm. Galvanized sheet-metal boxes having a 1760-L capacity served as the inhalation chambers. Anhydrous DMA gas was mixed with air and injected into the inhalation chamber. DMA concentration was maintained using a dual-syringe feeder pump and analyzed periodically during the exposure period. Actual DMA concentrations ranged from 152 to 195 ppm for the high-dose group (183 ppm) and 92 to 98 ppm for the low-dose group (97 ppm).

The eyes of rats, guinea pigs, and rabbits were examined 9 and 45 days after the start of exposure. Slight to moderate corneal damage to the eyes of guinea pigs and rabbits exposed to 97 or 183 ppm DMA was observed after 9

days, but did not progress through 45 days of exposure. However, no adverse effects of treatment were noted in body weights, organ weights, or clinical chemistry and hematology parameters. Histopathological evaluation revealed centrilobular fatty degeneration and necrosis of the liver parenchymal cells of rats, rabbits, and mice at both dose levels. These lesions were also noted in female guinea pigs exposed to 183 ppm. The authors also reported testicular tubule degeneration in one rabbit (at 183 ppm) and in the monkey (exposed to 97 ppm). The available hematoxylin and eosin-stained slides were reexamined by Quast (1981). Because of lost slides, inadequate animal coding, and other problems, Quast could not conclude that the observed testicular pathology was primarily the result of subchronic DMA inhalation.

In studies conducted by Coon et al. (1970), male and female Sprague-Dawley and Long-Evans rats and Princeton-derived guinea pigs and male New Zealand albino rabbits, squirrel monkeys, and beagle dogs (age and weights were not specified) were exposed to 9 mg/m^3 (approximately 4.9 ppm) DMA continuously for 90 days. A modified Rochester-type inhalation chamber containing 15 rats, 15 guinea pigs, 3 rabbits, 3 monkeys, and 2 dogs was loaded in a typical experiment. DMA concentrations were continuously monitored using a hydrogen flame-ionization detector. No signs of toxicity or mortality were observed during the exposure period. Animals were killed by an overdose of pentobarbital immediately after exposure. No changes in hematology parameters were observed. Histological evaluation of the lung revealed only minor interstitial inflammation in all species tested. Dilation of the bronchi was noted in rabbits and monkeys. These effects were not considered to be chemically induced. Apparently, sections of the nasal turbinates were not collected; therefore, evidence of possible lesions of the respiratory and olfactory epithelia was not obtained. However, this study does support earlier cited evidence of only minor lung involvement during inhalation of DMA (Buckley et al., 1984).

Although no subchronic studies reporting nasal epithelial findings after DMA inhalation were found in the literature, Lynch et al. (1986) studied the effects of diethylamine (DEA) exposure on Fischer 344 rats. One hundred rats per sex were exposed to 25 or 250 ppm DEA for 6 hours/day, 5 days/week for 6 months. Body weight gains of the 250-ppm rats were decreased throughout the exposure period when compared to control animals. Sneezing, tearing, and reddened noses were also noted in the 250-ppm animals. Histological evaluation revealed squamous metaplasia, suppurative (pus containing) rhinitis, and lymphoid hyperplasia of the respiratory epithelium. Therefore, although lesions of the nasal or olfactory epithelium were not reported in the DMA subchronic studies reviewed, the possibility that they occur cannot be ruled out.

4.1.3 Chronic Toxicity

A 2-year chronic toxicity study was conducted in rats and mice (interim report - Buckley et al., 1985; Chemical Industries Institute of Toxicology, 1987). Male and female Fischer 344 rats and B6C3F1 mice were exposed by inhalation to 0, 10, 50, or 175 ppm DMA for 6 hours/day, 5 days/week for 1 year. Ninety-five animals (6-10 wk old)/sex/species were randomly assigned to groups. Rats were individually housed and mice were group-housed five/cage in suspended stainless steel wire cages within the exposure chambers, which

were described as stainless steel and glass whole-body inhalation chambers (8 m^3). Airflow was maintained at 2,200 L/minute. DMA concentrations were generated by metering "pure" DMA directly from the cylinder into the chambers using a flow meter. Concentrations were analyzed four times/hour using IR spectrometry. Results of the chamber DMA analyses indicated that the average analytical concentrations of DMA were approximately 142, 44, and 8 ppm for the 175-, 50- and 10-ppm chambers, respectively.

Necropsies were performed on fasted animals after 6, 12, and 24 months of exposure. No male mice were killed at the 12-month interval because of unexpectedly high mortality in all groups. Prior to necropsy, blood was collected for hematology and serum chemistry analyses. Specified tissues and gross lesions were collected. The lung, liver, kidneys, and brain were weighed. The nasal passages were flushed and the lungs were inflated with formalin prior to fixation.

Body weight gains for rats in the 175-ppm group were consistently and significantly decreased (by approximately 10%) when compared to controls after 3 weeks of exposure. In addition, mice exposed to 175 ppm DMA exhibited sporadic, significantly decreased body weight gains. No clinical signs of toxicity or treatment-related mortalities were noted. The high mortality throughout all groups observed in male mice was attributed to fighting. Possible treatment-related changes observed in hematology parameters were decreased platelet count in 175-ppm male rats, increased numbers of atypical lymphocytes in 175-ppm female rats, and decreased mean red blood cell volume in 175-ppm female mice when compared to controls. Statistically significant changes in serum chemistry values after 12 months of exposure consisted of decreased protein concentration and increased alkaline phosphatase activity in 175-ppm female rats and increased glucose levels in 175-ppm female mice.

Histological evaluation revealed that exposure-related lesions were confined to the nasal passages and were similar in nature for rats and mice. In rats, there was a progression in severity of degeneration of the olfactory epithelium with increasing exposure time whereas in mice, no apparent progression was observed between 6 and 12 months of DMA exposure. Areas of involvement included the respiratory epithelium and underlying tissues adjacent to the vestibule and the olfactory epithelium in the mid portion of the dorsal meatus with variable involvement of more posterior olfactory areas. In the animals exposed to 175-ppm, variable destruction of the anterior portions of the naso- and maxilloturbinates and fenestration of the nasal septum were observed. The surfaces of the turbinates and septum were covered with nonkeratinizing squamous epithelium. There were both focal and diffuse mucosal and submucosal infiltration of mononuclear leukocytes and neutrophils, indicating an inflammatory response. Little exudate was present. Epithelial hypertrophy and hyperplasia, focal epithelial ulceration, and focal to diffuse squamous metaplasia were observed. In rats, mild to severe goblet cell hyperplasia on the ventral portion of the nasal septum was also observed. The lesion of the olfactory region most frequently observed in rats and mice was degeneration of olfactory sensory cells with variable vacuolation of the olfactory epithelium. Atrophy of olfactory nerves in the lamina propria usually accompanied these lesions. Accumulation of hyaline eosinophilic material in the sustentacular cells, which were markedly hypertrophic, was also frequently noted. This eosinophilic material was also observed in the associated airway

(possibly a secretory product of the sustentacular cells) and in large submucosal glands at the junction of the olfactory and respiratory epithelium. Hypertrophy and focal hyperplasia were also noted in Bowman's glands. Severe degeneration of the olfactory epithelium was followed by replacement with well-differentiated, ciliated respiratory epithelium, which was sometimes continuous with ciliated ducts of hypertrophic and hyperplastic Bowman's glands. In rats, foci of fusiform cells were observed near the basal layer in areas of respiratory metaplasia in the dorsal meatus. The basement membrane of the underlying, edematous connective tissue appeared to be thickened and separated from the epithelium. Basal cell hyperplasia in the olfactory epithelium was also frequently observed in rats.

In the 50-ppm groups, changes in the respiratory nasal epithelium were confined to focal squamous metaplasia in the free margins of the turbinates after 6 months and to epithelial hypertrophy and hyperplasia after 12 months of DMA exposure. The majority of animals exposed to 50 ppm DMA exhibited olfactory epithelial lesions. These lesions consisted of loss of sensory cells and olfactory nerves.

In the 10-ppm groups, chronic inflammation of the vestibule and respiratory nasal epithelium was noted. Lesions consisting of focal degeneration of olfactory epithelium located in the dorsal meatus were observed. These results indicate that the olfactory sensory cell is highly sensitive to the toxic effects of DMA, with minor lesions being produced in rats and mice even at 10 ppm which is the current TLV for humans.

Chronic inhalation exposure of Wistar rats to 0, 0.005, 0.033, or 0.93 mg/m^3 (0, 0.003, 0.02, and 0.5 ppm, respectively) of DMA was reported by Artem'eva and Dobrinskii (1973). It should be noted that very few details of the experimental procedure were reported and especially the length of exposure was not specified. The authors reported that DMA levels of 0.93 and 0.033 mg/m^3 caused changes in the normal ratio of muscle-antagonist chronaxy, a decrease in blood cholinesterase activity, a decrease in -SH groups in serum, an increase in urinary elimination of coproporphyrins, a disturbance of immune reaction of the body, and a decrease in ascorbic acid in the organs. Histological evaluation revealed infiltration of lung perivascular connective tissue and thickening of interalveolar septa with congestive hyperemia of veins and alveolar capillaries. Vacuolization of the cytoplasm with partial tigrolysis was noted in some neurons and subcortical ganglia of the cerebral cortex in the brain. No changes were observed in the 0.005-mg/m^3 group when compared with controls. These experimental findings need confirmation by additional well-conducted studies.

4.1.4 Carcinogenicity

Groups of Fischer 344 rats and B6C3F1 mice of both sexes were exposed to nominal concentrations of 0, 10, 50, or 175 ppm DMA for up to 24 months (Chemical Industries Institute of Toxicology, 1987). Decreases in body weight were noted in either sex of both rats and mice at exposure levels of 175 ppm. The complete report giving specific body weights for both species is not yet available (December 1989), but a few animals from this study were used by Gross et al. (1987). Control 2 yr rats weighed an average of 355.8 $\pm$ 11.92g (SEM) compared to exposed rats' weight of 346.50 $\pm$ 9.82g. Nasal toxicity characterized by dose-related increases in incidence of inflammatory,

degenerative, and hyperplastic lesions at the nasal passages was noted. There were no increased incidences of tumors that could be attributed to DMA exposure. The authors concluded that DMA is not carcinogenic to rats or mice. Further information will have to await the release of the full experimental docket by CIIT.

4.2 Oral Toxicity

4.2.1 Acute Toxicity

The acute effects of oral administration (method not specified) of aqueous DMA in rats, mice, guinea pigs, and rabbits (strain, sex, age, and weight were not specified) were reported by Dzhanashvili (1967). In addition, because of the severe irritating effects of aqueous DMA, the dosing solution neutralized with hydrochloric acid was also given to rats, rabbits, and guinea pigs to determine LD_{50} concentrations. The LD_{50} values for mice, rats, guinea pigs, and rabbits given aqueous DMA were 316, 698, 240, and 240 mg/kg body weight, respectively (Table 4-1). The LD_{50} values for the neutralized DMA were 5- to 11-fold higher.

Clinical signs noted included transient excitation followed by sluggishness, prostration, and disturbances in motor coordination. At necropsy, extensive hemorrhage of the stomach and intestinal walls was noted in animals receiving the unneutralized DMA solutions, indicating that the acute oral toxicity of aqueous DMA was largely due to local action on the gastrointestinal mucosa.

4.2.2 Subchronic Toxicity

The subchronic oral toxicity of DMA neutralized with hydrochloric acid was described by Dzhanashvili (1967). Dose levels of 107 and 160 mg/kg body weight of DMA (1/10 of the reported LD_{50}) neutralized with hydrochloric acid were administered orally to 30 guinea pigs and 15 rabbits, respectively, daily for 6 weeks (animal strain, sex, weight, and age were not reported). Increases in blood hemoglobin, blood cholinesterase activity, blood urea nitrogen (BUN) concentration, and coproporphyrin excretion in urine were reported. Some statistical differences were indicated. Relative liver weight was increased and vitamin C content in the organs was decreased.

In addition, Dzhanashvili (1967) reported the effects of oral administration (method not specified) of neutralized DMA to rats and guinea pigs for 8 months. Albino rats received 0.007, 0.035, or 0.35 mg/kg body weight of DMA and guinea pigs received 0.035, 0.35 or 3.5 mg/kg body weight of DMA daily. Again, strain, age, weight, and sex of the animals were not specified. No control values were determined or reported. In guinea pigs, 3.5 mg/kg body weight of DMA caused increases in BUN concentrations, relative liver weight, and coproporphyrin excretion in the urine. There were also decreases in vitamin C content in the adrenals. Daily doses of 0.35 mg/kg body weight resulted in transient (noted in first 4 months) increases in BUN and the number of white blood cells and decreases in vitamin C content in the adrenals. No other changes were noted for guinea pigs.

In rats, daily doses of 0.35 mg/kg body weight resulted in decreases in the phagocytic activity of blood leukocytes and increases in absolute liver weight. The authors also reported a higher nervous activity in the animals. This was evaluated using the motor-alimentary method, which tests the animal's capacity to develop new temporary nerve connections. This test is reported to be widely used in the Soviet Union to determine hygienic standards for water, but does not appear frequently in the U.S. literature. The rats were grouped according to their conditioned reaction to a single positive stimulus represented by a bell. The effect of DMA on the conditioned reflexes was then evaluated. A dose of 0.035 and 0.35 mg/kg body weight resulted in higher nervous activity of the rats. No other changes were noted.

4.2.3 Chronic Toxicity

No pertinent data on the chronic oral toxicity of DMA were found in the literature.

4.2.4 Carcinogenicity

No pertinent data on the carcinogenicity of DMA after exposure via the oral route were found in the literature.

4.2.5 Interactions and Synergistic Toxicity

4.2.5.1 Acute Exposure

The effects of combined DMA-nitrite administration have been investigated by several laboratories. The acute effects of sodium nitrite ($NaNO_2$) and DMA•HCl in adult male HaM/ICR mice was studied by Asahina et al. (1971). Dose levels of administered DMA were 500, 1,000, 2,000, or 2,500 mg/kg body weight, whereas doses of $NaNO_2$ were 100 or 150 mg/kg body weight. No mortality was noted in mice receiving $NaNO_2$ or DMA alone. Toxicity in the form of relative weight losses, mortality, and liver necrosis was evidenced in animals given $NaNO_2$ and DMA simultaneously or DMA followed by nitrite at time intervals of up to 3 hours. Toxicity was decreased when nitrite was administered prior to DMA at increasing time intervals. Livers from animals receiving 2,500 mg/kg body weight of DMA and 150 mg/kg body weight of $NaNO_2$ were swollen, mottled, hemorrhagic, necrotic, and fragile. Microscopic examination revealed widespread centrilobular and midzonal parenchymal liver necrosis, sinusoidal and portal congestion, and hemorrhage. The authors stated that these findings were consistent with the *in vivo* formation of DMNA.

The influence of intestinal microflora on acute hepatotoxicity of DMA and nitrite was studied in 30-day-old germ-free and conventional CFW and Swiss-Webster mice by Pollard et al. (1972). Mice were fed $NaNO_2$, DMA, or $NaNO_2$ and DMA (doses of DMA were 2,500 or 3,500 mg/kg body weight and doses of $NaNO_2$ were 75 or 100 mg/kg body weight) and observed for mortality for 3 days. Conventional and germ-free mice demonstrated similar patterns of susceptibility. Increased doses of DMA and $NaNO_2$ caused increases in deaths and hepatic necrosis. From these results, the authors concluded that intestinal microflora do not play a role in the synthesis of the toxic agent, which probably was DMNA. Sumi and Miyakawa (1983) conducted studies comparing the effects of DMA and nitrite on liver necrosis and serum

glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) levels of treated conventional and germ-free Wistar rats. Administration of DMA and nitrite or DMNA alone by stomach tube produced hepatic necrosis; after 48 hrs, 30- to 40-fold elevations in SGOT and SGPT levels were found in germ-free rats with no changes in conventional rats. DMA and $NaNO_2$ administered simultaneously to male Swiss albino mice produced synergistic acute inhibition of liver protein and nuclear RNA synthesis (Friedman et al., 1972). These findings provide further evidence of *in vivo* nitrosamine synthesis since similar effects have been noted after administration of DMNA.

Several acute studies have been conducted to evaluate the possible inhibition of DMA-$NaNO_2$ hepatotoxicity by antioxidants. Cardesa et al. (1974) reported complete inhibition of DMA-nitrite-produced liver necrosis and associated marked increases in SGOT and SGPT in male Wistar rats (250-400 g) by oral doses of 90 to 720 mg/kg body weight of ascorbic acid (1,500 mg/kg body weight of DMA and 125 mg/kg body weight $NaNO_2$). Propyl gallate and tert-butylhydroquinone at equimolar levels to nitrite were also shown to inhibit the effects of hepatotoxicity elicited by DMA-$NaNO_2$ (enzyme induction and hepatic necrosis) in male Sprague-Dawley rats (Astill and Mulligan, 1977). Antioxidants are thought to inhibit the formation of nitrosamines.

4.2.5.2 Subchronic and Chronic Exposure

The combination of DMA and $NaNO_2$ has been shown to cause acute toxicity in rats and mice, presumably due to the formation of DMNA *in vivo*. Several studies have been conducted to determine the long-term toxicity of DMA and $NaNO_2$ and the possible carcinogenicity of the combination of these chemicals.

Kunisaki et al. (1974) fed rats (strain, age, weight, number, and sex were not specified) $NaNO_2$, DMA, or $NaNO_2$ and DMA (10 mg/day) for 6 months. Administration of DMA and $NaNO_2$ resulted in fatty degeneration of the liver and hemorrhagic lesions in the kidney. DMA or $NaNO_2$ alone had no effect.

In another study, male Wistar rats, five per group, were given the following concentrations of DMA and $NaNO_2$ simultaneously in their drinking water for 78 days: 0.5, 2.5, or 5.0 g/L $NaNO_2$ plus 4 mL/L DMA (Oka et al., 1974). Also, three groups of five male rats were given 1 g/L salicylic acid in addition to the concentrations of DMA and $NaNO_2$ given above. Vitamin A content and histopathology of the liver were evaluated. Mean body weights of the high-dose animals (5.0 g/L $NaNO_2$, 4 mL/L DMA with and without salicylic acid) were significantly lower than controls, and vitamin A was decreased when compared to other dose groups. The authors reported that the high-dose animals developed a skin disorder described as loss of luster and "disturbance" of the body coat after 10 days on study; this disorder persisted to study termination. The skin disorder was attributed to decreases in vitamin A. Addition of salicylic acid had no effect. Because of the significant decrease in hepatic vitamin A observed in this study, additional experiments were conducted to test the potential hepatic carcinogenicity of combined DMA-nitrite administration.

Oka et al. (1974) performed a study with male albino Wistar rats weighing approximately 100 g (five rats/group) which were given 5, 15 or 30 g/L $NaNO_2$

plus 4 mL/L DMA in the drinking water for 410 days. Vitamin A content and histopathology of the liver were evaluated. All animals in the 15- and 30-g/L-$NaNO_2$:4-mL/L-DMA groups exhibited the skin disorder described earlier and died within 14 days of study initiation. Death was attributed to $NaNO_2$ toxicity. No liver changes were noted in these animals. In the 5-g/L- $NaNO_2$: 4-mL/L-DMA group, there were decreases in body weight and vitamin A content in the liver. Two of four rats in this group developed sarcomas of the liver. One rat, dying on day 318, had what was described as a large metastatic liver sarcoma with involvement of the mesentery and spleen. The other tumor-bearing rat was sacrificed on schedule (day 410); its tumor was not metastatic. The authors concluded that combined oral administration of DMA and nitrite to rats over a long period of time was carcinogenic.

The validity of the authors' conclusion, however, is questionable because of numerous deficiencies with the study protocol. Only four rats survived longer than 2 weeks. Only one dose level of DMA was tested. Control groups receiving DMA or $NaNO_2$ alone were not included; therefore, the toxicity noted could have been due to $NaNO_2$. Analyses of test solutions were not performed; therefore, chemical conversion of DMA to DMNA could have occurred in the drinking water. Therefore, the study performed by Oka et al. (1974) is an unacceptable study, and the evidence for carcinogenicity is questionable.

Garcia Roche et al. (1983) studied the effects of DMA and $NaNO_2$ on male Wistar rats. Six groups of eight rats each were given oral doses of 10 or 20 mg of DMA•HCl (110 or 220 mg/kg body weight, respectively), 10 mg $NaNO_2$, 10 mg $NaNO_2$ and 10 mg DMA•HCl, or 10 mg $NaNO_2$ and 20 mg DMA•HCl for 30 days. The rats were 30 to 40 days of age and weighed approximately 90 g at study initiation. At the end of exposure, body and liver weights were measured, and SGPT analysis and histopathological evaluation of the liver and kidneys were performed. No significant differences were found in any of the parameters evaluated. Histopathological evaluation did not reveal any significant changes in the liver or kidneys of any exposed animals. The only exposure-related observation noted upon necropsy was ascites fluid in the abdomen of three animals from the 10 mg $NaNO_2$:20 mg DMA group.

In another experimental study, groups of 30 weanling male Wistar rats were given DMA (0.2 percent), $NaNO_2$ (0.2 percent), DMA and $NaNO_2$, butylated hydroxytoluene (BHT, 0.5 percent), or BHT, DMA, and $NaNO_2$ in the drinking water for 9 months (Darad et al., 1983). At study termination, the animals were killed and hepatic microsomes were isolated for *in vitro* analysis of lipoperoxidation and lysosomal enzyme activities (acid phosphatase and cathepsin). Results indicated that $NaNO_2$ or DMA alone caused significantly higher peroxidation, but when administered simultaneously, there was no increase in peroxidation when compared to controls. BHT administration resulted in a significant reduction in peroxidation of lipids. However, BHT, DMA, and $NaNO_2$ administered simultaneously had no effect on peroxidation; values were comparable to controls. In rats given DMA or $NaNO_2$, the free activities of both lysosomal enzymes were increased while the total activities were decreased. The reasons for this were not clear. In rats receiving BHT, the free activities of both enzymes were decreased while the total activities were increased. Rats given DMA and $NaNO_2$ had increases in free activities and decreases in total activities of the lysosomal enzymes while animals given DMA, $NaNO_2$, and BHT had free activities that were comparable to controls.

The authors concluded that DMA and $NaNO_2$ may induce toxicity through some free radical reactions and BHT can provide some protection against toxicity.

Karpilovskaya and Rubenchik (1977) studied the effect of DMA, $NaNO_2$, and the combination of the two on DMNA demethylase activity in the rat liver. Young male rats weighing 140 to 200 g (strain not reported) were fed 150 mg/kg DMA, 38 mg/kg $NaNO_2$, DMA and $NaNO_2$ (concentrations equal to above levels), DMA plus $NaNO_2$ plus ascorbic acid (150 mg/kg), or DMNA (6 mg/kg) in the diet (supplemented with casein, 2 g/rat) for 3.5 months. Animals were then killed, and hepatic microsomes were isolated to determine DMNA demethylase activity. Results indicated that administration of DMA caused a significant increase ($p < 0.01$) in DMNA demethylase activity when compared to controls, suggesting that DMA is a demethylase inducer and may, therefore, increase endogenously-formed DMNA toxicity.

4.3 Mutagenicity

Several *in vitro* and *in vivo* genetic toxicology assays on DMA have been published. These have been categorized into gene mutation (category 1) and chromosomal aberration assays (category 2) and those studies that assess other mutagenic mechanisms (category 3). The findings from the studies are discussed below.

4.3.1 Gene Mutation Assays (Category 1)

4.3.1.1 Reverse Mutation in Prokaryotes.

Three reverse mutation assays with *Salmonella typhimurium* were reported. Takeda and Kanaya (1982) exposed *S. typhimurium* TA98 and TA100 to the nitroso derivative of DMA (50 mM DMA reacted with 500 mM $NaNO_2$ at pH 3.4). The assay was conducted in the absence and presence of an S9 mix (hepatic microsomes from rats induced with polychlorinated biphenyls plus appropriate cofactors in buffered solution). No response was seen in *S. typhimurium* TA98 (±S9). It was stated that the effect observed in *S. typhimurium* TA100 in the presence of S9 was comparable to that observed with DMNA. However, no data were reported and consequently the results of this study are considered inconclusive.

When tested at concentrations of 1 to 5 mg/plate and in the absence of an S9 mix, DMA was not mutagenic in *S. typhimurium* TA1530, TA1531, TA1532, or TA1964 strains (Green and Savage, 1978). However, since DMA was spot tested rather than incorporated into the medium, these results provide only preliminary qualitative evidence of a negative response. In the presence of mouse S9, 0.005 to 0.5 M DMA in suspension with these four tester strains produced a dose-related increase in the mutation frequency (MF) of only *S. typhimurium* TA1530 at 0.05, 0.15, and 0.5 M DMA. These doses were slightly cytotoxic (>80 percent survival). Although this study provides acceptable evidence of an S9-activated mutagenic response in the base-pair substitution strain TA1530, the findings should be interpreted with caution because activity was only seen at very high doses (i.e., 0.5 M DMA, which is equivalent to 22,540 µg/plate) and the results have not been confirmed.

4.3.1.2 *Mammalian Cell Gene Mutation.*

A survey study of 101 chemicals that included DMNA and DMA as a carcinogenic/noncarcinogenic pair, respectively, listed DMA as negative in the Chinese hamster ovary cell (CHO) hypoxanthine guanine phosphoribosyl transferase (HGPRT) assay with and without rat S9 activation (Hsie et al., 1978). Similarly, DMA was also reported to be negative by San Sebastian et al. (1979) in a blind CHO/HGPRT assay of carcinogenic/noncarcinogenic compound pairs. However, it appears that the reports of Hsie et al. (1978) and San Sebastian et al. (1979) are abstracts of results from the same study; no data were presented.

4.3.1.3 *In Vivo Gene Mutation (Host-Mediated Assays).*

Several investigators conducted mouse and/or rat host-mediated assays with either DMA or DMA and $NaNO_2$; the indicator organisms, which in all cases, were histidine-deficient strains of *S. typhimurium* (Edwards et al., 1979; Whong et al., 1979; Green and Savage, 1978; Braun et al., 1977; Couch and Friedman, 1975). None of the assays conducted with DMA were considered acceptable. The study by Edwards et al. (1979) was reported in an abstract and lacked sufficient data for evaluation, whereas the other four assays showed no evidence of overt animal toxicity or bacterial cytotoxicity. However, the data collectively suggest that DMA administration by oral gavage or intramuscularly at nontoxic doses up to 2 g/kg did not induce a mutagenic response in the indicator organisms. In contrast, mutagenic effects were achieved when DMA was administered orally either in combination or in sequence with $NaNO_2$ to female mice or rats (Edwards et al., 1979; Whong et al., 1979; Couch and Friedman, 1975). The results further suggest that activity was detected at high doses of DMA ranging from 0.2 to 2 g/kg in the presence of high doses of $NaNO_2$. The study by Whong et al. (1979) was noteworthy because the assays were conducted with mice and rats. Test animals (female CD1 mice or CD rats) received intravenous inoculations of *S. typhimurium* G 46 10 minutes prior to gavage with 0.4 g/kg DMA or 0.2 g/kg $NaNO_2$ or sequential gavage with 0.07 to 0.4 g/kg DMA and 0.1 g/kg $NaNO_2$. An additional group of mice and rats were dosed with 0.4 g/kg DMA and 0.2 g/kg $NaNO_2$. Bacterial cells were harvested 2 hours posttreatment and plated for total survivors and mutants. Mutation frequencies (MFs) were then calculated. Results for both mice and rats showed that neither DMA nor $NaNO_2$, tested separately, induced a mutagenic response. However, dose-related increases in the MFs for both species were observed with increasing concentrations of DMA + 0.1 g/kg $NaNO_2$. At comparable doses, the response was approximately 50 percent higher in rats than mice and the mutagenic effect was enhanced in both species at the highest test dose by doubling the concentration of $NaNO_2$.

Although the data clearly show a dose-related mutagenic response associated with DMA-nitrite interaction, the results should be viewed with caution for the following three reasons. (1) If DMA in the presence of $NaNO_2$ was converted to nitrosamines, as suggested by the authors, the marked increase in the mutagenic response of bacterial cells harvested from rats rather than mice is both unexpected and inconsistent with other studies. Prival et al. (1979) have shown that *in vitro* conversion of DMNA to a reactive mutagenic metabolite is species specific and S9 microsomal fractions derived from mice are more effective in metabolizing DMA than are rat S9 fractions.

(2) The findings with DMA in the presence of $NaNO_2$ conflict with the results presented by the authors from host-mediated assays with DMNA. In these studies, higher mutagenic activity was observed in bacterial cells recovered from mice than from rats. (3) Both DMA and $NaNO_2$, tested separately, were negative; however, in combination, an interactive mutagenic effect was noted. In general, the effect was proportionate to the dose of DMA (2-fold increase in MF with doubling concentrations of DMA) while the level of $NaNO_2$ was held constant. However, increasing the concentration of $NaNO_2$ by 50 percent at the highest DMA dose in both rodent species (0.4 g/kg + 0.2 g/kg $NaNO_2$) caused a 4- to 5-fold increase in mutagenesis. Although the higher concentration of $NaNO_2$ may have enhanced the rate of nitrosation of DMA, $NaNO_2$ is also a direct-acting base-pair substitutional mutagen in the *S. typhimurium* G 46 derivative strains TA1535 and TA100 (McCann et al., 1975) and is frequently used as a positive control in the *S. typhimurium* microsome mutagenicity (Ames) assay.

Thus, while the study of Whong et al. (1979) discussed above was technically sound, the relevance of the findings is unclear.

Braun et al. (1977) also performed host-mediated assays with DMA and DMA + $NaNO_2$ using male mice as the host and *S. typhimurium* TA1950 (derivative strain of G 46). The authors reported that DMA, at doses ranging from 0.1 to 0.2 g/kg, was not mutagenic. In contrast to previous studies showing an interreactive mutagenic effect for DMA and $NaNO_2$, Braun et al. (1977) reported no mutagenic activity when 2 g/kg DMA was administered orally to mice with 0.2 g/kg $NaNO_2$. However, no data were presented.

4.3.2 Chromosomal Aberration Assay (Category 2)

San Sebastian et al. (1979) tested DMA as the nonclastogenic (negative control) analogue for DMNA in a blind *in vitro* CHO S9-activated and nonactivated chromosomal aberration assay. DMA was reported negative; however, no data were presented. Thus, this study provides only supportive evidence of a nonclastogenic response.

4.3.3 Other Mutagenic Mechanisms (Category 3)

4.3.3.1 Sister Chromatid Exchange (SCE)

DMA was also reported negative at unspecified doses in an S9-activated and nonactivated CHO sister chromatid exchange assay by San Sebastian et al. (1979).

4.3.3.2 DNA Repair in Rat Hepatocytes

Groups of three partially hepatectomized male rats were gavaged with DMA (doses not reported) or 160 to 640 mg/kg DMA plus 80 mg/kg $NaNO_2$ (Hosokawa and Miyamoto, 1976). Hepatocytes were harvested 2 hours posttreatment and assayed for increased DNA-repair activity using the alkaline elution method. The authors reported that DMA alone (no data presented) was negative in this assay. No toxic, cytotoxic, or genotoxic effects were observed in primary rat hepatocytes harvested from animals exposed to 160, 320, or 640 mg/kg DMA in the presence of 80 mg/kg $NaNO_2$. Histopathological examination of the livers from the test animals revealed no cellular damage.

Although DMA and nitrosated DMA were negative, the lack of evidence suggesting compound interaction with the target organ precludes full acceptance of this study.

4.3.4 Conclusions

Based on the limited number of available genetic toxicology studies, it was concluded that the data were insufficient to establish a genotoxic profile for DMA. Numerous data gaps exist and none of the reviewed studies were considered valid by current standards of acceptability. Collectively, the weight of evidence from *in vivo* gene mutation host-mediated assays suggests that DMA is probably not mutagenic and a mutagenic response can only be achieved if DMA, at high doses, is reacted with high doses of $NaNO_2$. While it is known that secondary amines can be converted intragastrically to nitrosamines, the excessive doses of both DMA and $NaNO_2$ required to demonstrate synthesis of a mutagenic product cast doubts on the relevance of this conversion under normal dietary conditions. In addition, although Whong et al. (1979) presented data showing that the interactive mutagenic product was more readily detected in rats than in mice, this result conflicts with the findings of others and suggests that a mutagenic product other than nitrosamines may have been formed.

4.4 Teratogenicity and Reproductive Effects

No pertinent data on the teratogenicity or reproductive effects of DMA were available in the literature.

4.5 Summary of Animal Toxicology

DMA, a gas at room temperature and atmospheric pressure, is highly water soluble. Aqueous solutions of DMA are strongly basic. These two physical properties of DMA contribute greatly to the compound's toxicity. Acute inhalation exposures in rats and mice produce immediate signs of ocular and sensory irritation (Buckley et al., 1984; Steinhagen et al., 1982). The RD_{50} values for rats and mice, 573 and 511 ppm, respectively, are much lower than the LC_{50} values (4,540 and 7,650 ppm for rats and mice, respectively) with mortality at 3,983 ppm in rats. In rats exposed to DMA concentrations of 600 ppm for 6 hours, pathological lesions were limited mainly to the eyes and nasal mucosa. As the DMA concentration approached lethal levels, greater toxicity to the lung and liver were observed. For all doses tested, however, the tissues of the nasal cavity were most severely affected, and a distinct anterior-posterior severity gradient was observed; the lung was minimally affected (Buckley et al., 1984; Steinhagen et al., 1982).

The irritant properties of aqueous DMA also appear to be mainly responsible for its acute oral toxicity. The oral LD_{50} values for aqueous DMA in mice, rats, guinea pigs, and rabbits are 5 to 11 times lower than for neutralized DMA (Dzhanashvili, 1967). Liquid DMA is also highly irritating to the eyes of rabbits (Mellerio and Weale, 1966).

The results from studies on subchronic and chronic inhalation toxicity of DMA in rodents show the same basic trends as those found with acute exposures. In mice and rats exposed to DMA at 0, 10, 50, or 175 ppm for 6 hours/day, 5 days/week for up to 24 months, the most sensitive tissue was the

nasal mucosa (Chemical Industries Institute of Toxicology, 1987; Buckley et al., 1985). No other tissue, including liver and lung, was affected. Body weights, however, were approximately 10 percent lower in the 175-ppm group than in controls. Slight pathological lesions were observed in the olfactory sensory cells of rats and mice in the 10-ppm groups. Effects of long-term exposure to DMA that were different from those reported by Chemical Industries Institute of Toxicology (1987) and Buckley et al. (1985) have been reported by Artem'eva and Dobrinskii (1973), Coon et al. (1970), and Hollingsworth et al. (1959). However, these latter studies would not be considered adequate for determining the subchronic or chronic toxicity of DMA by today's standards. Therefore, reports of hepatic, testicular, pulmonary, immunological, and central nervous system effects from long-term, low-level exposure to DMA are questionable.

The 2-year CIIT study was used to calculate a preliminary value for a chronic inhalation reference concentration (RfC) for humans. At 25°C and 760 mmHg, the 10 ppm NOAEL gives a duration-adjusted (6 hrs/day and 5 days/wk), for human equivalent concentrations = 3.3 mg/m^3. After dosimetric adjustment for the respective surface areas of the respiratory tract involved, a Respiratory Gas Dosimetric Ratio of 0.18 was applied. Uncertainty factors used to calculate RfC for humans are 10 for extrapolation of animal data to man; 10 for individual sensitivity, and 3 for quality of data base. The inhalation RfC for DMA for humans is 2.0 μg DMA/m^3 (1.1 ppb) of air, as verified by the 11/89 RfC workgroup.

No evidence for carcinogenicity or mutagenicity resulting from exposure to DMA has been found. A 2-year chronic inhalation study revealed that DMA is not carcinogenic to rats or mice (Chemical Industries Institute of Toxicology, 1987). The available genetic toxicology studies are mostly inadequate and thus the data are inconclusive for determining mutagenic potential. Several studies indicate that combined administration of DMA and nitrite produces signs of toxicity similar to those observed after DMNA administration. These include liver damage, mutagenicity, and carcinogenicity. However, the doses of nitrite and DMA required to produce these effects are extremely high, making the theory of DMA conversion to the carcinogenic DMNA under normal dietary or inhalation exposure conditions questionable.

No information was found in the available literature on teratogenic and reproductive effects of DMA.

5. Human Health Effects

A search of the primary literature failed to produce any reports on the human health effects associated with exposure to DMA. Similarly, no reports on the human health effects of DEA were found. However, several secondary sources have reported a variety of acute toxic effects associated with DMA exposure (Mackinson et al., 1981; Sittig, 1981; Braker and Mossman, 1980).

All reported effects of DMA in humans are related to the compound's irritancy. After short-term exposure to DMA vapors produces irritation of the eyes with conjunctivitis and corneal edema. Inhalation of concentrations higher than 100 ppm can cause irritation of the nose and throat and lung irritation with dyspnea and cough. The vapors may also produce primary skin irritation and dermatitis. Direct contact with the liquid can produce severe and sometimes permanent eye damage or skin burns. The effects of long-term, low-level exposure to DMA are not known.

6. References

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