SUMMARY OF DATA FOR CHEMICAL SELECTION

METHYLAMINE
CAS NO. 74-89-5

BASIS OF NOMINATION TO THE CSWG

The nomination of methylamine to the CSWG is based on high production volume and exposure potential. Dr. Elizabeth Weisburger, a member of the American Conference of Governmental Industrial Hygienists (ACGIH) TLV Committee as well as the Chemical Selection Working Group (CSWG), provided a list of 281 chemical substances with ACGIH recommended TLVs for which there were no long term studies cited in the supporting data and no designations with respect to carcinogenicity. She presented the list to the Chemical Selection Planning Group (CSPG) for evaluation as chemicals which may warrant chronic testing: it was affirmed at the CSPG meeting held on August 9, 1994 that the 281 "TLV Chemicals" be reviewed as a Class Study. As a result of the class study review, methylamine is presented as a candidate for testing by the National Toxicology Program because of:

- potential for occupational exposures based on high production volume
- evidence of occupational exposures based on TLV and other literature documentation
- universal potential for general population exposures based on endogenous and exogenous occurrence in many consumed products and environmental media
- lack of chronic toxicity data.

Sources of human exposure to methylamine can be consumer, occupational or environmental; and the exposure potential is considered high based on a combined reported production capacity of over 100 million lbs, an estimated United States annual production volume range of 51 to 106 million pounds, an estimate of 10,891 worker exposures (1,410 female) reported in the NOES database, and widespread occurrence in consumed food and beverage products.

Suspicion of carcinogenicity is based on reported potential to be converted endogenously to nitrosamines and is further supported by some positive data for short-term genotoxic effects, including positive results in *E. coli*, mouse lymphoma, and rat inhalation dominant lethal assays, evidence of DNA methylation, and comutagenic effects.

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SELECTION STATUS

ACTION BY CSWG: 12/6/95

Studies Requested:

- Carcinogenicity
- Comparative pharmacokinetics studies by inhalation and oral routes

Priority: High

Rationale/Remarks:

- High human exposure
- Present in many consumer products and in the environment
- Potential for metabolism to carcinogenic products, e.g., formaldehyde, a known rodent carcinogen
- Positive genotoxicity test results

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY:

Dr. John Walker, Executive Director of the TSCA Interagency Testing Committee, was contacted at the Environmental Protection Agency (EPA) for information on the total annual production level of methylamine. Dr. Walker reported it to be within a range of 51 to 106 million pounds for 1989 (Walker, 1995a). He also provided a summary of actions of the TSCA ITC on this chemical (see Regulatory Status section).

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CHEMICAL IDENTIFICATION

CAS Registry Number:	74-89-5
Chemical Abstract Name:	Methanamine (9CI); methylamine (8CI)
Synonyms:	Aminomethane; carbinamine; monomethylamine; MMA
Structural Class:	Primary aliphatic amine

Structure, Molecular Formula and Molecular Weight:

CH_3NH_2

CH_5N Mol. wt.: 31.06

Chemical and Physical Properties

Description:	Colorless gas with a strong ammonia-like odor; at low concentrations it has a fishy odor (Sittig, 1985; Lewis, 1993)
Boiling Point:	-6.3°C (Lide, 1993)
Melting Point:	-93.5°C (Lide, 1993)
Density/Specific Gravity:	0.6628 at 20°C (Lide, 1993)
Flash Point:	Gas: -10°C; 30% solution: 1.1°C (TOC) (Lewis, 1993)
Solubility:	Soluble in water, ethanol, diethyl ether, acetone, and benzene (Lide, 1993)
Volatility:	Vapor pressure, 2 mm Hg at 10°C; relative vapor density (air = 1), 1.55 (ACGIH, 1993)
Reactivity:	Incompatible with mercury, strong oxidizers, and nitromethane (NIOSH, 1994)
Log $K_{o/w}$:	-0.57 (Jaworska & Schultz, 1994)

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Technical Products and Impurities: Methylamine is commercially available from Aldrich Chemical Co. (1994) in the following forms: anhydrous, 98+%; 2.0 M solution in methyl alcohol; 2.0 M solution in tetrahydrofuran; and 40 wt. % solution in water. It is offered by DuPont as an anhydrous liquefied gas (methylamine, 99.3% min.; dimethylamine, 0.5% max.; trimethylamine, 0.2% max.; ammonia, 0.05% max.; water, 0.3% max.) and as 40%, 42% and 50% aqueous solutions with small amounts of dimethylamine (0.1, 0.3, and 0.1% max., respectively), trimethylamine (0.03, 0.05, and 0.04% max., respectively), and ammonia as NH_3 (0.05, 0.05, and 0.05% max., respectively) (DuPont, 1992, 1994a,b, 1995).

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EXPOSURE INFORMATION

Production and Producers: Methylamines are produced by the interaction of methanol and ammonia over a catalyst (zinc chloride) at high temperature. The mono-, di-, and trimethylamines are all produced, and yields are regulated by reaction conditions. They are separated by azeotropic or extractive distillation. Methylamine can also be synthesized by heating ammonium chloride and formaldehyde (Budavari, 1989; Lewis, 1993).

Methylamine is listed in the EPA's TSCA Inventory (NLM, 1995). The production capacity of mono- di-, and trimethylamines in the United States is presented in Table 1. The relative production of the three can vary, but is roughly in a 2:3:1 ratio for 1988 and 1991 and in a 1.5:3:1.5 ratio for 1994. Most material is used captively for downstream products. Current producers of methylamine are Air Products & Chemicals, Inc. and E.I. DuPont de Nemours & Co., Inc. Air Products & Chemicals, Inc. increased capacity above 200 million lbs in 1993 as a result of a debottlenecking project in late 1993. E.I. DuPont de Nemours, & Co., Inc. raised capacity above 180 million lbs. through expanded distillation and planned to add capacity through debottlenecking in early 1995. Questra Chemicals, purchased by Rhone-Poulenc in late 1989, closed its 22-million-lb facility in 1991 (Anon., 1985, 1988, 1991, 1994).

Table 1. Production Capacity in the United States (million lbs)

Producer	1985	1988	1991	1994
Air Products Pensacola, FL	150	150	150	230
DuPont Belle, WV	150	180	180	200
Questra (Rhone-Poulenc) Terre Haute, IN	--	--	22	--
GAF Calvert City, KY	10	10	--	--
Pitman-Moore (IMC) Terre Haute, IN	21.5	22	--	--

Source: Anon., 1985, 1988, 1991, 1994

Annual production of methylamine, according to information submitted to the US International Trade Commission (USITC, formerly the US Tariff Commission), grew from about 2 million lbs in 1957 to about 52 million lbs in 1987. Since that time the USITC has

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not disclosed annual production. According to non-confidential data received by the EPA, however, annual production of methylamine in 1989 was in the range of 51 to 106 million lbs (Walker, 1995a). Table 2 presents annual production and companies reporting manufacture of methylamine in the USITC publication *Synthetic Organic Chemicals, United States Production and Sales* (USTC, 1969, 1974; USITC, 1977, 1978, 1981-1994a,b; Walker, 1995a).

Distributors of methylamine listed in recent chemical directories include Allchem Industries, Inc., Coyne Chemical, Primachem, Inc., and UCB Chemical Sector (Hunter, 1994; Van, 1994). In addition, methylamine hydrochloride is available from Eastern Chemical, Esprit Chemical Co., R.S.A. Corp., and Spectrum Chemical Manufacturing Corp. (Hunter, 1994; Kuney, 1994; Van, 1994).

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Table 2. Annual U.S. Production of Methylamine

Year	Production (thousand lbs)	Companies Reporting Production[1]
1957	2,043	COM, DUP, RH
1958	3,008	COM, DUP, PAS, RH
1961	8,951	COM, DUP, PAS, RH
1967	17,200	COM, DUP, GAF, ESC, PAS, RH
1972	33,063	AIP, COM, DUP, GAF
1975	undisclosed	AIP, COM, DUP, GAF
1977	53,227	AIP, DUP, GAF, IMC
1980	undisclosed	AIP, DUP, GAF, X
1981	48,106	AIP, DUP, GAF, IMC, X
1982	41,858	AIP, DUP, GAF, IMC
1983	39,083	AIP, DUP, GAF, IMC
1984	47,973	AIP, DUP, GAF, IMC
1985	52,317	AIP, DUP, GAF, IMC
1986	37,134	AIP, DUP, GAF, IMC
1987	51,997	AIP, DUP, GAF, IMC
1988	undisclosed	AIP, DUP, GAF, IMC
1989	undisclosed	AIP, DUP, IMC, QTR
1990	undisclosed	AIP, DUP, IMC, RDA
1991	undisclosed	AIP, DUP, IMC
1992	undisclosed	AIP, DUP
1993	undisclosed	AIP, DUP

[1] AIP: Air Products & Chemicals, Inc.; COM: Commercial Solvents Corp.; DUP: E.I. DuPont de Nemours & Co., Inc.; ESC: Escambia Chemical Corp.; GAF: GAF Corp.; IMC: Pitman Moore; PAS: Pennwalt Chemicals Corp.; QTR: Questra Chemical Corp.; RDA: Rhone-Poulenc, Inc.; RH: Rohm & Haas Co.; X: unidentified company
Source: USTC, 1958, 1959, 1962, 1969, 1974; USITC, 1977, 1978, 1981-1994a,b
Demand for methylamines is presented in Table 3.

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Table 3. Demand for Methylamines

Year	Volume (million lbs)
1984	183
1985	187
1987	190
1988	195
1990	190
1991	193
1993	243
1994[1]	250
1995 (projected)	205
1998 (projected)	280

[1] Figures include exports of 35 million lbs in 1993 but not imports of 30 million lbs
Source: Anon., 1985, 1988, 1991, 1994

Use Pattern: Methylamine has many applications in various industries. It is an important intermediate in the manufacture of a variety of products including pharmaceuticals (e.g., ephedrine), pesticides (e.g., 1-naphthyl-N-methyl carbamate, Vapam), explosives, surfactants, and accelerators. It is commonly used in the tanning and dyeing industries and as a fuel additive. It is also used as a polymerization inhibitor, a component of paint removers, a solvent, in the manufacture of photographic developers (e.g., N-methyl-p-aminophenol sulfate), and as a rocket propellant (Anon., 1963; Budavari, 1989; ACGIH, 1993; Lewis, 1993). Methylamine has also been reported to be a precursor chemical used in the illicit manufacture of methamphetamine (Skeers, 1992).

An overview of the use pattern for methylamine over the last decade is presented in Table 4.

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Table 4. Use Pattern of Methylamine

Use	1985	1988	1991	1994
Pesticides, including methyl isocyanate-based and methamsodium	36%	25%	22%	37%
N-Methylpyrrolidone	15%	25%	28%	35%
Alkylalkanolamines	18% (other)	22% (other)	13%	15%
Surfactants			5%	5%
Miscellaneous, including pharmaceuticals			7%	5%
Explosives	31%	28%	25%	3%

Source: Anon., 1985, 1988, 1991, 1994

Human Exposure: There is potential for occupational, consumer, and environmental exposure to methylamine.

Occupational

The National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983, estimated that 10,891 workers, including 1,410 female employees, were potentially exposed to methylamine in the workplace. The NOES database does not contain information on the frequency, level, or duration of exposure to workers of any chemical listed therein (NIOSH, 1990).

Consumer

There is the potential for consumer exposure to methylamine through the consumption of foods and beverages that contain methylamine as well as from the consumption of foods and beverages that contain substances that metabolize endogenously to methylamine.

Several studies contain data on estimated exposure to methylamine through the diet. Pfundstein and coworkers (1991) calculated a mean daily intake for Germans of primary amines of 29 mg/day for women and 37 mg/day for men, of which the contribution of methylamine was 13.6 and 16.6 mg/day, respectively. Siddiqi and coworkers (1992) reported increased exposure to dietary amines, including methylamine, and nitrate in a population at

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high risk for esophageal and gastric cancer in the Kashmir region in northern India. They concluded that regular consumption of the vegetable, Hak, and salted tea with indiscriminate use of sun-dried red chilies by the natives is responsible for their high exposure to methylamine (3.9 mg/day) and noted that the population has a high nitrate dietary burden (237 mg/day) which is largely due to the consumption of nitrate-accumulating *Brassica* vegetables. Specific information from these and other studies on the levels of methylamine in food is presented in the following section, Environmental Occurrence. In addition, Atawodi & Spiegelhalder (1994) found exposure to methylamine through the consumption of Nigerian medicinal plants and suggested that this might contribute to the endogenous formation of carcinogenic N-nitroso compounds and account for some of the cancer of unknown etiology in Nigeria.

There is also implication for exposure to methylamine as a metabolite of drugs containing N,N-dimethylamino groups. A study on the application of a method of assaying deaminase activity found that methylamine is a minor metabolite formed in the liver microsomes of rats, rabbits, and guinea pigs during *in vitro* deamination of drugs containing N,N-dimethylamino groups (Yamada *et al*., 1993).

Environmental

There is potential for exposure to methylamine in illicit methamphetamine manufacture because of its use as a precursor chemical. Heating of the chemicals to produce the drug produces vapors which permeate the interior materials of buildings, including sheetrock, carpets and other porous surfaces; and residues may continue to volatilize long after the illegal laboratory is dismantled (Skeers, 1992).

There is also potential for environmental exposure to methylamine through its occurrence in ambient air and rainwater.

Environmental Occurrence: Methylamine occurs naturally in a variety of foods and beverages. Pfundstein and coworkers (1991) analyzed 264 food and beverage items purchased in 1989-1990 from supermarkets in West Germany for the presence of primary and secondary amines. They found that methylamine was the most abundant amine in the diet and was found at the highest concentrations. The main dietary sources were cooked and smoked fish products. High concentrations were also found in meat products, cheese, bread, vegetables, spices, and

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coffee. Table 5 presents the reported levels of methylamine in these foods and beverages. An earlier study by Neurath and coworkers (1977) also reported the presence of methylamine in fresh vegetables, grains, green salad, apples, bean salad, pickled cabbage, herring, cod roe, cheese, coffee, cocoa, and black tea purchased in Germany.

Methylamine has also been shown to occur as a metabolite following exposures of humans and animals to the industrial chemical methyl isocyanate (MIC) (Varma *et al*., 1990).

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Table 5. Methylamine Concentrations in Foods and Beverages in West Germany in 1989-1990

Foodstuff	Mean Level (mg/kg; ppm)	Range of Levels (mg/kg; ppm)
Meat joints	32	4.3-52
Poultry	48	43-51
Offals	27	15-38
Meat products	8.7	2.2-25
Sausage	14	0.8-33
Bacon, ham	24	10-43
Fish, fresh	125	6-232
Fish, smoked	43	7.6-152
Fish, tinned	19	4.0-37
Milk, dairy products	3.3	0.1-21
Cheese	7.0	0.8-20
Animal fats	11	7.7-15
Plant fats	0.4	0.2-0.9
Bread	12	1.7-22
Biscuits	5.4	0.2-12
Vegetables, fresh	13	0.4-156
Vegetables, preserved	23	3.8-82
Fruit, fresh	2.1	0.01-17
Fruit products	21	0.6-71
Non-alcoholic beverages	1.2	ND-2.8
Coffee	51	28-71
Tea	1.5	0.2-3.3
Wine	1.5	0.6-3.5
Spirits and liquors	0.3	ND-1.2
Beer	1.0	0.04-1.8
Malt	19	7.6-26
Cereal products	9.3	0.2-36
Spices	37	ND-95
Soups	24	0.8-118
Confectionery	3.3	0.1-11

ND = not detected; limit of detection = 10 µg/kg
Source: Pfundstein *et al*. (1991)

Siddiqui and coworkers (1992) identified methylamine as one of the most prevalent primary amines in foods and beverages in the Kashmir region of India. Table 6 presents the levels of methylamine detected in the various fresh and preserved vegetables, red chilies, and salted tea.

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Table 6. Methylamine Concentrations in Foods and Beverages in the Kashmir Region of India

Foodstuff	Level (ppm)
Fresh Vegetables	
Spinach	12.5
Hak	12.5
Tomato	6.5
Kohlrabi (*Brassica oleracea*)	
Leaves	30.0
Stems	3.5
Cabbage	5.5
Radish	10.0
Preserved Vegetables	
Spinach	23.0
Hak	81.2
Tomato	31.3
Gaurd	14.0
Aubergine	20.0
Other	
Red Chilies	24.0
Prepared Salted Tea	60.0

Source: Siddiqi *et al*. (1992)

Methylamine has also been detected in milk (7.9 µmol/100 g), cheese pizza (2.9 µmol/100 g), green beans (4.9 µmol/100 g), commercial samples of wine (0.19 µg/mL in red wine, 0.14 µg/mL in white wine), uncured and cured pork (1,490 µg/kg and 730 µg/kg, respectively), and at high levels in squid, octopus, and other seafoods (up to a mean of 255 ppm). Broiling of seafoods caused an elevation of methylamine (Patterson & Mottram, 1974; Lin & Chang, 1983a,b, 1984; Zeisel & DaCosta, 1986; Ibe *et al*., 1991).

Methylamine also occurs in herring brine, in certain plants such as *Mentha aquatica*, in crude methanol together with di- and trimethylamine (Budavari, 1989), and in Nigerian medicinal plants (Atawodi & Spiegelhalder, 1994).

In addition, methylamine has been detected in ambient air and rainwater. A Japanese study detected methylamine in air samples from a poultry farm (0.52 ppb) and a fermentation system for poultry wastes (0.97 ppb) and in emission gas from an incinerator of poultry

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wastes (12.4 ppb) (Kuwata *et al*., 1983). Methylamine was also identified in ambient air and rainwater samples collected in 1991 from several sites in southern Sweden. The concentration of methylamine in air samples collected about 1 kilometer from agricultural areas ranged from 150-1200 pmol/m^3, was 480 and 1100 pmol/m^3 in samples collected from rural areas, was 200 pmol/m^3 in a sample collected from a coastal area, and ranged from 60-160 pmol/m^3 in samples collected from residential areas. The concentration of methylamine in rainwater samples collected about 1 kilometer from agricultural areas ranged from 30-280 nM, was 90 nM in a sample collected from a rural area, was 40 nM in a sample collected from a residential area, and was <10 nM in a sample collected from a coastal area (Gronberg *et al*., 1992). Methylamine was measured at concentrations ranging from not detected to 231 nM in precipitation samples collected over a 1-year period (April 1988 - April 1989) in central Virginia (Gorzelska *et al*., 1992).

Following a rail accident that spilled the soil fumigant VAPAM into the Sacramento River in July, 1991, methylamine was identified at trace levels in Lake Shasta, California. It was not detected 1 week after the spill (del Rosario *et al*., 1994).

Regulatory Status: The ACGIH-recommended threshold limit value-time weighted average (TLV-TWA) for methylamine is 5 ppm (6.4 mg/m^3). The short-term exposure limit (STEL) is 15 ppm (19 mg/m^3) (ACGIH, 1994). The OSHA permissible exposure limit (PEL) is 10 ppm (12 mg/m^3) averaged over an 8-hour work shift. A STEL has not been determined (OSHA, 1994). The NIOSH-recommended exposure limit for methylamine is 10 ppm (12 mg/^{3}), averaged over a 10-hour work shift (NIOSH, 1994).

The following actions have been taken by the TSCA Interagency Testing Committee (ITC) on methylamine (Walker, 1995b).

- A dossier (IR-481) was completed in June 1986.
- Methylamine was deferred April 9, 1987 for environmental effects because releases of the chemical from manufacturing and processing do not appear to contribute significantly to the level of the chemical in the environment, where the amines are rapidly degraded.
- Relatively high levels of the methyl amines occur naturally in a variety of animal and plant species.

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- Methylamine was deferred for health effects because a worker exposure assessment by EPA concluded that worker exposures to methylamines during production and use would be quite low.

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EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the association of exposure to methylamine and cancer risk in humans were identified in the available literature. However, the formation of the carcinogen N-nitrosodimethylamine (NDMA) when large amounts of nitrate were added to human gastric fluid which contained methylamine was reported by Zeisel *et al*. (1988). The ACGIH (1993) summarized available human study information as follows. Transient eye, nose, and throat irritation was produced by brief exposure at 20 to 100 ppm methylamine. No evidence of irritation was produced from exposure at less than 10 ppm. In an unpublished report, allergic or chemical bronchitis was reported in a worker exposed to methylamine at concentrations ranging from 2 to 60 ppm; and some irritation was noted at about 25 ppm. It is unclear from the report what the actual exposure concentrations were. No accounts of long-term effects, systemic reactions, and skin sensitization have been reported in the literature. Although there is limited human exposure data, it appears that there is evidence of irritation at 25 ppm and no or minimal irritation at 10 ppm.

Animal Data:

Acute

Methylamine has not been evaluated for skin absorption potential; however, it has been shown to be irritating to the skin of guinea pigs and the eyes of rabbits, and may be irritating to the gastrointestinal tract of guinea pigs following oral administration (Goffman & McGuire, 1980; ACGIH, 1993).

Reported acute toxicity values are presented in Table 7.

Recent studies on the comparative pulmonary toxicity of methyl isocyanate (MIC) and its hydrolytic derivatives in Wistar rats found that single exposure by both the inhalation (19 µmol/l of methylamine vapors for 30 minutes) and subcutaneous (sc) routes (5.75 mmol/kg) caused interstitial pneumonitis at the acute (24 hours), subacute (4 weeks) and chronic (10 weeks) phases progressing to fibrosis, suggesting involvement in the subsequent inflammatory response and contribution to the long-term pulmonary damage of MIC (Jeevaratnam & Sriramachari, 1994; Sriramachari & Jeevaratnam, 1994).

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Table 7. Acute toxicity values for methylamine

Endpoint	Species	Value	Reference
oral LD_{50}	Rat	100 mg/kg	NLM, 1995; Kinney *et al*., 1990
inhalation LC_{50}	Rat	448 ppm/2.5 hr	NLM, 1995; Sarkar & Sastry, 1992
inhalation LC_{50}	Mouse	2,400 mg/m^3/2 hr	NLM, 1995
inhalation LC_{50}	Mammal	2,400 mg/m^3	NLM, 1995
subcutaneous LD_{lo}	Rat	200 mg/kg	NLM, 1995
subcutaneous LD_{lo}	Mouse	2,500 mg/kg	NLM, 1995; Budavari, 1989
subcutaneous LD_{lo}	Guinea Pig	200 mg/kg	NLM, 1995
inhalation TC_{lo}	Rat	750 ppm/6 hr/2 wk	NLM, 1995; Kinney *et al*., 1990

Subchronic

Groups of 10 male rats were exposed by nose-only inhalation (6 hours/day, 5 days/week) for 2 weeks to 75, 250, or 750 ppm of methylamine (99.9% pure). Rats were sacrificed immediately following exposure or following a 14-day recovery period. Exposure to 75 ppm produced mild irritation to the nasal turbinate. Exposure to 250 ppm produced mild, irreversible focal erosion and/or ulceration of the respiratory mucosa of the nasal turbinates. Exposure to 750 ppm produced toxic effects including mortality, severe body weight loss, clinical pathologic changes suggestive of liver damage, nasal degenerative changes, and hematopoietic changes; not all effects were reversible during the recovery period (Kinney *et al*., 1990).

Chronic/Carcinogenicity

No 2-year carcinogenicity studies of methylamine in animals were identified in the available literature. However, the *in vivo* conversion of amines to nitrosamines has been reported in the literature. Nitrosamines are known animal carcinogens, and there is evidence to suggest

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that nitrosamines have carcinogenic potential for humans. The extent of this conversion and relevance to human cancer have not yet been determined (ACGIH, 1993).

Several chemical reaction studies and animal studies have reported that methylamine reacts to form carcinogens and precursor chemicals, including NDMA, N-nitrosomethyl-methoxymethylamine (NMMA), methylurea, and azoxymethane. These studies are summarized below.

- Obiedzinski and coworkers (1980) found that methylamine can react with acidic nitrite under a variety of conditions to form N-nitrosodialkylamines. They determined that NDMA was formed when methylamine was reacted with acidic nitrite. At pH 5, there was a 3-fold increase in the yield of NDMA when the reaction was carried out in the presence of formaldehyde and a 4-fold increase in the presence of thiocyanate. At pH 2, the yield of NDMA in the uncatalyzed reaction was about half that at pH 5, and there was no catalysis by the thiocyanate ion but the yield of NDMA was increased more than 4-fold by formaldehyde. NMMA, a moderately potent lung carcinogen in Sprague-Dawley rats, was also formed in the presence of formaldehyde. They noted that the probable reaction pathways for these transformations involve intermediates identical to those postulated to occur during the metabolic activation of dialkylnitrosamines to carcinogens. They suggested that if nitrosation of a primary amine were to occur at or near a site of biological action, subsequent interactions with biological macromolecules could be indistinguishable from those of the metabolites of the corresponding N-nitrosodialkylamine. They also noted that, although this condition of proximity would not often be met, it is conceivable that chronically high levels of nitrite and amine in, for example, the stomach, might contribute to the metaplasia that precedes tumors in some populations at high risk of gastric cancer. The authors further suggested that, if human exposure to N-nitroso compounds is partly due to *in vivo* nitrosation of amines, then it may be important to consider the contribution of primary amines when assessing the significance of these reactions.

- Lin & Chang (1983b) reported that reaction of nitrite in acidic medium with aqueous extracts of squid, which contains high levels of methylamine and dimethylamine, yielded appreciable amounts of NDMA. They commented that endogenous production of N-nitroso compounds by dietary amines and nitrite in the gastrointestinal tract is a likely factor in the etiology of stomach cancer and other gastrointestinal tumors.

- Kodama & Saito (1980) reported that methylurea, a precursor of the carcinogen methylnitrosourea, was formed by incubating methylamine and carbamyl phosphate in neutral buffer. They noted that the presence of methylamine and carbamyl phosphate in preserved, fermented foods provided a suitable condition for the formation of methylurea.

- Fiala (1980) reported that simple oxidation of methylamine in aqueous solution or in methanol leads to the formation of significant amounts of azoxymethane, a strong carcinogen in rodents. However, the reaction conditions (0^{o}C with perbenzoic acid or a monopersulfate) did not appear relevant to the usual physiological conditions.

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Short-Term Tests: Methylamine was not mutagenic with or without metabolic activation (S9) in the *Salmonella* preincubation assay when tested at doses up to 10,000 µg/plate in strains TA98, TA100, TA1535, and TA1537 (Mortelmans *et al*., 1986); when tested in the dose range 0.037-29.44 mg/plate (corrected dose for 0.08-64 mg/plate of methylamine hydrochloride) in strains TA98, TA100, and TA104; or when tested in strains TA97a or TA102 (Meshram *et al*., 1992).

Methylamine (dose range 0.25, 0.5, 1.0 M) in combination with nitrite (0.25 or 0.5 M) was mutagenic in *Escherichia coli* Sd-4 (Hussain & Ehrenberg, 1974). Methylamine and 2-aminoethanol also enhanced the mutagenic effect of ethyl nitrite in *E. coli*. The authors noted that the synergistic action of primary amines could be interpreted as a mutagenic action of monoalkylnitrosamines which are rapidly converted to the corresponding highly reactive diazonium ions (Ehrenberg *et al*., 1980).

Methylamine induced mutagenic responses at the tk locus in the mouse lymphoma cell forward mutation assay in the absence of S9 at concentrations in the range of 200-300 nl/ml (3-4 mM) and became lethal at approximately 400 nl/ml (5mM) (Caspary & Myhr, 1986; Shelby *et al*., 1987). A rat inhalation dominant lethal test found that methylamine was mutagenic at 10 µg/m^3 (NLM, 1995).

Huber & Lutz (1984a,b) showed *in vitro* and *in vivo* methylation of DNA, indicative of DNA damage, from the reaction of methylamine and nitrite. Increased amounts of 7-methylguanine were detected when DNA from calf thymus was incubated with 1.2 mM methylamine (as the hydrochloride) and up to 66.0 mM sodium nitrite (78.8, 78.8, 50.4 mM) and in the stomach and small intestine of male Sprague-Dawley rats gavaged with methylamine (30 µmol/kg bw as the hydrochloride) and sodium nitrite (700 µmol/kg bw). Methylation of DNA *in vivo* was at least 330 times lower than after an *in vitro* incubation of DNA with the reactants.

Tsimis & Yarosh (1990) demonstrated the induction of the adaptive response to DNA alkylation, in which DNA repair genes are coordinately induced to express enzymes which reduce the toxic and mutagenic effects of DNA damage, in *E. coli* MV1601 cells treated with methylamine and nitrite. The adaptive response was induced in proportion to the concentration of methylamine up to a peak at 40 mM. No induction was observed either with

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nitrite and no methylamine, or with methylamine and no nitrite. Inhibition of bacterial nitrosation provided additional evidence that the induction of the adaptive response was due to nitrosation of methylamine. The authors suggested that the adaptive response evolved as a defense against environmental mutagens produced by bacteria themselves.

Metabolism: Zeisel and coworkers (1983) reported that humans and rats excrete methylamine in their urine after eating choline or lecithin, compounds found in many common foodstuffs. They found that almost 1 mmol per day of methylamines was excreted in the urine of humans who consumed a normal diet, almost 2 mmol/day after consumption of 27 mmol of choline chloride, and 0.8 mmol/day after ingestion of lecithin. Rats excreted 0.015 to 0.018 mmol/day of methylamine after consuming a choline-free diet. Excretion of methylamine was similar after administration of 2 mmol/kg b.w. of choline chloride or lecithin. They noted that these methylamines could be substrates for the formation of carcinogenic nitrosamines.

In a later study, Zeisel and coworkers (1988) showed that biological fluids from fasting humans and experimental animals contained methylamine. In humans that had fasted overnight, the concentration of methylamine in gastric fluid (3.7 nmol/ml) was similar to that in saliva (5.0 nmol/ml)) and blood (3.8 nmol/ml), but was lower than that in urine (156.4 nmol/ml). The concentration of methylamine in the gastric fluid of dogs (11.8 nmol/ml), ferrets (17.4 nmol/ml), or rats (23.1 nmol/ml) was considerably higher, possibly reflecting differences in metabolism or in the amine content of the diet. When large amounts of nitrite were added to the human gastric fluid, NDMA was formed.

The toxicokinetics of methylamine has been studied in the rat. Streeter and coworkers (1990) observed biphasic first-order elimination following a single intravenous (iv) bolus dose of 18.9 µmol/kg [^{14}C]- methylamine with a terminal half-life of 19.1 minutes. The apparent steady state volume of distribution, systemic blood clearance, and renal blood clearance were 1.21 liter/kg, 53.4 ml/min/kg, and 5.72 ml/min/kg, respectively. The amount of unchanged methylamine excreted in the urine within 24 hours was 10%. Urinary excretion of total radioactivity was 12.3%, in good agreement with a value of 12% reported for intraperitoneal (ip) doses of 7.5 µmol/kg in the rat by Krishna & Casida (1966). In another study in rats, Schwartz (1966) found 24% of the unchanged compound in the urine following an ip dose of 400 µmol/kg. Streeter *et al*. (1990) commented that this was probably the result of saturation

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of the metabolic capacity of the animal leading to more methylamine being eliminated unchanged in the urine. Streeter and coworkers (1990) also administered a single intragastric (ig) dose of 81.9 µmol/kg [^{14}C]-methylamine to male rats and found that 69% of the dose reached the systemic circulation unchanged out of a total of 93% absorbed from the gut.

Reported metabolites of methylamine include monomethylurea (Dar & Bowman, 1985) and formaldehyde and formate as metabolic intermediates in the conversion of methylamine to carbon dioxide (Keefer *et al*., 1987). Carbon dioxide has been reported to account for approximately 50% of the elimination of methylamine in rats administered the compound ip (Krishna & Casida, 1966; Dar *et al*., 1985). Streeter and coworkers (1990) noted that a similar extensive conversion to this metabolite would be expected following an iv dose. Methylamine can be metabolized in the rat to dimethylamine to a small extent (Asatoor & Simenhoff, 1965).

Studies by Krishna & Casida (1966) and Schwartz (1966) determined that negligible amounts of unchanged methylamine were excreted in the expired air following ip doses of 7.5 or 400 µmol/kg to male rats.

Krishna & Casida (1966) did not observe accumulation of radioactivity in the fat of rats at 48 hours after dosing with [^{14}C]-methylamine. Steeter and coworkers (1990) commented that high lipophilicity with resulting accumulation in the fat is not likely to occur since methylamine would be expected to be ionized at physiological pH values.

Semicarbazide-sensitive amine oxidase (SSAO) in homogenates of rat aorta, porcine aorta, human umbilical artery, and rat white and brown adipose tissue showed deaminating activity towards methylamine. Formaldehyde was the metabolic product of methylamine deamination by SSAO from rat and porcine aorta (Precious *et al*., 1988; Boor *et al*., 1992; Conforti *et al*., 1993). Measurement of urinary levels in rats, before and after treating them with drugs capable of inhibiting either SSAO or mitochondrial monoamine oxidase (MAO) activities, indicated that MAO is not involved in methylamine degradation. These results were consistent with the possibility that SSAO, or related enzymes, may be involved in endogenous methylamine turnover (Lyles & McDougall, 1989). Streeter and coworkers (1990) commented that if SSAO is able to metabolize methylamine *in vivo* in the rat, not all of the dose would reach the venous sampling site following iv administration, with a consequent

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overestimation of the apparent volume of distribution at steady state. They also noted that an overestimation of the apparent volume of distribution at steady state might occur if an uptake process were occurring in the liver or other organs of the rat because the concentration at the sampling site would not be representative of that within the tissues. Solheim & Seglen (1983) found that isolated hepatocytes can accumulate methylamine intracellularly to concentrations in excess of those in the extracellular medium.

Methylamine is also a substrate for the related soluble enzyme, human plasma oxidase (McEwen, 1965).

Methylamine is formed in rats from the metabolism of endogenous compounds such as epinephrine (Schayer *et al*., 1952), sarcosine, glycine, and creatine (Davis & deRopp, 1961). It is also a metabolite of a large number of xenobiotics such as nicotine (McKennis *et al*., 1962), carbaryl in rats (Krishna & Casida, 1966), N-methylformamide in rats and mice (Threadgill *et al*., 1987; Tulip & Timbrell, 1988), dazomet in rats and mice (Lam *et al*., 1993), metham in mice (Lam *et al*., 1993), methylhydrazine in rats (Schwartz, 1966), azoxymethane in rats (Fiala *et al*., 1978), and NDMA in rats (Heath & Dutton, 1958; Burak *et al*., 1991).

Other Biological Effects:

Reproductive Effects/Teratology

In reproduction studies in which 6 female Wistar rats were orally administered 5 mg/kg bw methylamine daily and mated to untreated males, Sarkar and Sastry (1990) found no effect on the estrous cycle, reproductive indices of fertility, gestation, live birth, lactation, the average weight of pups at birth, and weaning. However, the average litter size of the treated group decreased significantly ($P < 0.05$) from the control group. The investigators noted that this effect may be due to either resorption of the fetus or some other reason. In an earlier study in rats, Miller (1971) found that a single intracardial injection of methylamine hydrochloride (dose not stated) on day 13 of gestation did not result in any gross malformations.

The reproductive toxicity of methylamine has also been studied in mice. Methylamine did not exert any maternal or fetal toxicity when injected ip (3 mmol/kg) during midgestation (day 8) to pregnant Swiss mice or when injected ip at levels up to 5 mmol/kg (as the hydrochloride salt) from days 1 to 17 of gestation to groups of pregnant CD-1 mice (6-8

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animals per group) (Varma *et al.*, 1990; Guest & Varma, 1991). When cultured for 48 hours with 8-day-old mouse embryo cells, however, methylamine (0.75, 1.0, 2.0 mM) caused dose-dependent decreases in size, DNA, RNA, and protein content as well as embryo survival, suggesting teratogenic potential. The authors speculated that methylamine may act as an endogenous teratogen under certain conditions (Guest & Varma, 1991).

Structure/Activity Relationships: Four structurally related chemicals were selected for evaluation of relative biological effects. A summary of information found in the available literature is presented in Table 8 followed by a more detailed discussion. No information on carcinogenicity or mutagenicity for the structurally related compound n-propylamine [107-10-8] was found. Information on carcinogenicity was identified for only one of the compounds. Dimethylamine was nontumorigenic in rats by the oral route and negative results were also seen in rats and mice following inhalation assays. Mutagenicity data were available on three of the structurally related compounds. Test results were negative for two of these compounds, trimethylamine and ethylamine. Although most indicators of genotoxicity were negative for dimethylamine, three studies reported some activity. It was weakly mutagenic in *S. typhimurium* strain TA1530, positive in *Saccharomyces cerevisiae* strain D7, and marginally active in Chinese hamster ovary (CHO) cells for chromosomal aberrations (CA) and sister chromatid exchange (SCE). The formation of carcinogenic nitrosamines from the interaction of nitrite and dimethylamine or trimethylamine has been reported. In addition, pyrolysates of dimethylamine and trimethylamine have exhibited mutagenicity in *S. typhimurium* strains TA98 and TA100.

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Table 8. Summary of Information on Methylamine and Structurally Related Compounds

Chemical name [CAS RN]	Carcinogenicity data	Mutagenicity data
Methylamine [74-89-5] CH_3NH_2	The *in vivo* conversion of amines to carcinogenic nitrosamines has been reported. The extent of conversion and relevance to human cancer have not yet been determined (ACGIH, 1993)	negative in *S. typhimurium* TA98, TA100, TA104, TA97a, TA102, TA1535, and TA1537 with and without activation (Mortelmans *et al*., 1986; Meshram *et al*., 1992) positive in mouse lymphoma L5178Y without activation (Caspary & Myhr, 1986; Shelby *et al*., 1987) positive in rat inhalation dominant lethal test (NLM, 1995) *Effects of coadministration with nitrite* positive in *E. coli* Sd-4 (Hussain & Ehrenberg, 1974) enhanced mutagenic effect of ethyl nitrite in *E. coli* Sd-4 (Ehrenberg *et al*., 1980) *in vitro* and *in vivo* methylation of DNA (Huber & Lutz, 1984a,b) adaptive response to DNA alkylation in *E. coli* MV1601 cells (Tsimis & Yarosh, 1990)
Ethylamine [75-04-7] $CH_3CH_2NH_2$	NDF	negative in *S. typhimurium* TA100, TA1535, TA1537, and TA98 with or without activation (Mortelmans *et al*., 1986) negative for mouse testicular DNA synthesis inhibition (Seiler, 1981)

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Table 8. Summary of Information on Methylamine and Structurally Related Compounds (cont.)

Chemical name [CAS RN]	Carcinogenicity data	Mutagenicity data
Dimethylamine [124-40-3] H_3CNHCH_3	nontumorigenic in rats and mice following inhalation for 2 years (Buckley *et al*., 1985; CIIT, 1990) nontumorigenic in rats following administration in diet (PHS-149, 1979-1980; ACGIH, 1993) the formation of nitrosamines from the interaction of dimethylamine and nitrite has been reported (Scanlan *et al*., 1974)	weakly mutagenic in *S. typhimurium* TA1530 with activation (Green & Savage, 1978) negative in *S. typhimurium* TA1531, TA1532, and TA1964 with and without activation; negative in TA1530 without activation (Green & Savage, 1978) negative in *S. typhimurium* TA100, TA1535, TA1537, and TA98 with and without activation (Zeiger *et al*., 1987) negative in *S. typhimurium* TA1950, TA1951, TA1952, and TA1964 in host-mediated assay (Green & Savage, 1978) negative in *E. coli* Sd-4-73 (Szybalski, 1958) positive in *S. cerevisiae* D7 with activation; negative without activation (Galli *et al*., 1993) negative for mutagenicity at the *hgprt* locus, marginally active for CA and SCE in CHO cells with S9 (Hsie *et al*., 1987) negative for CA in CHL fibroblasts with or without activation (Ishidate *et al*., 1981) negative for UDS in primary rat hepatocytes (Martelli *et al*., 1983) pyrolysates of dimethylamine hydrochloride were mutagenic in *S. typhimurium* TA98, TA100 with activation; in absence of activation slight activity seen in TA100 (Ohe, 1982)
Trimethylamine [75-50-3] $N(CH_3)_3$	the formation of nitrosamines from the interaction of trimethylamine and nitrite has been reported (Scanlan *et al*., 1974; Oshima & Kawabata, 1978)	negative in *S. typhimurium* TA100, TA1535, TA1537, and TA98 with or without activation (Mortelmans *et al*., 1986) pyrolysates of trimethylamine hydrochloride were slightly mutagenic in *S. typhimurium* TA98, and TA100 with activation (Ohe, 1982)

NDF: no data found; CA: chromosomal aberration; SCE: sister chromatid exchange; CHO: Chinese hamster ovary; CHL: Chinese hamster lung; UDS: unscheduled DNA synthesis

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Carcinogenic Effects

Dimethylamine. In a 2-year inhalation study, groups of 95 male and female F344 rats and B6C3F1 mice were exposed to 0, 10, 50, or 175 ppm dimethylamine for 6 hours/day, 5 days/week. Histopathological examinations at 6, 12, 18, and 24 months found no evidence of a carcinogenic response. Concentration-dependent toxicity was characterized by decreased body weight (175 ppm only) and progressive inflammatory, degenerative, and hyperplastic lesions of the nasal passages (Buckley *et al.*, 1985; CIIT, 1990). Dimethylamine was nontumorigenic when 27 noninbred rats (sex not stated) were fed 1.6 g/kg diet for 2.5 years (PHS-149, 1979-1980; ACGIH, 1993).

A secondary or tertiary amine may react with nitrite under acidic conditions to give the carcinogenic nitroso compound (Ohshima & Kawabata, 1978).

Mutagenic Effects

Dimethylamine. At concentrations of 0.05-0.5 M with metabolic activation, dimethylamine was weakly mutagenic in *S. typhimurium* strain TA1530. It was not mutagenic in TA1530 without activation or in TA1531, TA1532, or TA1964 with or without activation. At 800 mg/kg it was also negative in the host-mediated assay with strains TA1950, TA1951, TA1952, and TA1964 (Green & Savage, 1978). At up to 4500 µg/plate, dimethylamine was negative with and without activation in *S. typhimurium* TA100, TA1535, TA1537 and TA98 (Zeiger *et al*., 1987). Dimethylamine was negative in strain Sd-4-73 of *E. coli* (dose not stated) (Szybalski, 1958). A dose dependent increase in convertants and revertants was observed in *S. cerevisiae* strain D7 when dimethylamine was tested at a maximal dose of 4 mM with S9 (Galli *et al*., 1993). In CHO cells, dimethylamine did not exhibit cytotoxic or mutagenic effects at up to 22 mM even with S9, and marginal effects on SCE and chromosome aberrations were seen in the presence of S9 (Hsie *et al*., 1987). Dimethylamine (dose not stated) was negative for chromosome aberrations in Chinese hamster lung fibroblasts with or without activation (Ishidate *et al*., 1981). It was also negative for UDS in rat hepatocytes at 3.3 mM (Martelli *et al*., 1983).

When dimethylamine hydrochloride was pyrolysed at 300° to 600°C for 3 minutes, the pyrolysates were mutagenic in *S. typhimurium* strains TA98 and TA100 with activation. The pyrolysates were also slightly mutagenic in TA100 without activation. At doses of 5-20 µmol, the mutagenic activity began to appear from the pyrolysates at 400°C and the pyrolysates at 600°C showed the highest mutagenic activity (Ohe, 1982).

Trimethylamine. No evidence for mutagenic activity of trimethylamine in *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 was detected at doses up to 1,000 µg/plate with or without activation (Mortelmans *et al*., 1986).

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When trimethylamine hydrochloride was pyrolysed at 300° to 600°C for 3 minutes, the pyrolysates were mutagenic in *S. typhimurium* strains TA98 and TA100. The pyrolysates at 600°C showed the highest mutagenic activity (Ohe, 1982).

Ethylamine. Ethylamine was negative when tested for mutagenicity in *S. typhimurium* strains TA100, TA1535, TA1537, and TA98 at doses up to 10,000 µg/plate. The preincubation assay was performed both with and without activation (Mortelmans *et al*., 1986). Ethylamine was inactive when administered in a mouse *in vivo* system to assess testicular DNA synthesis inhibition following intraperitoneal doses of 5, 15, or 50 mg/kg (Seiler, 1981).

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