ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
DIMETHYLAMINE
(CAS Reg. No. 124-40-3)

INTERIM

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicological and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels — AEGL-1, AEGL-2 and AEGL-3 — are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

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EXECUTIVE SUMMARY

Dimethylamine (DMA) is a water-soluble, basic (pK_a = 10.73) secondary aliphatic amine with a smell of ammonia and/or rotting fish. DMA is present in many foods (e.g., cabbage, fish), and is also formed endogenously by gut bacteria from DMA precursors. DMA is widely used in industry as a chemical intermediate and is a high production volume chemical. DMA vapor causes irritation of the eyes, skin, and respiratory tract in humans and animals that is manifested at lower concentrations as lacrimation and mild lesions in the nasal mucosa. At sufficiently high concentrations and/or exposure durations, animal studies reported severe nasal and lung lesions, and occasionally lesions of the liver, kidneys, and testes.

A level of distinct odor awareness (LOA) of 0.53 ppm was calculated for DMA. The LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, and about 10% of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception.

The AEGL-1 was based on a NOAEL for irritation and histopathological lesions in the nasal passages of male and female rats exposed to 100 ppm DMA for 6 hours/day for 13 weeks (Mitchell et al. 1982). Although nasal lesions were not observed at this concentration, DMA is an irritant, and acute exposures to higher concentrations have resulted in nasal pathology. A total uncertainty factor of 10 was applied, including 3 for interspecies uncertainty and 3 for human variability, because nasal irritation from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and is not likely to vary greatly between species or among humans (NRC 2001). Because there is adaptation to the mild irritation that defines the AEGL-1, the resulting 10 ppm concentration was applied to all AEGL-1 exposure durations.

The study chosen for AEGL-2 derivation was that of Gross et al. (1987), in which male rats were exposed to 175 ppm DMA for 6 hours. Rats had extensive nasal lesions and modified quantity, quality, and flow of mucus. Although reversibility was not addressed in this study, it should be noted that nasal and lung lesions were absent in the same strain of rats following a 13-week repeat exposure to the next lowest concentration, 100 ppm, also for 6 hours/day (Mitchell et al. 1982). A total uncertainty factor of 10 was applied, including 3 for interspecies uncertainty and 3 for human variability, because nasal irritation from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and is not likely to vary greatly between species or among humans (NRC 2001). An adjustment factor of 0.5 was applied because the effect was considered minor and below the definition of an AEGL-2 effect. Time-concentration scaling for 10 minutes to 8 hours was performed using the relationship $C^n \times t = k$ (ten Berge et al. 1986), where n = 2.8 was calculated from a linear regression of three LC_{50} studies with lethality data at five exposure durations, ranging from 6 minutes to 4 hours.

The 2-hour $BMCL_{05}$ for mice from the study of Mezentseva (1956), 1978 ppm, was used as the point of departure for the AEGL-3. A total uncertainty factor of 10, 3 for species variability and 3 for human variability was applied. The reasoning for the choice of uncertainty factors is the same as for the AEGL-1. Time-concentration scaling for 10 minutes to 8 hours was performed using the relationship $C^n \times t = k$ (ten Berge et al. 1986), where n = 2.8 was calculated from a linear regression of three LC_{50} studies with lethality data at five exposure durations, ranging from 6 minutes to 4 hours.

AEGL values for DMA are presented in Table 1.

TABLE 1. Summary of AEGL Values for Dimethylamine

Classification	10-min	30-min	1-h	4-h	8-h	End Points (References)
AEGL–1 (Non-disabling) [1]	10 ppm (18 mg/m³)	10 ppm (18 mg/m³)	10 ppm (18 mg/m³)	10 ppm (18 mg/m³)	10 ppm (18 mg/m³)	NOAEL for nasal irritation/lesions in rats in repeat-exposure study (Mitchell et al. 1982)
AEGL–2 (Disabling)	130 ppm (240 mg/m³)	85 ppm (160 mg/m³)	66 ppm (120 mg/m³)	40 ppm (74 mg/m³)	32 ppm (59 mg/m³)	Nasal lesions in rats, considered mild and reversible (Gross et al., 1987)
AEGL–3 (Lethal)	480 ppm (880 mg/m³)	320 ppm (590 mg/m³)	250 ppm (460 mg/m³)	150 ppm (280 mg/m³)	120 ppm (220 mg/m³)	Lethality threshold for mice (Mezentseva 1956)

[1]A Level of Distinct Odor Awareness (LOA) of 0.53 ppm was calculated for DMA, as shown in Appendix A. The LOA is defined as the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, and about 10% of the population will experience a strong odor intensity (Van Doorn et al. 2002).

1. INTRODUCTION

Dimethylamine (DMA) is a water-soluble, basic ($pK_a = 10.73$) secondary aliphatic amine that is a colorless gas with a smell of ammonia and/or rotting fish at room temperature. DMA vapor caused irritation of the eyes, skin, and respiratory tract in humans and animals that was manifested at lower concentrations as lacrimation and mild lesions in the nasal mucosa. At sufficiently high concentrations and/or exposure durations, animal studies reported severe nasal and lung lesions, and occasionally lesions of the liver, kidneys, and testes. DMA is present in many foods including cabbage, celery, corn, fish, and coffee, and is also formed endogenously by gut bacteria from DMA precursors including trimethylamine N-oxide.

DMA is widely used in industry, as a chemical intermediate in organic synthesis, in the manufacture of synthetic rubber and artificial resins, in the pharmaceutical industry, in paint and soap production, in the paper industry, and in food processing. DMA can be synthesized by the reaction of methanol and ammonia in the presence of a dehydrating agent, and by catalytic hydrogenation of nitrosodimethylamine. U.S. production of DMA and its salts was 6×10^6 lbs in 1992 (HSDB 2006). Selected physical and chemical properties of DMA are presented in Table 2.

TABLE 2. Chemical and Physical Properties of Dimethylamine		
Parameter	**Value**	**Reference**
Synonyms	DMA; *N*-methylmethanamine	O'Neil et al. 2001
Chemical formula	C_2H_7N; $(CH_3)_2NH$	O'Neil et al. 2001; Cavender 2001
Molecular weight	45.08	Cavender 2001
CAS Reg. No.	124-40-3	O'Neil et al. 2001
Physical state	Colorless gas; liquid below 6.7°C	NIOSH 2006a
Solubility in water	very soluble	Cavender 2001
Dissociation constant (pK_a)	10.73 at 25°C	HSDB 2006
Vapor pressure	2 atm at 25°C	Cavender 2001
Vapor density (air =1)	1.55	Cavender 2001
Liquid density (water =1)	0.6804 g/mL at 0°C/4°C	Cavender 2001
Melting point	-93 °C	Cavender 2001
Boiling point	7.4 °C	Cavender 2001
Flammability limits	2.8 -14.4%	NIOSH 2006a
Conversion factors	1 ppm = 1.84 mg/m^3 1 mg/m^3 = 0.542 ppm	Cavender 2001

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

There were no available human lethality data.

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold/Odor Awareness

DMA has a characteristic fishy smell at low concentrations, but at higher concentrations (100-500 ppm) the odor becomes similar to that of ammonia (Cavender 2001). Odor thresholds reported for DMA include 0.047 ppm (Leonardos et al. 1969), 0.046 ppm (Ruth 1986), 0.34 ppm (Amoore and Hautala 1983), 0.033 (Ruijten 2005), 0.089 ppm (Stephens 1971), and 0.005-0.016 ppm (Prusakov 1976). A compilation of "rejected/unreviewed" odor threshold data listed values of 0.012-1.6 ppm (AIHA 1989). Olfactory fatigue occurs after prolonged exposure to the methylamines (Sutton, 1963; Deichmann and Gerarde 1969).

A level of distinct odor awareness (LOA) of 0.53 ppm was calculated for DMA using the odor threshold provided by Ruijten (2005). The calculation is shown in Appendix A. The LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, and about 10% of the population will experience a strong odor intensity.

2.2.2. Occupational or Incidental Exposure

No studies were located with quantitative data for DMA concentration, exposure time, and the ensuing response. A group of amines, including DMA, has been reported to cause vision disturbances in workers exposed for several hours to concentrations "too low to cause discomfort

or disability" (Grant and Schulman 1993; Munn 1967). The workers complained of having "blue vision" or "gray vision" or seeing halos around objects. This phenomenon was due to edema of the corneal epithelium and/or light scatter from denatured proteins (Grant and Shulman 1993; Mellerio and Weale 1966), which cleared spontaneously by the next day unless exposure was severe. In that case, the edema and blurred vision took several days to clear and was sometimes accompanied by photophobia and discomfort from roughness of the corneal surface.

The "methylamines" [defined as DMA, TMA (trimethylamine), and MMA (monomethylamine)] have a pungent, fishy odor below 100 ppm, but at air concentrations "somewhere in the range of 100-500 ppm," their odor is indistinguishable from that of ammonia (Deichmann and Gerarde 1969). The authors state that "methylamine vapors" at >100 ppm cause irritation of the nose and throat, violent sneezing, coughing, a burning sensation of the throat, larynx constriction, difficulty breathing, pulmonary congestion, and lung edema. Since the authors do not attribute these effects to "monomethylamine," they are assumed to be applicable for all three methylamines. A secondary source reports that DMA is irritating at 95 ppm (Ruth 1986).

The concentration of DMA and several other amines in workroom air and in the workers' urine were measured over a 24-hour period in a German factory processing DMA (Bittersohl and Heberer 1980). Air measurements taken at 14 locations in the factory (30-minute sampling time) revealed DMA levels of 0.65-18 ppm (10/14 were <7 ppm), as well as MMA at 0.55-29 ppm (13/14 were <3 ppm), and ammonia at 1.4-50 ppm (9/14 ≤12 ppm). It was not noted whether the workers experienced any adverse effect from the exposures. The results of the excretion study are described in Section 4.1.

In 1981, NIOSH conducted a health hazard evaluation at a chemical plant in Kalamazoo, Michigan, in response to a request from the workers' labor union (McGlothlin et al. 1982). The request noted worker exposure to several chemicals, including DMA, inadequate ventilation, and a high rate of worker disability and premature death. Other chemicals used in the same building included epichlorohydrin, ethylene diamine, HCl, acrylamide, isopropyl alcohol, ammonium persulfate, and formaldehyde. NIOSH collected 5 general area and 3 personal air samples in the workers' breathing zone for approximately 3 to 5 hours (0.2 L/minute). DMA air levels ranged from not detected (<0.01 mg/m^3) to 0.63 mg/m^3 (0.34 ppm), thus being well within the OSHA PEL (Permissible Exposure Limit) of 18 mg/m^3. NIOSH personnel noted sharp, irritating odors on several occasions, which were the strongest during the initial charging of DMA into a reactor vessel. NIOSH concluded that the plant had "a potential health hazard from overexposure" to DMA and formaldehyde, and recommended engineering controls, but did not link exposure to the increased rate of worker disability.

2.3. Neurotoxicity

No information was located on neurotoxic effects in humans from DMA inhalation exposure. Simenhoff et al. (1977) examined the correlation between serum levels of DMA and two neurophysiological parameters in uremic dialysis patients: choice reaction time (CRT), and electroencephalograms (EEG). Uremic patients have elevated levels of DMA and trimethylamine (TMA) in the blood, cerebrospinal fluid, and brain relative to healthy people. Results showed a statistically significant correlation between increased CRT and serum DMA levels ($p<0.01$), a fair correlation ($p<0.15$) between serum DMA levels and abnormal EEGs, and significant correlations between serum TMA and both parameters ($p\leq0.003$).

2.4. Developmental/Reproductive Toxicity

No human data were located on potential reproductive or developmental DMA toxicity.

2.5. Genotoxicity

Only one potentially relevant study was found, which examined the ability of the DMA metabolite N-nitrosodimethylamine (NDMA) to form DNA adducts from ingested food (Fay et al. 1997). NDMA can methylate DNA at the 3-methyl position of adenine, and the resulting 3-methyladenine is rapidly removed from the DNA and is found in the urine. Ten male volunteers ate cooked fresh fish (1-23 mg DMA/300g) or cooked previously frozen fish (84-85 mg DMA/300g) for 2 days. Neither type of fish increased the urinary 3-methyladenine levels, suggesting that dietary DMA did not form significant amounts of the carcinogen NDMA, as measured by formation of the DNA adduct 3-MA.

2.6. Carcinogenicity

No human carcinogenicity studies with TMA were found. Because DMA is capable of forming the carcinogen N-nitrosodimethylamine (NDMA) *in vitro*, concern has arisen as to whether DMA is a carcinogen. No human (or animal) studies to date have shown that DMA is a carcinogen, by any route of administration. Fay et al. (1997) examined the urinary content of 3-methyladenine, a byproduct of NDMA methylation of DNA, in volunteers who ingested fish with known DMA content for two days. There was no increase in the urinary 3-methylene levels, indicating that dietary DMA did not form significant amounts of NDMA.

The ACGIH (2005) classifies DMA as A4: not classifiable as a human carcinogen, being an agent that causes concern but cannot be assessed conclusively due to a lack of human or animal data. The German MAK for DMA notes that "reaction with nitrosating agents can result in formation of carcinogenic N-nitrosodimethylamine."

2.7. Summary

No human acute lethality studies were located. The available non-lethal toxicity DMA data lacked either the DMA air concentration, exposure time, and/or the ensuing response. Reported DMA odor thresholds ranged from 0.006 to 1.6 ppm, the most reliable values being 0.047 to 0.34 ppm. Workers exposed to amines, including DMA, had edema of the corneal epithelium that caused "misty" vision with halos several hours after exposure to concentrations that did not cause discomfort (Grant and Schuman 1993; Munn 1967). Vapors of the "methylamines" (defined as DMA, TMA, and MMA) at >100 ppm cause irritation of the nose and throat, violent sneezing, coughing, a burning sensation of the throat, larynx constriction, difficulty breathing, pulmonary congestion, and lung edema (Deichmann and Gerarde 1969). Workplace air DMA concentrations of 0.65-18 ppm were measured in a German factory (Bittersohl and Heberer 1980), and <0.01-0.34 ppm was found in a U.S. chemical plant (McGlothlin 1982), although specific exposure durations and worker response were not provided. Identifying irritating MMA concentrations is confounded by the fact that olfactory fatigue occurs upon exposure to the methylamines (Sutton, 1963; Deichmann and Gerarde 1969; Braker and Mossman 1980).

No information was found on DMA-induced neurological, developmental, or reproductive toxicity in humans. Although there is concern about DMA carcinogenic potential

because it can form the carcinogen N-nitrosodimethylamine (NDMA) *in vitro*, no evidence exists that DMA is carcinogenic *in vivo*. Ingested DMA (from fish) did not increase DNA adduct formation via the putative DMA metabolite NDMA, as measured by urinary 3-methyladenine levels in human volunteers (Fay et al. 1997).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Data on acute inhalation toxicity of DMA for various species of laboratory animals are summarized in Table 3.

TABLE 3. Dimethylamine Acute Lethality Animal Studies

Species	Exposure Time	Concentration (ppm)	Mortality	Effects (Reference)
Rat	6 min	13,700 15,400 17,400 17,500 19,900	2/10 4/10 5/10 5/10 6/10	LC50 = 17,600; gasping, labored breathing, rales, corneal opacity, excessive lacrimation during 14-day observation period; decreased body weight gain during weeks 1 and/or 2 (IRDC 1992a)
	20 min	4620 5940 7740 7860 8860	0/10 4/10 5/10 5/10 8/10	LC50 = 7340; observations as for 6 minute exposure except one female exposed to 8860 ppm had tremors (IRDC 1992a)
	60 min	4900 5040 5080 5120 5920	2/10 1/10 4/10 7/10 8/10	LC50 = 5290 ppm; observations as for 6-minute exposure with decreased body weight gain seen only during week 1 (IRDC 1992a)
	4 hours	2218 – 6624	LC_{50}=4700 ppm	Respiratory dyspnea, restlessness, apathy, convulsions, severe irritation of the eyes and respiratory tract; broncho-pneumonia persisting for 8-14 days (Koch et al. 1980)
	6 hours	600 1000 2500 3983 4740 5058 6119 4540	0% mortality 0% mortality 0% mortality 20% mortality 40% mortality 83% mortality 80% mortality LC_{50}	All had eye irritation, gasping, bloody nose secretion, at ≥3983 ppm there was mortality, salivation, lachrymation, corneal opacity; lesions of nasal passages (all groups), lungs (all groups), liver (≥2500 ppm), eyes (≥1000 ppm) (Steinhagen et al. 1982)
Mouse	2 hours	815 1630 2720 5440 8150 10,900 13,600 26,100	0% mortality 0% mortality 6% mortality 69% mortality 94% mortality 100% mortality 100% mortality LC50	All had lachrymation, face rubbing; at ≥2720 ppm there was mortality, hunched posture, gasping; early decedents had internal organ hemorrhage, especially the lungs; survivors had scattered lung hemorrhage (Mezentseva 1956)
	6 hrs/day for 5 days	510	3/24	Decreased body weight; severe ulceration and necrosis of nasal epithelium; moderate degeneration of olfactory nerves, partly reversed after 72 hrs.; 3/24 died during

TABLE 3. Dimethylamine Acute Lethality Animal Studies				
Species	Exposure Time	Concentration (ppm)	Mortality	Effects (Reference)
				exposure (Buckley et al. 1984)

[a] Mortality estimated from Figure 2 of Steinhagan et al. (1982).

3.1.1. Rats

Koch et al. (1980) investigated the effects of a 4-hour DMA exposure on 8 week old female Wistar rats (10/group) in three experiments (VI, VIIa, and VIIb). In experiments VI and VIIa, rats were exposed to 2218 – 6624 ppm at approximately 22°C, in experiment VIIb, rats were exposed to 2500-6221 ppm at 29°C. A control group was included. Animals were observed for two weeks, as well as during the 4-hour exposure, which was conducted in colorless transparent cages. The chamber humidity, temperature, and CO_2 content (<0.2 vol %) were controlled, and DMA concentration was monitored by gas chromatography. The individual test concentrations were not stated, only that they were a geometric progression series using a factor of 1.25. Within the first hour of exposure, all rats exhibited respiratory dyspnea (sooner at the higher temperature) and at least half the animals exhibited restlessness, apathy, convulsions, rough unkempt fur, and severe irritation of the eyes and respiratory tract (mucous membrane redness and/or hemorrhage of the mouth and nose, conjunctivitis, copious salivation, and spasmodic eye closures). The animals did not eat for 2-3 days and had noisy breathing (whistling, rattling) due to bronchopneumonia, which was associated with lethality. The symptoms increased in severity with dose and persisted for 8-14 days after exposure. A few animals died during exposure, most died on post-exposure days 1-6, and the last death occurred on day 11. The mean survival time was approximately 4.7 days at either temperature, and LC_{50} values calculated using the statistical method of Spearman and Kärber and by probit analysis values were approximately 4700 ppm at 22°C and approximately 5000 ppm at 29°C.

Male Fisher-344 rats were exposed to 600-6119 ppm DMA for 6 hours in an acute lethality study with an observation period of only 48 hours (Steinhagen et al. 1982). A total of 90 rats were split into 7 groups, but the number of animals/group was not stated. Animals were exposed whole-body in 99 L glass and Teflon chambers, and DMA levels were monitored continuously with infrared (IR) spectroscopy. Only 5 of the 7 test concentrations were specified: 600, 1000, 2500, 4000, and 6000 ppm (latter two were also referred to as 3983 and 6119 ppm), but from Figure 2 of the study report, it appears that approximately 4740 and approximately 5060 ppm were also tested. Tissues evaluated microscopically included the lungs, nasal turbinates (4 sections), liver, and eyes.

No animals died at 600, 1000, or 2500 ppm (Steinhagen et al. 1982). The incidence of mortality was not stated, but from report Figure 2 the percent mortality can be estimated to be 20% at 4000 ppm, 40% at 4740 ppm, 90% at 5060 ppm, and 80% at 6000 ppm, indicating a very steep lethality vs. concentration curve. The LC_{50} value was computed as 4540 ppm, although the authors speculated that, based on the severity of the lung lesions at 2500 ppm, an LC_{50} value <4540 ppm would have been obtained with a 14-day observation period. Cageside observations in all groups included eye irritation, gasping, and bloody nose secretion that increased in severity with dose. Rats exposed to ≥4000 ppm also had salivation and lacrimation within an hour of exposure, and corneal opacity after 3 hours. Microscopic evaluation of all groups showed similarly severe congestion, ulcerative rhinitis, and necrosis of the nasal turbinates (most severe

in anterior section), and serous rhinitis of the olfactory epithelium. All groups also had lung lesions including ulcerative tracheitis, epithelial hyperplasia, and emphysema. The severity of the lung lesions was concentration-related, being mild at 600 ppm and progressively more severe and including tracheal bacterial colonization at 2500-6000 ppm. Liver lesions occurred at ≥2500 ppm (fatty degeneration and focal necrosis), and eye lesions at ≥1000 ppm (corneal edema, ulceration, keratitis; degeneration of the iris and lens at ≥4000 ppm).

In an inhalation acute lethality study conducted by the International Research and Development Corporation (IRDC 1992a), CD Sprague-Dawley rats (5/sex/dose; 49-63 days old) were exposed whole-body to anhydrous DMA for 6 minutes (13,700-19,900 ppm), 20 minutes (4620-8860 ppm), or 60 minutes (4900-5920 ppm). Exposure concentrations were generated by diluting DMA gas with air, and were quantitated by IR spectroscopy. Animals were observed daily for 14 days and weighed on days 0, 7, and 14. All animals were necropsied. Observations in all groups included gasping, labored breathing, rales, and corneal opacity immediately after exposure and during the 14-day recovery period. One female exposed for 20 minutes to 8860 ppm had tremors. Decreased body weight gain occurred in all groups during the 1st week, and in some 6 and 20-minute exposure groups during the second week. Necropsy revealed eye lesions (corneal opacity) in most animals at all test concentrations, and lung congestion (red, discolored lungs) of which the incidence roughly increased with test concentration, and was correlated with lethality. Mortality was generally dose-related, and occurred primarily the first two days after exposure. The reported LC_{50} values were 17,600 ppm for 6 minutes, 7340 ppm for 20 minutes, and 5290 ppm for 60 minutes, as calculated by the method of C.I. Bliss (1938). Subsequent analysis of the 6-, 20-, and 60-minute mortality data using EPA BenchMark dose software (Version 1.3.2.) yielded LC_{50} values of 17,650, 7340, and 5290, respectively, and $BMCL_{05}$ values of 380, 2990, and 3500 ppm, respectively. The 60-minute values are not biologically plausible and were associated with the lowest degree of confidence (p-value of 0.076 vs. 0.97 for 6 minutes and 0.41 for 20 minutes), reflecting the poor dose-response of this data set.

3.1.2. Mice

Mezentseva (1956) evaluated lethality in white mice exposed for two hours to 815-26,100 ppm DMA, as shown in Table 4, with a 20-day observation period. Animals (10-16/group) were exposed by a static method in a 100 L chamber, where DMA vapor was generated by blowing air over a predetermined volume of 20% liquid DMA. It was not stated if the DMA concentrations were determined analytically. No deaths occurred at 815 or 1630 ppm. Mice exposed to 815 or 1630 ppm had immediate eye irritation, characterized by lacrimation and pawing of the face. At ≥2720 ppm, the mice had hunched posture, gasped, and one died. At ≥8150 ppm, mice died during exposure, preceded by convulsions and cyanosis of the face and paws. Necropsy of premature decedents revealed hemorrhage of all internal organs, which was severe in the lungs, and peripheral emphysema. The survivors had scattered lung hemorrhage but other organs appeared intact. LC_{50} values were not presented, but Steinhagen et al. (1982) calculated the 14-day LC_{50} as 4725 ppm, and the EPA BenchMark Dose software yields an LC_{50} of 4630 ppm and $BMCL_{05}$ of 1978 ppm.

TABLE 4. Cumulative Mortality of Mice Exposed to DMA for 2 Hours

Concentration (ppm)	No of mice	Observation day (n = 16)						Effects
		0	1	2	6	10	14	
26,100	16	16	16	16	16	16	16	High mortality, gasping, eye irritation, cyanosis, and convulsions; hemorrhage of multiple
13,600	16	16	16	16	16	16	16	

10,900	16	8	11	14	16	16	16	internal organs especially the lungs; survivors had scattered lung hemorrhage
8150	16	3	6	8	14	14	15	
5440	16	0	1	3	8	10	11	
2720	16	0	0	0	0	0	1	One death, eye irritation, gasping, hunched posture; survivors had scattered lung hemorrhage
1630	16	0	0	0	0	0	0	Eye irritation; scattered lung hemorrhage
815	10	0	0	0	0	0	0	

Source: Mezentseva 1956.

The respiratory tract injuries in mice caused by exposure to 510 ppm DMA for 6 hours/day, for 5 days, were examined (Buckley et al. 1984) because 510 ppm was previously determined to be the mouse RD_{50} (Steinhagen et al. (1982) (see Section 3.2.2.). Male Swiss-Webster mice (24) were exposed in a 102-litre glass dynamic exposure chamber, and the DMA concentration was analyzed hourly with IR spectrometry (MIRAN Model 1A). After the last exposure, half of the mice were sacrificed immediately, and the others 72 hours later. The head, trachea, and lungs were evaluated microscopically. Three animals died during exposure. Body weight of all groups was decreased by 10-25% compared to the controls, but returned to normal after 3 days. Respiratory tract lesions occurred primarily in the anterior respiratory epithelium (severe exfoliation, erosion, ulceration, and necrosis) and in the olfactory epithelium in the dorsal meatus (severe ulceration and necrosis; moderate degeneration of olfactory nerves). Mice that were examined 72 hours after exposure ended had decreased nasal inflammation and exudation, but little recovery of the nasal ulceration or degeneration.

3.2. Nonlethal Toxicity

Studies in which animals were treated with one to nine DMA exposures and lethality did not occur are summarized in Table 5.

TABLE 5. Summary of Nonlethal Single and Repeat-Dose Studies

Species	Exposure Time	Concentration (ppm)	Effect	Reference
Rat	10 min	49 – 1576	Respiratory rate inhibition ranged from approximately 8% at 105 ppm to 78% at 1576 ppm; RD_{50} = 573 ppm	Steinhagen et al. 1982
	4 hrs	3140 ppm	Eye and nose discharge, salivation, closed eyes, dyspnea, hunched posture, abnormal gait, swelling; 2/10 F did not recover by 14 days	BASF 1979
	6 hours/day for 1, 2, 4, or 9 days	175	Only nasal tissues examined. Extensive nasal lesions and modified quantity, quality, and flow of mucus. Lesion severity was independent of number of exposures.	Gross et al. 1987
	6 hrs/day x 3 6 hrs/day x 5	500 175, 250	Ulcerative rhinitis, severe congestion, squamous metasplasia in the "respiratory tract", most severe in anterior nasal area (limited study description)	Buckley et al. 1985

TABLE 5. Summary of Nonlethal Single and Repeat-Dose Studies				
	6 hrs/day x 9	175	Inhibited mucociliary function in nasal passages	Morgan et al. (1985)
Mouse	10 min	49 – 1576	Respiratory rate inhibition from approximately 20% at 100 and 200 ppm to 72% at 1576 ppm; RD_{50} = 511 ppm	Steinhagen et al. 1982
	15 min	45-98	RD_{50} = 70 ppm	Gagnaire et al. 1989

3.2.1. Rats

The effect of DMA on the respiratory rate of male Fisher 344 rats was evaluated by Steinhagen et al. (1982). Twenty animals (3-4/concentration) were exposed head-only to 49-1576 ppm DMA for 10 minutes in a glass chamber. DMA concentration was monitored continuously with IR spectroscopy. The animals' respiratory rate was measured using an airtight body plethysmograph. The maximum decrease in the respiratory rate (which occurred in 2-7 minutes), was plotted against concentration to determine the RD_{50}, i.e., the concentration that caused a 50% decrease in the respiratory rate. Respiratory rate inhibition ranged from approximately 8% at 105 ppm to 78% at 1576 ppm (estimated from Figure 1), and an RD_{50} of 573 ppm was calculated by the authors.

Sprague-Dawley rats (10/sex) exposed whole-body to 3140 ppm DMA for 4 hours had no mortality within the 14-day observation period (BASF 1979). The DMA concentration was measured by continuous total carbon analysis. Body weights were measured on day 0, 7, and 14, and found to be decreased in the males (not stated when). The daily clinical signs consisted of watery to red eye and nose discharge, snout wiping, shut eyes, slight salivation, dyspnea, hunched posture, abnormal gait, swelling, and sticky coat. These signs were resolved within 10 days in all rats except 2 females. All animals were necropsied but no gross lesions were found. No further experimental details were provided in the summary report available for this study, the results of which are inconsistent (i.e., much less severe) with the overall body of the DMA data.

F-344 rats exposed five days (6 hours/day) to 175 or 250 ppm DMA, or exposed for three days (6 hours/day) to 500 ppm DMA, had nasal lesions including ulcerative rhinitis, severe congestion, and squamous metaplasia in the "respiratory tract" (undefined) (Buckley et al. 1985). The anterior regions of the nasal passages were the most severely affected. No other study details were provided.

Morgan et al. (1985) studied the effects of inhaled DMA on nasal mucociliary system by video analysis of rapidly excised tissue. Rats were exposed to 175 ppm DMA for 6 hours/day, for 9 days. DMA inhibited the mucociliary function in the posterior half of the maxillary in the nasal passages with normal ciliary activity in the ventral channel. Samples of discharged mucus on the lateral wall were modified by DMA.

Male F-344 rats (6/group) were exposed whole-body to 175 ppm DMA 6 hours/day for 1, 2, 4, or 9 days (or 2 years; see Section 3.3.), to examine the effect of DMA on nasal histopathology and mucociliary function (Gross et al. 1987). Only nasal tissues were examined in the animals. Control animals breathed clean air. Animals were exposed in stainless steel and glass 8 m^3 dynamic airflow chambers, and DMA concentration was measured by an IR

spectrometer every 15 minutes. Animals were sacrificed within 1 hour after exposure, at which time the nasal cavity was dissected and tissues examined microscopically for surface appearance, histology, and mucociliary function, and video recordings were made to determine mucus flow rates. At all time points, treated rats had erosion of the margin of the naso- and maxilloturbinate with fenestration of the adjacent septum, altered mucus flow patterns, and decreased mucus flow rate in the anterior nasoturbinates. Mucus flow was seen bypassing the nasal lesions in some rats exposed for 9 days. Severe histopathological changes occurred in all treated groups, particularly in the anterior nasal passages, and paralleled alterations in mucociliary function. Lesions were seen in the squamous epithelium (focal ulceration, neutrophil accumulation, necrosis, blood vessels plugged with thrombi), respiratory epithelium (erosion and inflammation of nasoturbinates, extensive vacillation of cuboidal, columnar, ciliated, and nonciliated cells), and olfactory epithelium (severe vacuolation, loss of olfactory sensory cells). The severity of the nasal lesions was similar for all exposure durations, possibly due to tissue repair over time.

3.2.2. Mice

Steinhagen et al. (1982) determined the RD_{50} in male Swiss-Webster mice. Thirty animals (3-4/test concentration) were exposed head-only to 49 to 1576 ppm DMA for 10 minutes in a glass chamber. DMA concentration was monitored continuously by IR spectrophotometry. The animals' respiratory rate, as measured during exposure using an airtight body plethysmograph, was maximally decreased after 2-7 minutes. Respiratory rate inhibition ranged from approximately 20% at 100 ppm to 72% at 1576 ppm (estimated from Figure 1), and an RD_{50} of 511 ppm was calculated using the exposure-maximal response curve.

Gagnaire et al. (1989) exposed male Swiss-OF_1 mice oronasally to 45-98 ppm DMA for 15 minutes while measuring the animals' respiratory rate by a plethysmographic technique. The mice were exposed in 200-liter steel inhalation chambers, the vapor was generated by running air through the liquid amine, and the ethylamine concentration was determined by HPLC. A decrease in the respiratory rate was considered to be an indicator of upper airway irritation, and was seen within 30-60 seconds of exposure. The respiratory rate returned to normal within one minute after the end of exposure. The concentration that reduced the respiratory rate by 50% (RD_{50}) was calculated as 70 ppm.

Gagnaire et al. (1989) noted that the RD_{50} of 511 ppm obtained by Steinhagen (1982) using Swiss-Webster mice was 7.3 times higher than the RD_{50} of 70 ppm, although the two laboratories found comparable RD_{50} values for several other aliphatic amines (n-propylamine, n-butylamine). Gagnaire (1989) was unable to explain the discrepancy for DMA, and pointed out that the main difference between the two studies may have been that Steinhagen et al. (1982) used Swiss-Webster mice, whereas Gagnaire et al. (1989) used Swiss-OF_1 mice.

3.3. Subchronic and Chronic Toxicity

The available subchronic and chronic animal studies are summarized in Table 6.

TABLE 6. Summary of Subchronic and Chronic Dimethylamine Exposure Animal Studies

Species	Exposure Time	Conc. (ppm)	Effect	Reference
Monkey, dog, rabbit, rat, guinea pig	90 days continuous	5	Mild pulmonary inflammation in all species; dilated bronchi in rabbits and monkeys	Coon et al. 1970
Rat	6 hr/day, 5 days/wk for 90 days	10	No effects noted	Mitchell et al. 1982
		30	Lower early body weight gain; females had increased absolute weight of lung (approximately 20%), heart, liver, kidney (6-11%)	
		100	Lower early body weight; grossly observed red areas in the liver red in females; increased relative (to body weight) lung weight for males, females (approximately 20%) without histopathological changes	
Monkey (M: 97 ppm; F: 183 ppm), rat, mouse, rabbit, guinea pig	7 hr/day, 5 days/wk, 18-20 wks; eye exam of rat, rabbit, guinea pig at 9 & 45 days	97	Very slight (guinea pig) or slight (rabbit) corneal injury after 9 and 45 days; lesions in liver (rat, rabbit, mouse), kidney (rat, pig); testicular lesions (monkey)	Hollingsworth et al. 1959
		183	Moderate (guinea pig) or slight (rabbit) corneal lesion after 9 and 45 days; increased lung weight in mice; lesions in liver (all but monkey), kidney (rat, pig), testes (rabbit)	
Rat	6 hr/day, 5 days/wk, for 2 years	175	Only nasal tissues were examined. Impaired mucociliary function; nasal lesions most severe in anterior area (squamous metaplasia, inflammation); posterior goblet cell hyperplasia	Gross et al. 1987
Rat, mouse	6 hr/day, 5 days/wk, for 24 mo.	10	Minimal nasal lesions: mice at ≥6 mo.; rats at ≥12 mo.	CIIT 1990
		50	Minimal-moderate nasal lesions, inflammation at ≥6 mo.	
		175	Decreased body weight gain, severe nasal lesions at ≥6 mo.	

Five species of animals were exposed to 0, 97, or 183 ppm DMA for 7 hours a day, 5 days a week, for 18-20 weeks (Hollingsworth et al. 1959). The species included monkey (1 male at 97 ppm, one female at 183 ppm), rats (10/sex/dose), rabbits (2/sex/dose), guinea pigs (6/sex/dose), and mice (5 females/dose). Animals were exposed in a dynamic flow chamber and DMA concentration was measured periodically during exposure. No individual animal data were reported. The eyes of rats, guinea pigs, and rabbits were examined after 9 and 45 days of exposure (after fluorescein staining), revealing slight and moderate corneal injury in guinea pigs and rabbits at 97 ppm and 183 ppm, respectively. The male monkey (97 ppm) was sick and had diarrhea at the end of the exposure period, but it was unclear if this was treatment-related. Mean

lung weight was increased slightly in mice at 183 ppm, but all other organ weights (heart, liver, kidneys, spleen, testes) were unaffected. Microscopic evaluation showed central lobular fatty degeneration and necrosis of the parenchymal cells of the liver in rats, rabbits, and mice at 97 and 183 ppm, and also of guinea pigs at 183 ppm. Slight cloudy swelling of the renal tubular epithelium was seen in rats and guinea pigs at both concentrations. Testicular tubular degeneration was found in the male rabbit at 183 ppm, and in the male monkey (97 ppm), but the male guinea pig tissue was unavailable. A re-analysis of the testicular tissue slides (originally evaluated in 1951, subsequently in 1981) found no treatment-related changes in rats, changes within the limits of normal variability in the rabbits, and moderately reduced spermatogenic activity in the one available monkey tissue section. However, since normal seminiferous tubules were also present on the monkey slide, the pathologist concluded that it was "questionable" if the testicular changes were treatment-related.

Five species of animals were subjected to continuous inhalation exposure of 9 mg/m^3 (5 ppm) DMA for 90 days (Coon et al. 1970). Animals tested were 3 male squirrel monkeys, 2 male beagle dogs, 15 male and female rats (Sprague-Dawley and/or Long-Evans), 15 male and female Princeton-derived guinea pigs, and 3 male New Zealand albino rabbits. The test atmosphere was generated by diluting DMA gas with a stream of air, and the pre-diluted air concentration was measured with a hydrogen flame-ionization detector. Blood samples were collected before and after exposure, and tissue samples were taken from the heart, lungs, liver, kidneys, and spleen from all animals. Analysis revealed no effects on hematology or clinical chemistry parameters, but mild pulmonary inflammation in all species (incidences not reported), and dilated bronchi in 3/3 rabbits and 2/3 monkeys. Results for the controls were not reported. It is unclear why the report also stated that "specific chemically induced histopathological changes were not noted."

In a pilot study, Mitchell et al. (1982) exposed Fisher-344 rats (10/sex/group) whole-body to DMA for 6 hours/day, 5 days/week, for 13 weeks. Nominal test concentrations were 0, 10, 30, or 100 ppm DMA, which corresponded to mean daily analytical (IR spectrophotometer) concentrations of 0.4, 10.5, 29.0, and 99.9 ppm, respectively. The control atmosphere was 2.2-2.6 ppm DMA for the first 6 exposure days, 0.5-0.6 ppm for the final 4 exposure days, and was 0.1 or 0.2 ppm for most other days. No treatment-related clinical signs were observed. No treatment-related effects were noted in the 10 ppm group. The 13-week body weight gain was similar for the control and test groups, although a slightly lower gain occurred during the first two weeks in males and/or females at 30 and 100 ppm. One female exposed to 100 ppm had retinal degeneration, which was not considered treatment-related. All rats were necropsied, and the only gross lesion with an increased incidence was liver red areas (on surface or border) in 3/10 of the females exposed to 100 ppm, vs. none in any other group. Microscopic analysis of the control and tissues from the 100-ppm group did not reveal any differences between the two groups, i.e., incidences of rhinitis or nasal lymphoid hyperplasia, tracheitis, and lung inflammation/lesions did not differ between the two groups. Because the body weight of the rats differed significantly before and after the 22-hour fast preceding necropsy, absolute organ weights were compared to both the pre-fasting and the post-fasting (terminal) body weight. The 30 and/or 100 ppm females had increased absolute and relative weight (to pre-fasting body weight) of the heart (10-11%, $p<0.05$), kidney (6-9%, $p<0.05$), and liver (absolute 6-8%, N.S.; relative 6%, $p<0.05$). The 100 ppm males and 30 ppm females had notably increased absolute lung weight (17%, N.S.; 23%, $p<0.05$), as well as lung-to-prefasting body weight ratio (+18%, $p<0.05$; +22%, $p<0.05$), and lung-to terminal body weight ratio (18%, $p<0.05$; 21%, N.S.). The biological significance of the organ weight changes is unclear.

The effect of lifetime DMA exposure on the mucociliary system in rats was studied in male F-344rats (6/group) exposed to 175 ppm DMA 6 hours/day for 2 years (Gross et al. 1987). Only nasal tissues were examined in the animals. The study methods, and the effects of DMA exposure for 1-9 days in the same study, are described in Section 3.2.1. After exposure for 2 years, the rats had destruction of the anterior third of the nasoturbinate and the anterodorsal margins of the maxilloturbinate. The areas of tissue destruction had modified mucus flow patterns to bypass the affected regions, although regions of mucus pooling were evident. The most severe lesions were found in the anterior nasal passages, and consisted of focal or regional squamous metaplasia and chronic inflammation that correlated with impaired or absent mucociliary function. More posterior changes included moderate to severe goblet cell hyperplasia and posterior extension of ciliated respiratory epithelium into olfactory regions. The effects on mucociliary function and nasal lesions were only minimally more severe than those seen after a single 6-hour exposure (see Section 3.2.1.). This indicates that the mucociliary system continues to function in nasal passages of chronically exposed rats, albeit less efficiently, and that the nasal tissues were repaired to some extent over time.

The Chemical Industry Institute of Toxicology (CIIT 1990) conducted a 2-year chronic toxicity and carcinogenicity study in which female and male F-344 rats and B6C3F1 mice (95/sex/species) were exposed to 0, 10, 50, or 175 ppm DMA for 6 hr/day, 5 days a week. Portions of the study results were published by Barrow et al. (1983), Buckley et al. (1985), and Swenberg et al. (1990). Animals were exposed whole-body under dynamic conditions in stainless steel and glass 8 m^3 chambers, and the DMA concentration was measured analytically (MIRAN 801 IR spectrometer) four times per hour. The animals were weighed weekly or biweekly. Interim sacrifice of 9-10 animals/sex/species was conducted after 6, 12, and 18 months, except male mice were not sacrificed after 12 or 18 months due to excessive mortality from accidental trauma and fighting (housed 5/cage). Animals were observed twice daily and weighed weekly or bi-weekly. Blood was drawn for hematology and serum chemistry evaluation prior to necropsy. Gross pathology and the weight of the liver, kidneys, and brain were evaluated for all animals. Microscopic analysis was conducted on all organs for the control and high dose animals, and on nasal tissues (nose was cut at four levels) and tissues with gross abnormalities from all animals.

After six months, rats and mice exposed to 175 ppm had 5-15% lower weight gain than controls, and nasal lesions were seen at 10 (mice only) 50 and 175 ppm (Buckley et al.1983). No gross pathological changes were seen in rats or mice. Microscopic changes were seen in the nasal mucosa of both species, the most sensitive being the olfactory mucosa. At 10 ppm, mice had minimal focal degeneration of the olfactory nerve bundles. At 50 ppm, both species had moderately severe destruction of olfactory epithelial sensory cells and olfactory nerves (particularly the dorsal meatus), which became severe at 175 ppm. Mild or moderate respiratory epithelial lesions were seen at 175 ppm in both species (non-keratinizing hyperplasia, inflammation with neutrophilic infiltrates), and more severe lesions were in the anterior-most regions (focal epithelial erosion in rats and necrosis in mice). Also at 175 ppm, mice had minimal squamous metaplasia (non-keratinizing) and rats had mild to moderate goblet cell hyperplasia.

The decreased body weight gain persisted throughout the study (up to 23%), and microscopic lesions were restricted to the nasal passages for both species (Barrow et al. 1983, Buckley et al. 1985, Swenberg et al. 1990). Similar types of lesions were seen after 6 months as after 12, 18, 24 months, and the severity increased somewhat after 18 months. The nasal lesions occurred in the respiratory epithelium (focal destruction of the anterior nasoturbinate and nasal

septum, chronic inflammation, and squamous metaplasia in both species, and goblet cell hyperplasia in rats) as well as the olfactory epithelium (loss of olfactory nerves, hypertrophy of Bowman's glands, and distended Bowman's gland ducts). Lesion severity and incidence increased with test concentration but were similar for males and females: 10 ppm caused minimal respiratory epithelium lesions in rats, and in the olfactory epithelium in both species; at 50 ppm both species had minimal changes in the respiratory epithelium and moderate changes in the olfactory epithelium, and mild chronic inflammation; and at 175 ppm, rats had mild goblet cell hyperplasia, and both species had moderate chronic inflammation and severe respiratory and olfactory epithelium lesions that were somewhat more extensive in rats than mice. Chronic exposure to DMA did not increase the incidence of neoplasia in the nasal passages, or any other organ, of rats or mice.

3.4. Neurotoxicity

Neurotoxic effects were seen in several animal studies at concentrations that also caused severe respiratory and ocular lesions, and in some cases death. Koch et al. (1980) found that female Wistar rats exposed for four hours to 2218 – 6624 ppm DMA exhibited restlessness, apathy, convulsions, and rough unkempt fur within the first hour of exposure, which increased in severity with dose and persisted for 8-14 days after exposure. Sprague-Dawley rats that inhaled 3140 ppm DMA for 4 hours had slight salivation, hunched posture, and abnormal gait which resolved within 10 days in most animals (BASF 1979).

Several rat and mouse studies found that repeated exposure to non-lethal DMA concentrations caused degeneration of the olfactory nerves in the anterior nasal epithelium. Swiss-Webster mice exposed to 510 ppm DMA 6 hours/day for 5 days had moderate olfactory nerve degeneration (Buckley et al. 1984). F-344 rats and B6C3F1 mice inhaling 10, 50, or 175 ppm DMA 6 hr/day, 5 days/week for 2 years had minimal olfactory nerve degeneration at 10 ppm, which became moderately severe at 50 ppm, and severe at 175 ppm (CIIT 1990).

3.5. Developmental and Reproductive Toxicity

DMA inhalation developmental or reproductive toxicity studies were not available, but DMA maternal and fetal toxicity was evaluated in two intraperitoneal injection (ip) studies. Pregnant Swiss mice given 13, 45, or 135 mg/kg DMA on gestation day (GD) 8 and sacrificed on GD 18 had no maternal or fetal toxicity, but at 135 mg/kg the implantation loss was increased (20% vs. 8% in controls) with a resulting decrease in litter size (9.8 vs. 10.7 in controls) (Varma et al. 1990). In another study, pregnant CD-1 mice were injected ip with 0.25, 1, 2.5, or 5 mmol/kg DMA daily from gestational day 1 to 17 and dams were killed on GD 18 (Guest and Varma 1991). Embryos were dissected from untreated dams on GD 8 and cultured with up to 2.0 mM DMA. The *in vivo* study showed no maternal toxicity or embryotoxicity, whereas mouse embryo development in culture (growth and macromolecular content) was inhibited.

Testicular tubular degeneration was found in one monkey exposed to 97 ppm and in two rabbits exposed to 183 ppm DMA 7 hours a day, 5 days a week, for 18-20 weeks (additional study details are in Section 3.3.) (Hollingsworth et al. 1959). Microscopic analysis showed degeneration of approximately 10% and 90% of the tubules in the rabbits and monkey, respectively.

3.6. Genotoxicity

The preponderance of the data indicated that DMA is not genotoxic. Negative results were obtained in the Ames *Salmonella typhimurium* reverse mutation test by a number of investigators testing DMA up to cytotoxic levels (>3 mg/plate), with or without metabolic activation. The studies tested *Salmonella* strains TA1535, TA1537, TA97, TA98 and TA100 (Zeiger et al. 1987), strains TA1530, TA1531, TA1532, and TA1964 (a positive response was obtained for TA1530 only with metabolic activation) (Green and Savage 1978), strains TA98, TA100, and TA1538 (Khudoley et al., 1986), strains TA98 and TA100 (Kilkichko et al., 1993), and strains TA100, TA1535, TA1537, and TA1538 (NTP 1980). DMA (≤ 25 μL) was also not mutagenic in *Escherichia coli* Sd-5-73 in the paper disk streptomycin-independence assay (Szybalski 1958).

DMA was not mutagenic in several host-mediated assays (HMA) using the male mouse as the host. In one HMA, male mice were injected intramuscularly with 800 mg/kg DMA and intraperitoneally with *Salmonella* strains TA1951, TA1952, TA1534, or TA1950 (Green and Savage 1978). In another HMA, mice were given 2000 mg/kg DMA by gavage immediately followed by ip injection of *Salmonella* LT2 strain G46 (Couch and Friedman 1975). Mutations were not induced in a mouse HMA when using *Schyzosaccharomyces pombe* as the indicator organism (Dow Chemical Co., 1982).

DMA did not increase the incidence of mutations at the HGPRT locus in Chinese hamster ovary cells (CHO), and was not cytotoxic, when tested at up to a concentration of 22 mM (Hsie et al. 1987). Mayer (1971, 1973) found that DMA did not induce petite mutants or mitotic crossing over in *Saccharomyces cerevisiae*. However, incubation with up to 4 mM DMA induced mitotic gene conversion (*trp* locus) and point reverse mutation (*ilv* locus) in *S. cerevisiae* D7 only in the presence of S9 metabolic activation (Galli et al. 1993).

Chromosome aberrations were not induced in Chinese hamster line cells incubated for 48 hours with 0.012 – 1.47 mM DMA-HCl (Ishidate and Odashima 1977). Three doses were tested, including the 50% inhibition dose. DMA did not increase the incidence of chromosome aberrations or SCE in Chinese hamster lung cells incubated with 6×10^{-4} or 1.2×10^{-3} mL/mL DMA-HCl in saline (Abe and Sasaki 1977). Male Wistar rats that inhaled 0.027 or 0.54 ppm DMA continuously for 15 or 90 days had no increase in bone marrow structural chromosome breakage (Isakova et al. 1971). The incidence of aneuploidy (hyperploid and hypoploid cells), however, approximately doubled in both treatment groups after 90 days of exposure. No increase was found in the incidence of chromosomal aberrations, such as gaps, breaks, and translocations, in the bone marrow and hepatic cells of mice administered an approximately minimum lethal dose of DMA, or in the Chinese hamster cell line KC-1 or in the Yoshida ascites sarcoma line (Odashima, 1976). Hsie et al. (1987), however, saw a marginal increase in SCE in CHO cells from exposure to ≤ 2 mM DMA and in chromosome aberrations from incubation with ≤ 10 mM DMA, using a 2-fold criterion. The marginal increases were seen only in the presence of rat liver S9, and were thought to be possibly due to contaminants.

Unscheduled DNA synthesis was not increased in primary cultures of rat hepatocytes incubated with 3.3 mM DMA (Martelli et al. 1983). DMA did not inhibit mouse testicular DNA synthesis when administered orally to mice at doses of 1000 or 2000 mg/kg, but when DMA was administered together with sodium nitrite, inhibitions of 57 to 65% were observed (Friedman and Staub, 1976). DNA repair levels were not increased in bacterial strains w3110/pol A, WP2try$^-$ (hcr$^-$ and hcr$^+$), H-17, M-45, HJ-15 or HLL3g (Odashima, 1976).

Pool et al. (1990) showed that DMA caused single-strand DNA breaks in hepatocytes of rats, hamsters, and pigs using a 1 or 3-hour culture suspension technique. The breaks were seen in liver cells after treatment with 1 mg/kg DMA, and in kidney and lung cells at 20 mg/kg DMA.

3.7. Carcinogenicity

Because the known human and animal carcinogen dimethylnitrosamine (DMNA) can be produced *in vitro* by reaction of DMA and various N-O derivatives (e.g. sodium nitrite, nitrogen dioxide, etc.), there is a concern about the potential carcinogenicity of DMA *in vivo*. The available chronic studies, however, show no evidence of DMA neoplastic potential. F-344 rats and B6C3F1 mice exposed to 0, 10, 50, or 175 ppm DMA for 6 hr/day, 5 days/week for 2 years had nasal lesions that increased in severity and incidence with test concentration, but there was no increase in the incidence of neoplasia in either species (CIIT 1990; study described in Section 3.2.1.). Benemansky et al. (1981) found that white rats that continuously inhaled 0.08 or 0.4 mg/m^3 DMA (0.04 and 0.22 ppm) for a year did not have a credible increase in blastomas in relation to the level of random tumor formation.

The lack of DMA neoplastic potential was also shown in several oral feeding studies. Groups of 27 rats fed 1600 mg/kg/day of DMA for 2.5 years had no tumors, whereas tumors were found in 12/43 rats simultaneously given 390 mg/kg of sodium nitrite, and in 15/27 rats fed 33 mg/kg DMNA (Rubenchik et al., 1980). Mice (20/sex) given 47 mg/day dietary DMA-HCl (approximately 900 mg/kg/day DMA) for 28 weeks, and held for 12 weeks, had an incidence of lung adenomas and other tumors comparable to, or lower than, the incidence in untreated control mice (Greenblatt et al. 1971).

3.8. Summary

The predominant effect of DMA exposure in all of the available studies was eye and respiratory irritation, which were manifested as lacrimation, nasal lesions, lung lesions, and corneal opacity. Toxicity was also seen in other organs (liver, kidneys, testes) in several studies concomitant with the nasal and eye effects. The calculated 50% decrease (i.e., RD_{50}) in the respiratory rate of male Fisher 344 rats that inhaled DMA for 10 minutes was 573 ppm and in Swiss-Webster mice was 511 ppm (Steinhagen et al. 1982), whereas another laboratory obtained an RD_{50} of 70 ppm from a 15-minute exposure using male Swiss-OF_1 (Gagnaire et al. 1989).

Acute lethality rodent studies determined LC_{50} values of 4700 ppm for female Wistar rats exposed for 4 hours (Koch et al. 1980); approximately 4540 ppm for male Fisher-344 rats exposed for 6 hours but observed only for 48 hours (Steinhagen et al.1982); 17,600 ppm, 7340 ppm, and 5290 ppm for CD Sprague-Dawley rats exposed for 6, 20, and 60 minutes, respectively (IRDC 1992a); and approximately 4700 ppm for white mice exposed for 2 hours (Mezentseva 1956). Reported effects included respiratory dyspnea, gasping, rales, decreased body weight gain, bloody nose secretion, salivation, lacrimation, severe eye irritation, restlessness, apathy, convulsions, and microscopic lesions of the nasal passages, lungs, liver, and eyes.

The effects of single and/or multiple exposures to lower DMA concentrations ($\leq$ 200 ppm) were also primarily characterized by respiratory and ocular irritation, with some degree of nasal tissue repair evident after repeated exposures. F-344 rats exposed for 13 weeks to 10, 30, or 100 ppm DMA had no detectable effects at 10 ppm, and had slightly lower body weight, an increased incidence of liver surface red areas, and increased lung weight at 30 and/or 100 ppm (Mitchell et al. 1982). Only nasal tissues were examined in F-344 rats exposed to 175 ppm for 1,

2, 4, or 9 days, or for 2 years, and the nasal tissues had altered mucus flow patterns and nasal lesions that were similar in nature and severity from exposure for 1-9 days, but were more pervasive and severe after 2 years, suggesting some nasal tissue repair (Gross et al. 1987). F-344 rats and B6C3F1 mice that inhaled 10, 50, or 175 ppm DMA for 2 years had similar types of nasal lesions after 6 12, 18, and 24 months, which increased in severity with test concentration (CIIT 1990).

Two studies evaluated the effect of DMA inhalation on species in addition to rodents. Squirrel monkeys, beagle dogs, rats, guinea pigs, and rabbits that inhaled 5 ppm continuously for 90 days had mild pulmonary inflammation, and rabbits and monkeys also had dilated bronchi (Coon et al. 1970). Guinea pigs and rabbits (but not rats) had slight or moderate corneal lesions after 9 or 45 days of exposure to 97 or 183 ppm DMA (7 hours/day, 5 days/week; Hollingsworth et al. 1959). In the same study, which also tested monkeys, rats, guinea pigs, and mice and total exposure was 18-20 weeks, mice had slightly increased lung weight at 183 ppm; rats, rabbits, mice and guinea pigs had liver and or kidney lesions at 97 and 183 ppm, and testicular tubular degeneration was found in the male rabbit at 183 ppm, and in the male monkey at 97 ppm.

Neurotoxic effects (restlessness, apathy, convulsions, salivation, hunched posture, abnormal gait, and olfactory nerve degeneration) were seen in several animal studies at concentrations that also caused severe respiratory and ocular lesions, and in some cases death. Insufficient data were available to determine DMA developmental and reproductive toxicity. The vast majority of the data indicated that DMA is not genotoxic. Although DMA can form the carcinogen DMNA *in vitro*, several chronic inhalation (and oral) studies found no evidence that DMA induced neoplasia in rodents *in vivo*.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Limited information was available on the metabolism and disposition of DMA by humans. DMA, MMA, and ammonia were measured in the urine of workers over a 24-hour period in a German factory processing DMA (Bittersohl and Heberer 1980). Air levels of the amines at 14 locations in the factory were 0.65-18 ppm DMA (10/14 were <7 ppm), 0.55-29 ppm MMA (13/14 were <3 ppm), and 1.4-50 ppm ammonia (9/14 were ≤12 ppm). Throughout the work day, the exposed workers had significantly greater excretion of DMA than unexposed workers, and a slight increase in urinary pyrrolidine and piperidine. The urinary DMA excretion increased quickly, in parallel with increased DMA exposure, and did not return to pre-exposure levels within 24 hours. Urinary MMA levels were about 10 to 30-fold lower than DMA levels and remained fairly constant throughout the 24-hour period. Four male volunteers (22-37 years old) given 15 mg ^{14}C-DMA-HCl (8.29 mg free base) orally excreted 87% of the administered radioactivity in the urine during the first 24 hours, and 94% over 72 hours (Zhang et al. 1994a). The feces and expired air contained 1-3% of the radioactivity. The vast majority (95%) of the excreted radioactivity was identified as unchanged DMA, and the remainder (5%) was demethylated to MMA.

Pharmacokinetic studies indicated DMA was absorbed rapidly ($t_{½}$ = 8 min) and extensively (bioavailability = 82%) from the gastrointestinal tract, and was quickly excreted ($t_{½}$ = 6-7 h) with a plasma clearance of 190 mL/min. In a sparsely detailed older study, the urine of one test subject who swallowed 8 g DMA-HCl contained 91.5% of the ingested DMA (unchanged) within a day of exposure, after accounting for the endogenous urinary DMA

(Rechenberger 1940). The subject did not experience any adverse effects from the test compound.

The disposition, plasma pharmacokinetics, and metabolism of DMA after a 6-hour inhalation exposure to 10 or 175 ppm ^{14}C-DMA was examined in male F-344 rats (McNulty and Heck 1983). Animals (4/group) were exposed head-only in a 5 L glass chamber and DMA concentration was monitored continuously by IR spectroscopy. Immediately after the 6-hour exposure, some rats were killed for analysis and others were placed in glass metabolism cages for 72 hours to collect ^{14}C excreted in the urine, feces, and air. Blood was collected from the jugular vein of 175 ppm rats periodically for 72 hours after exposure. Urinary metabolites were identified from rats injected i.v. with 20 μCi of ^{14}C-DMA (0.02 mg) and held in metabolism cages for 24 hours.

The distribution of radioactivity 72 hours after exposure was similar at 10 and 175 ppm: 78-87% in urine, 5-12% in feces, 7-8% in tissues and carcass, and 1.5% was exhaled as $^{14}CO_2$. Immediately after exposure to 10 ppm, the respiratory nasal mucosa contained the highest concentration of ^{14}C, followed by 3-fold lower levels in the olfactory mucosa, and 200 to 800-fold lower levels (in decreasing order) in the kidneys, liver, lungs, testes, and brain. Tissue distribution at 175 ppm was similar to that at 10 ppm, but radioactivity levels in the nasal mucosa were only approximately 4-fold greater than at 10 ppm (18 to 21-fold greater for internal organs). The authors speculate that the ability of nasal tissue to absorb DMA was approaching saturation at 175 ppm, and/or DMA elimination was limiting. This is consistent with the finding of similarly severe nasal lesions in rats from a 6-hour exposure to 600 to 6000 ppm, but a dose-related increase in severity of the concomitant tracheal and lung lesions (Steinhagen et al. 1982). At 72 hours after treatment, appreciable ^{14}C levels were found only in the nasal mucosa.

Non-metabolized DMA accounted for 98.7% of the urinary radioactivity, the remainder being unidentified compounds (not MMA) (McNulty and Heck 1983). The finding of exhaled $^{14}CO_2$ suggests that some DMA oxidative metabolism occurred, which appeared to be limiting at 175 ppm, as the rate of $^{14}CO_2$ exhalation for the first two hours after treatment was lower than at 10 ppm. Plasma radioactivity decreased in a biphasic manner, with a half-life of 45 and 64 hours for the two treated rats. The authors speculate that the long half-life may be due to the formation of formaldehyde (plasma $t_{½}$ = 55 hours) as an intermediate in the metabolism of DMA to CO_2, and incorporation of ^{14}C into serum proteins. This theory was supported by a concurrent study by the same laboratory (McNulty et al. 1983), which showed that after the 6-hour exposure to 10 or 175 ppm DMA, the nasal respiratory and olfactory mucosa contained low levels of unextractable radioactive DNA, RNA, and protein. *In vitro* studies (McNulty et al. 1983) showed that microsomes from rat liver and from nasal and tracheal mucosa metabolized DMA to formaldehyde and possibly dimethylhydroxylamine, with the rate of metabolism to formaldehyde being greater in olfactory than respiratory microsomes. Pre-incubation of microsomes with the P-450 inhibitor *n*-octylamine inhibited formaldehyde formation, suggesting that DMA was metabolized by both cytochrome P-450 and FAD-containing monooxygenase.

Zhang et al. (1994b) studied the metabolism and excretion of ^{14}C-DMA-HCl (0.9 mg/kg DMA) administered intragastrically to male Wistar rats and CD-1 mice (4/species). The feces, urine, and exhaled air were collected for 3 days from animals individually housed in glass metabolism cages. Practically identical excretory profiles were determined for the rats and mice, with the urine being the main route of excretion. After 24 hours, the majority of the radioactivity (mean of 90.4% for rats and 90.7% for mice) was found in the urine, indicating that DMA is rapidly absorbed and excreted. The total 72-hour excretion in the urine, feces, exhaled air, and

carcass was 93%, 2%, 1%, and 1%, respectively, of the administered radiolabel. The majority of the 24-hour urinary radiolabel was (unchanged) DMA for both species: rat urine contained 96.6% DMA and 3.4% MMA, and mouse urine contained 95.5% DMA and 4.5% MMA.

4.2. Mechanism of Toxicity

The mechanism of DMA toxicity has not been defined, although its irritant properties are likely related to its high alkalinity (pK_a of 10.73 at 25°C) and corrosiveness to exposed tissues such as skin, eyes, and the respiratory mucosa. Thus, DMA has been reported to cause respiratory and ocular irritation in both humans and animals, which at sufficiently high concentrations caused breathing difficulties, lesions of the eyes and lungs, and death associated with lung lesions. DMA vapor is also associated with systemic effects in animals (neurotoxicity, lesions of liver and kidneys), the etiology of which is less clear.

4.3. Structure-Activity Relationships

Several sets of studies were available which tested DMA, MMA, and TMA, and in some cases also EA, allowing comparison of toxicity among these amines. Gagnaire et al. (1989) exposed male Swiss-OF_1 mice to a series of aliphatic amines including MMA, DMA, TMA, and EA. The mice were exposed oronasally for 15 minutes while their respiratory rates were measured by a plethysmographic technique. A decreased respiratory rate was considered to be an indicator of upper airway irritation. The respiratory rate was decreased within 30-60 seconds of exposure, and returned to normal within one minute after the end of exposure. The concentration that reduced the respiratory rate by 50% (RD_{50}) was calculated to be 61 ppm for TMA, 70 ppm for DMA, 141 ppm for MMA, and 151 ppm for ethylamine. This suggests that as upper respiratory irritants, TMA and DMA are more potent than MMA and EA. Gagnaire et al. (1989) also tested 16 other less closely structurally related aliphatic amines that had RD_{50} values of 51-202 ppm.

The acute toxicities (i.e., LC_{50}) of MMA, DMA, TMA, and/or EA were evaluated by two sets of investigators, with somewhat different results. Koch et al. (1980) compared the toxicity of MMA, DMA, and TMA in female Wistar rats exposed for 4 hours and observed during exposure and for 14 days thereafter. The clinical effects of acute MMA and DMA toxicity were similar, but differed considerably from that of TMA. All three amines caused inspirational dyspnea, but the severity was markedly greater for MMA and DMA than for TMA. MMA and DMA caused severe irritation of exposed mucous membranes (hemorrhage, reddening, salivation, nasal secretion, conjunctivitis, and lacrimation), and the main factor affecting lethality was lung damage (bronchopneumonia). Most deaths occurred on post-exposure days 1-6, and the last deaths were on day 11 or 12. TMA exposure caused a lower incidence and severity of mucous membrane irritation than MMA or DMA, and its primary clinical effect was central nervous system disturbance (excitability, convulsions, and tremors). The CNS effects frequently led to death during exposure, and the last deaths occurred on day 4. CNS effects were barely detectable for MMA or DMA. The LC_{50} values for MMA, DMA, and TMA were approximately 4800, 4600, and 4300 ppm, respectively, indicating relative toxicity of TMA>DMA>MMA.

The International Research and Development Corporation (IRDC 1992a,b; 1993a,b) found somewhat different relative potencies (LC_{50} values) than Koch et al. (1980) for MMA, DMA, TMA, and ethylamine (EA) when exposing Sprague-Dawley rats for 6, 20, or 60 minutes. All four amines caused gasping and/or labored breathing, rales, and corneal opacity during the exposure and recovery period, and decreased body weight primarily during the first week after

exposure. Necropsy revealed eye abnormalities (corneal opacity) and lung congestion (red, discolored lungs) at almost all test concentrations, from treatment with each of the amines. The incidence of gross lung lesions generally correlated with lethality. Most deaths occurred within 3 days of exposure to MMA, within 2 days of exposure to DMA, during exposure to TMA, and the time of death was not specified for EA. LC_{50} values for MMA, DMA, TMA, and EA were, respectively 24,400, 17,600, not determined for TMA, and 22,200 ppm for 6 minutes; 9600 7340, 12,000, and 9136 ppm for 20 minutes; 7110, 5290, 7910 and 5540 ppm for 60 minutes. Thus the relative acute toxicities (causing lethality) for all exposure durations were DMA>EA>MMA>TMA.

DMA is part of a group of amines that has been implicated as causing visual disturbances in workers (blue vision, halos due to corneal edema), as has the structurally related compound dimethylethylamine . Ståhlbom et al. (1991) evaluated the ability of known concentrations of dimethylethylamine to cause eye irritation and visual disturbances in a group of four male volunteers (age 33-53, non-smokers). Exposure for 8 hours to 3.3 or 6.7 ppm was without effect, whereas 13 ppm was irritating to eyes of 3/4 workers and caused visual disturbances in 1 worker. Exposure for 15 minutes to 27 or 53 ppm was irritating to eyes of 3/4 workers but caused no visual disturbance.

4.4. Other Relevant Information

4.4.1. Species Variability

The conducted acute lethality and non-lethal toxicity studies indicated that rats and mice are similarly sensitive to DMA toxicity. Rats and mice both experienced primarily respiratory tract and ocular lesions in the acute lethality studies. Although the two species were exposed for different durations, there appeared to be little difference in their LC_{50} values [e.g. rat LC_{50} for 1 and 4 hours of 5,290 ppm and 4,700 ppm, respectively (IRDC 1992a; Koch et al., 1980) vs. mouse 2-hour LC_{50} of 4725 ppm (Mezentseva 1956)]. Rats and mice also had similar toxic effects, primarily nasal lesions, in a 2-year study where they were exposed 6 hours/day to 10, 50, or 175 ppm DMA (CIIT 1990).

Variability among other species was less clear, as only multiple-exposure studies were available, and there were some inconsistencies among the findings. Monkeys, rats, dogs, guinea pigs, and rabbits that inhaled 5 ppm continuously for 90 days all had mild pulmonary inflammation, but the rabbits and monkeys also had dilated bronchi (Coon et al. 1970). Thus it is possible that rabbits and monkeys are somewhat more sensitive to DMA lung toxicity than rats, dogs, and guinea pigs, but it is unclear if a perceptible difference in sensitivity would exist for a single exposure.

Hollingsworth et al. (1959) exposed monkeys, rats, mice, guinea pigs, and rabbits to 97 and/or 183 ppm DMA 7 hours/day, 5 days/week for 18-20 weeks. Lesions were found in the cornea (rabbits, guinea pigs, not mice, others not examined), liver (all but monkey) kidney (rats, guinea pigs) and testes (male rabbit, monkey). Liver and kidney lesions were not reported for mice or rats in the 2-year CIIT (1990) study, which found primarily nasal lesions. The report by Hollingsworth et al. (1959) did not specify that the nasal passages were examined in detail and may have missed the nasal lesions seen by CIIT (1990). Despite these differing results, this study helps to define species variability for DMA-induced eye lesions, which were of comparable severity and increased with dose in guinea pigs and rabbits, the latter being a good model for human eyes.

4.4.2. Susceptible Populations

No susceptible human populations were identified.

4.4.3. Concentration-Exposure Duration Relationship

No concentration-exposure scaling was used to derive the AEGL-1 values, and the same value was adopted for 10 minutes to 8 hours, because the critical endpoint of mild sensory irritation is not expected to vary greatly over time.

Values for AEGL-2 and AEGL-3 were time scaled using the concentration-time relationship $C^n \times t = k$ (ten Berge et al. 1986). ten Berge et al. (1986) determined that the concentration-time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranged from 0.8 to 3.5. Three LC_{50} studies with lethality data at five exposure durations were used to obtain a value of n = 2.8 by linear regression, including the IRDC (1992a) 6, 20, and 60-minute rat LC_{50} values, the Mezentseva (1956) 2-hour mouse LC_{50}, and the 4-hour LC_{50} from Koch et al. (1980), as shown in Appendix B. The Steinhagen et al. (1982) acute lethality rat study was not used because the animals were observed for only 2 days after exposure. Because the value of n was derived from data which ranged from 6 minutes to 4 hours, time scaling was performed for 10 minutes to 8 hours for the AEGL-2 and AEGL-3 derivations.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

The available human DMA studies are fragmented and lack quantitative exposure-response data, and are therefore inappropriate for derivation of AEGLs. For example, worker exposure to unknown DMA concentrations reportedly caused temporary vision disturbances (mistiness of vision, halos due to corneal edema), and in severe cases was accompanied by photophobia and corneal surface roughness (Grant and Schulman 1993; Munn 1967). Secondary sources reported that DMA exposure (duration unknown) is irritating at 95 ppm (Ruth 1986), and that "methylamines" (defined as DMA, TMA, and MMA) at >100 ppm cause irritation of the nose and throat, difficulty breathing, pulmonary congestion, and lung edema (Deichmann and Gerarde 1969).

5.2. Summary of Animal Data Relevant to AEGL-1

DMA inhalation studies that are potentially useful for AEGL-1 derivation include:

(1) the 13-week study in which Fisher-344 rats were exposed for 6 hours/day, 5 days/week to 10, 30, or 100 ppm DMA (Mitchell et al. 1982). No effects were noted at 10 ppm; the 30 and/or 100 ppm rats had initially lower body weight gain and increased lung weight (approximately 20%), and females had slightly increased weight of heart, liver, and kidneys (6-11%). No treatment-related signs of irritation in the nasal passages and no lesions of the lungs were observed;

(2) the respiratory rate inhibition study (Steinhagen et al. 1982) in which male Fisher 344 rats and Swiss-Webster mice were exposed to 49 to 1576 ppm DMA for 10 minutes. Inhibition for rats ranged from approximately 8% at 105 ppm to 78% at 1576 ppm

(RD_{50} of 573 ppm) and for mice ranged from approximately 20% at 100 ppm to 72% at 1576 ppm (RD_{50} of 511 ppm);

(3) the RD_{50} study of Gagnaire et al. (1989), in which male Swiss-OF_1 exposed to 45-98 ppm DMA for 15 minutes had a calculated RD_{50} of 70 ppm;

(4) the studies in which male F-344 rats exposed to 175 ppm for 6 hours/day for 1-9 days or 2 years had altered mucus flow and extensive nasal lesions that were similar after 1-9 days of exposure, and minimally more severe after two years (Morgan et al. 1985; Gross et al. 1987), but only the nasal tissues were examined;

(5) the multi-species study in which squirrel monkeys, dogs, rats, guinea pigs, and rabbits that continuously inhaled 5 ppm DMA for 90 days had mild pulmonary inflammation, and rabbits and monkeys had dilated bronchi (Coon et al. 1970);

(6) the multi-species study where monkeys, rats, rabbits, guinea pigs, and mice inhaled 97 and/or 183 ppm DMA 7 hours/day, 5 days/week, for 18-20 weeks, but the eyes of guinea pigs, rabbits, and rats were examined after fluorescein staining on days 9 and 45 (Hollingsworth et al. 1959). At either time point, guinea pigs had very slight and rabbits had slight corneal injury at 97 ppm, which at 183 ppm was moderate in guinea pigs and slight in rabbits;

(7) the 2-year chronic study in which F-344 rats and B6C3F1 mice were exposed to 10, 50, or 175 ppm DMA (6 hours/day, 5 days/week) (CIIT 1990). At 6 months and thereafter, all groups had lower body weight gain and nasal lesions that increased in severity with test concentration, and only moderately with time (after ≥18 months).

5.3. Derivation of AEGL-1

The AEGL-1 was derived from the Mitchell et al. (1982) study, based on the absence of histopathological lesions in male and female F-344 rats following exposure to 100 ppm for 13 weeks. Although nasal lesions were not observed at this concentration, DMA is an irritant, and acute exposure to a higher concentration, 175 ppm for 6 hours, resulted in nasal pathology (Gross et al. 1987). A total uncertainty factor of 10 was applied, including 3 for interspecies uncertainty and 3 for human variability, because nasal irritation from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and is not likely to vary greatly between among species or humans (NRC 2001). Because there is adaptation to the mild irritation that defines the AEGL-1, the resulting 10 ppm concentration was applied to all AEGL-1 exposure durations (Table 7). Calculations are summarized in Appendix C. A category graph of the AEGL values in relation to the data is in Appendix D.

TABLE 7. AEGL-1 Values for Dimethylamine

10-min	30-min	1-h	4-h	8-h
10 ppm (18 mg/m³)	10 ppm (18 mg/m³)	10 ppm (18 mg/m³)	10 ppm (18 mg/m³)	10 ppm (18 mg/m³)

The AEGL-1 is supported by the sensory irritation study of Steinhagen et al. (1982) conducted with male Swiss-Webster mice. According to Alarie (1981), exposure to the RD_{50}

(510 ppm) is intolerable to humans, 0.1 of the RD_{50} (i.e., 51 ppm) for several hours to days causes sensory irritation in humans, 0.01 x RD_{50} (5 ppm) should cause no sensory irritation, and 0.03 x RD_{50} (15 ppm) in an estimate of an occupational exposure threshold limit value (TLV). The AEGL-1 of 10 ppm falls between the non-irritating concentration and the estimated occupational exposure threshold value.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

The limited human data summarized for AEGL-1 in Section 5.1. are inadequate for direct derivation of AEGL-2 values, but provide useful reference information. Secondary sources reported that workers exposed to unknown DMA concentrations had temporary vision disturbances that were in severe cases accompanied by photophobia and corneal surface roughness. DMA is irritating at 95 ppm, and "methylamines" (DMA, TMA, and MMA) at >100 ppm cause irritation of the nose and throat, difficulty breathing, pulmonary congestion, and lung edema (Deichmann and Gerarde 1969; Ruth 1986; Grant and Schulman 1993).

6.2. Summary of Animal Data Relevant to AEGL-2

(1) Only one acute-exposure study was available, in which rats exposed for 6 hours to 175 ppm had severe nasal lesions, but no other tissues were examined (Gross et al. 1987). This study has the drawback that only one exposure concentration was tested, and it was unknown if the threshold of AEGL-2 effects was reached, particularly since 9 daily exposures (6 hours/day) to 175 ppm caused lesions of similar severity. The other available repeat exposure studies either found only nasal lesions, or found lesions in additional organs, but after exposure for ≥90 days. Single-exposure acute lethality studies were considered for AEGL-2 derivation, utilizing concentrations at which no lethality occurred. These include:

(2) the IRDC (1992a) rat study in which a 20-minute exposure to 4620 ppm caused gasping, labored breathing, rales, corneal opacity, lacrimation, decreased body weight gain (histopathology not performed), and the next higher concentration (5940 ppm) caused mortality; an adjustment factor of 3 could be applied to 4620 ppm because toxicity exceeded the scope of AEGL-2, to yield a 20-minute POD of 1386 ppm;

(3) the Steinhagen et al. (1982) mouse study with a 48-hour observation period in which all test concentrations (600-6000 ppm) caused eye irritation, gasping, bloody nose secretion, and lesions of the lungs and nasal passages, and lesions were seen in the eyes at ≥1000 ppm, liver at ≥2500 ppm, and mortality occurred at ≥4000 ppm; an adjustment factor of 2 could be applied to 600 ppm because toxicity exceeded the scope of AEGL-2, to yield a 6-hour POD of 300 ppm; and

(4) the LC_{50} mouse study of Mezentseva (1956), in which all test groups (815-26,100 ppm) had lacrimation, face rubbing, effects at ≥2720 ppm included mortality, hunched posture, and gasping, and animals that survived the 14-day observation had scattered lung hemorrhage; an adjustment factor of 3 could be applied to 815 ppm because toxicity exceeded the scope of AEGL-2, to yield a 2-hour POD of 272 ppm.

6.3. Derivation of AEGL-2

The study chosen for AEGL-2 derivation was that of Gross et al. (1987), in which male F-344 rats were exposed to 175 ppm DMA for 6 hours. Rats had extensive nasal lesions and modified quantity, quality, and flow of mucus. Although reversibility was not addressed in this study, it should be noted that nasal and lung lesions were absent in male and female F-344 rats following a 13-week repeat exposure to the next lowest concentration, 100 ppm, also for 6 hours/day (Mitchell et al. 1982). A total uncertainty factor of 10 was applied, including 3 for interspecies uncertainty and 3 for human variability, because nasal irritation from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and is not likely to vary greatly between species or among humans (NRC 2001). An adjustment factor of 0.5 was applied because the effect was considered mild and below the definition of an AEGL-2 effect. Time-concentration scaling for 10 minutes to 8 hours was performed using the relationship $C^n \times t = k$ (ten Berge et al. 1986), where n = 2.8 was calculated from a linear regression of three LC_{50} studies with lethality data at five exposure durations, ranging from 6 minutes to 4 hours. The derived AEGL-2 values are shown in Table 8, and the calculations are detailed in Appendix C. A category graph of the AEGL values in relation to the data is in Appendix D.

TABLE 8. AEGL-2 Values for Dimethylamine

10-min	30-min	1-h	4-h	8-h
130 ppm (240 mg/m³)	85 ppm (160 mg/m³)	66 ppm (120 mg/m³)	40 ppm (74 mg/m³)	32 ppm (59 mg/m³)

The AEGL-2 is supported by the sensory irritation study of Steinhagen et al. (1982) conducted with male Swiss-Webster mice. According to Alarie (1981), exposure to the RD_{50} is intolerable to humans, 0.1 of the RD_{50} (i.e., 51 ppm) for several hours to days causes sensory irritation in humans, 0.01 x RD_{50} (5 ppm) should cause no sensory irritation, and 0.03 x RD_{50} (15 ppm) in an estimate of an occupational exposure threshold limit value (TLV). The 1- to 8-hour AEGL-2 values fall close to or lower than the 51 ppm concentration predicted to be tolerable for hours to days. The 10- and 30-minute values are close to the 100 ppm concentration that failed to cause nasal lesions in a chronic study with rats (Mitchell et al. 1982).

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No appropriate human studies were located.

7.2. Summary of Animal Data Relevant to AEGL-3

Four acute lethality studies were available, of which three were considered for AEGL-3 derivation. The Steinhagen et al. (1982) rat 6-hour LC_{50} study was not used because the animals were observed for only 48 hours after treatment. The three sets of potentially useful lethality data consist of:

(1) the Mezentseva (1956) 2-hour white mouse data and calculated $BMCL_{05}$ of 1978 ppm; mice had lacrimation, face rubbing, hunched posture, gasping; early decedents had internal organ hemorrhage that was severe in the lungs, and survivors had scattered lung hemorrhage. A 2-hour $BMCL_{05}$ of 1978 ppm was calculated;

(2) the IRDC (1992a) CD Sprague-Dawley rat 6, 20, and 60 minute data and their calculated $BMCL_{05}$ values of 380, 2990, and 3500 ppm, respectively; the rats had gasping, labored breathing, rales, corneal opacity, lacrimation, decreased body weight gain, and reddened lungs (not examined microscopically). The 20-minute exposure data set was considered the most robust, since the 6-minute data yielded a $BMCL_{05}$ value that was not credible, and the 60-minute data had a low degree of statistical confidence due to a poor dose-response ($p = 0.14$); and

(3) the Koch et al. (1980) 4-hour female Wistar rat study, which cannot be used to calculate the $BMCL_{05}$, but 1/3 of the LC_{50} could be used as an approximation of the lethality threshold; the rats had respiratory dyspnea, restlessness, apathy, convulsions, severe irritation of the eyes and respiratory tract, and bronchopneumonia persisting for 8-14 days.

7.3. Derivation of AEGL-3

The 2-hour $BMCL_{05}$ of 1978 ppm for mice from the study of Mezentseva (1956) was used as the point of departure for the AEGL-3. A total uncertainty factor of 10, 3 for species variability and 3 for human variability was applied. Reasoning for the choice of uncertainty factors was the same as for the AEGL-1. Time-concentration scaling for 10 minutes to 8 hours was performed using the relationship $C^n \times t = k$ (ten Berge et al. 1986), where $n = 2.8$ was calculated from a linear regression of three LC_{50} studies with lethality data at five exposure durations, ranging from 6 minutes to 4 hours. The developed AEGL-3 values are supported by the IRDC (1992a) study in which rats were exposed to DMA for 20 minutes. A total uncertainty factor of 10 applied to the $BMCL_{05}$ of 2990 ppm yields slightly lower values. The derived AEGL-3 values are shown in Table 9, and calculations are detailed in Appendix C. A category graph of AEGL values in relation to the data is in Appendix D.

TABLE 9. AEGL-3 Values for Dimethylamine

10-min	30-min	1-h	4-h	8-h
480 ppm (880 mg/m³)	320 ppm (590 mg/m³)	250 ppm (460 mg/m³)	150 ppm (280 mg/m³)	120 ppm (220 mg/m³)

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

The AEGL-1 was based on a NOAEL for histopathological lesions of the nasal passages of the rat in a repeat-exposure study. No nasal lesions were observed in rats following exposure to 100 ppm for 6 hours/day for 13 weeks (Mitchell et al. 1982). In accordance with NRC (2001) in relation to direct sensory irritants, inter- and intraspecies uncertainty factors of 3 each for a total of 10 were applied. The resulting value of 10 ppm was not time-scaled because there is adaptation to the mild irritation that defines the AEGL-1.

The AEGL-2 was based on the study of Gross et al. (1987), in which male F-344 rats were exposed to 175 ppm DMA for 6 hours. Rats had extensive nasal lesions and modified quantity, quality, and flow of mucus. Although reversibility was not addressed in this study, it should be noted that nasal and lung lesions were absent in male and female F-344 rats following a 13-week repeat exposure to the next lowest concentration, 100 ppm, also for 6 hours/day

(Mitchell et al. 1982). A total uncertainty factor of 10 was applied, including 3 for interspecies uncertainty and 3 for human variability, because nasal irritation from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and is not likely to vary greatly between species or among humans. An adjustment factor of 0.5 was applied because the effect was considered minor and below the definition of an AEGL-2 effect. Time-concentration scaling for 10 minutes to 8 hours was performed using the relationship $C^n \times t = k$ (ten Berge et al. 1986), where n = 2.8 was calculated from a linear regression of three LC_{50} studies with lethality data at five exposure durations, ranging from 6 minutes to 4 hours.

The 2-hour $BMCL_{05}$ for mice (1978 ppm) from the study of Mezentseva (1956) was used as the point of departure for the AEGL-3. A total uncertainty factor of 10, 3 for species variability and 3 for human variability was applied. Reasoning for the choice of uncertainty factors was the same as for the AEGL-1. Time-concentration scaling for 10 minutes to 8 hours was performed using the relationship $C^n \times t = k$ (ten Berge et al. 1986), where n = 2.8 was calculated from a linear regression of three LC_{50} studies with lethality data at five exposure durations, ranging from 6 minutes to 4 hours.

A summary of the AEGL values for DMA and their relationship to one another are shown in Table 10. A derivation summary is provided in Appendix E.

TABLE 10. Summary of AEGL Values for Dimethylamine

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Non-disabling)	10 ppm (18 mg/m³)	10 ppm (18 mg/m³)	10 ppm (18 mg/m³)	10 ppm (18 mg/m³)	10 ppm (18 mg/m³)
AEGL-2 (Disabling)	130 ppm (240 mg/m³)	85 ppm (160 mg/m³)	66 ppm (120 mg/m³)	40 ppm (74 mg/m³)	32 ppm (59 mg/m³)
AEGL-3 (Lethal)	480 ppm (880 mg/m³)	320 ppm (590 mg/m³)	250 ppm (460 mg/m³)	150 ppm (280 mg/m³)	120 ppm (220 mg/m³)

8.2. Comparison with Other Standards and Guidelines

The existing standards and guidelines for DMA are shown in Table 11. The ACGIH (1996) TLV-TWA of 5 ppm and STEL of 15 ppm are based on chronic studies with rats and mice that found minimal lesions in the nasal passages after exposure to 10 ppm for 6 months to 2 years (Buckley et al. 1985; CIIT 1990). The ACGIH (2005) entry for DMA has a carcinogenicity notation A4, indicating that DMA is not classifiable as a human carcinogen, but is an agent of concern that cannot be assessed conclusively due to a lack of human or animal data. The AEGL-1 of 10 ppm is the same as the NIOSH REL and OSHA PEL. The ERPG-1 of 0.6 ppm is based on odor, whereas the AEGL-1 is based on sensory irritation, manifest at a higher concentration. The 1-hour ERPG-2 of 100 ppm is based on sensory irritation, particularly the studies of Steinhagen et al. (1982) and Barrow et al. (1983). It was believed that no adverse health effects would result from this exposure. The AEGL-2 1-hour value is slightly lower and is based on a different study of sensory irritation. The 1-hour ERPG-3 of 350 ppm was based on the studies conducted by IRDC (1992a), particularly the 60-minute data which yielded an LC_{10} for rats of 3500 ppm. The AEGL-3 is slightly lower and is based on a different lethality study. The NIOSH IDLH of 500 ppm was based on the Steinhagen et al. (1982) rat study, in which a 6-hour LC_{50} value of 4540 ppm was obtained upon testing 600-6000 ppm, and the rats had severe

eye and nasal irritation, corneal opacity, and severe nasal and lung lesions (NIOSH 2006b). The IDLH is higher than the 30-minute AEGL-2 and AEGL-3 values.

TABLE 11. Extant Standards and Guidelines for Dimethylamine (ppm)

Standard	Exposure Duration				
	10 min	**30 min**	**1 h**	**4 h**	**8 h**
AEGL-1	10	10	10	10	10
AEGL-2	130	85	66	40	32
AEGL-3	480	320	250	150	120
ERPG-1 (AIHA) [a]			0.6		
ERPG-2 (AIHA)			100		
ERPG-3 (AIHA)			350		
PEL-TWA (OSHA) [b]					10
IDLH (NIOSH) [c]		500			
REL-TWA (NIOSH) [d]					10
TLV-TWA (ACGIH) [e]					5
TLV-STEL (ACGIH) [f]	15 (15 min)				
MAK (Germany) [g]					2
MAK Peak Limit (Germany) [h]	4 (15 min)				
MAC (Netherlands) [i]					1

[a] **ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association** (AIHA 2005)
The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.

The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action.

The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects.

[b] **OSHA PEL-TWA (Occupational Safety and Health Administration, Permissible Exposure Limits - Time Weighted Average)** (OSHA 1989) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[c] **IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** (NIOSH 2006b) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

[d] **NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** (NIOSH 2006a) is defined analogous to the ACGIH-TLV-TWA.

[e] **ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH 2005) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[f] **ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit)** (ACGIH 2005) is defined as a 15-minute TWA exposure which should not be exceeded at any time during the workday even if the 8-hour TWA is within the TLV-TWA.

[g] **MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration])** (Deutsche Forschungsgemeinschaft [German Research Association] 2007) is defined analogous to the ACGIH-TLV-TWA.

[h] **MAK Spitzenbegrenzung (Peak Limit [Category I, excursion factor 2])** (Deutsche Forschungsgemeinschaft [German Research Association] 2007) constitutes the maximum average concentration to which workers can be exposed for a period of 15 minutes, no more than 4 times per shift at 1-hour intervals; total exposure may not exceed the 8-hour MAK.

[i] **MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration])** (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is defined analogous to the ACGIH-TLV-TWA.

9. REFERENCES

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APPENDIX A: Derivation of the Level of Distinct Odor Awareness

The level of distinct odor awareness (LOA) represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, and about 10% of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception. The LOA derivation follows the guidance given by van Doorn et al. (2002).

The odor detection threshold (OT_{50}) for dimethylamine was reported to be 0.033 ppm (Ruijten 2005).

The concentration (C) leading to an odor intensity (I) of distinct odor detection (I=3) is derived using the Fechner function:

$I = kw \times \log (C / OT_{50}) + 0.5$

For the Fechner coefficient, the default of kw = 2.33 will be used due to the lack of chemical-specific data:

$3 = 2.33 \times \log (C / 0.000032) + 0.5$ which can be rearranged to
$\log (C / 0.000032) = (3 - 0.5) / 2.33 = 1.07$ and results in
$C = (10^{1.07}) \times 0.033 = 0.388$ ppm

The resulting concentration is multiplied by an empirical field correction factor. It takes into account that in every day life factors such as sex, age, sleep, smoking, upper airway infections and allergy as well as distraction, may increase the odor detection threshold by up to a factor of 4. In addition, it takes into account that odor perception is very fast (about 5 seconds) which leads to the perception of concentration peaks. Based on the current knowledge, a factor of 1/3 is applied to adjust for peak exposure. Adjustment for distraction and peak exposure lead to a correction factor of 4 / 3 = 1.33

LOA = C x 1.33 = 0.388 ppm x 1.33 = 0.53 ppm

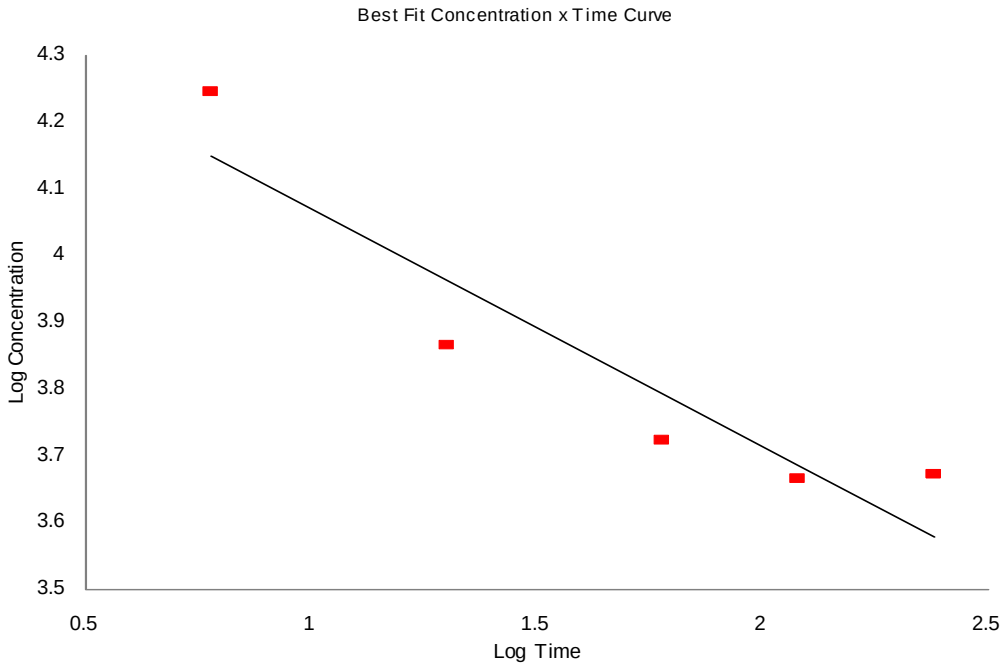
The LOA for dimethylamine is 0.53 ppm.

APPENDIX B: Time-Scaling Calculations

Since the minor effects associated with exposure to low concentrations of irritant gases do not increase over time, the AEGL-1 value was held constant over all time durations.

The DMA concentration-time relationship used to develop AEGL-2 and AEGL-3 values was described using the ten Berge et al. (1986) relationship $C^n \times t = k$. A value of n = 2.8 was calculated for the exponent n from a linear regression of the IRDC (1992a) 6, 20, and 60-minute rat LC_{50} values, the Mezentseva (1956) 2-hour mouse LC_{50}, and the 4-hour rat LC_{50} from Koch et al. (1980) (See Section 4.4.3).

		Log	Log		Regression Output:	
Time	**Conc.**	**Time**	**Conc.**			
6	17600	0.7782	4.2455			
20	7340	1.3010	3.8657		Intercept	4.4263
60	5290	1.7782	3.7235		Slope	-0.3558
120	4630	2.0792	3.6656		R Squared	0.8620
240	4700	2.3802	3.6721		Correlation	-0.9284
					Degrees of Freedom	3
n = 2.81 k = 2.8E+12					Observations	5



APPENDIX C: Derivation of AEGL Values

Derivation of AEGL-1

Key study: Mitchell, R.I., K.L. Pavkov, W.D. Kerns, and M.M. Connell. 1982. Final Report on a 90-day inhalation toxicology study in rats exposed to dimethylamine. Conducted by Battelle Laboratories, Columbus OH, for the CIIT. CIIT Docket #216N2. Submitted to U.S. EPA 02/03/1983; Doc. ID FYI-OTS-0282-0213SU.

Toxicity endpoint: NOAEL of 100 ppm for nasal irritation/lesions in a 6-hour/day 13-week repeat exposure study with rats

Scaling: None, because sensory irritation is not expected to vary greatly over time, and the key study exposure duration was 6 hours. Furthermore, there is adaptation to the mild irritation that defines the AEGL-1.

Uncertainty Factors: Total uncertainty factor: 10
Interspecies: 3: Sensory irritation from a direct-acting, alkaline irritant is not expected to vary greatly between species.
Intraspecies: 3: Sensory irritation or discomfort is a direct surface-contact effect not subject to pharmacokinetic differences between individuals; in addition, the key study was multiple-exposure.

Modifying Factor: None

Calculations:

10-minute AEGL-1	100 ppm/10 = 10 ppm [18 mg/m^3]
30-minute AEGL-1	100 ppm/10 = 10 ppm [18 mg/m^3]
1-hour AEGL-1	100 ppm/10 = 10 ppm [18 mg/m^3]
4-hour AEGL-1	100 ppm/10 = 10 ppm [18 mg/m^3]
8-hour AEGL-1	100 ppm/10 = 10 ppm [18 mg/m^3]

Derivation of AEGL-2

Key Study: Gross, E.A., D.L. Patterson, and K.T. Morgan. 1987. Effects of acute and chronic dimethylamine exposure on mucociliary apparatus in the nose of the F-344 rat. Toxicol. Appl. Pharmacol. 90: 359-376.

Toxicity Endpoint: Nasal lesions in rats following 6-hour exposure to 175 ppm, considered mild and reversible

Time scaling: $C^n \times t = k$ (ten Berge et al. 1986) where n = 2.8 was calculated from a linear regression of three LC_{50} studies with lethality data at five exposure durations, ranging from 6 minutes to 4 hours. Scaling was used for 10 minutes to 8 hours.

Uncertainty Factors: Total uncertainty factor: 10
Interspecies: 3: Sensory irritation from a direct-acting, alkaline irritant is not expected to vary greatly between species.
Intraspecies: 3: Sensory irritation from a direct-acting, alkaline irritant is not expected to vary greatly among humans.

Modifying Factor: 0.5; based on the absence of nasal irritation and lung inflammation/lesions in a 13-week repeat exposure study, 100 ppm for 6 hours/day (Mitchell et al. 1982), the endpoint was considered mild and reversible.

Calculations:

$$C^{2.8} \times t = k$$

$$(175 \text{ ppm})^{2.8} \times 360 \text{ minutes} = 6.87 \times 10^8 \text{ ppm}^{2.8}\text{-min}$$

10-min AEGL-2: $C^{2.8} \times 10 \text{ min} = 6.87 \times 10^8 \text{ ppm}^{2.8}\text{-min}$; C = 629 ppm
629/3x3x0.5 = 130 ppm (240 mg/m^3)

30-min AEGL-2 $C^{2.8} \times 30 \text{ min} = 6.87 \times 10^8 \text{ ppm}^{2.8}\text{-min}$; C = 425 ppm
583/3x3x0.5 = 85 ppm (160 mg/m^3)

1-hour AEGL-2 $C^{2.8} \times 60 \text{ min} = 6.87 \times 10^8 \text{ ppm}^{2.8}\text{-min}$; C = 330 ppm
330/3x3x0.5 = 66 ppm (120 mg/m^3)

4-hour AEGL-2 $C^{2.8} \times 240 \text{ min} = 6.87 \times 10^8 \text{ ppm}^{2.8}\text{-min}$; C = 202 ppm
202/3x3x0.5 = 40 ppm (74 mg/m^3)

8-hour AEGL-2 $C^{2.8} \times 480 \text{ min} = 6.87 \times 10^8 \text{ ppm}^{2.8}\text{-min}$; C = 158 ppm
158/3x3x0.5 = 32 ppm (59 mg/m^3)

Derivation of AEGL-3

Key Study: Mezentseva, N.V. 1956. Data on the Toxicity of Dimethylamine. Gigiyena i Sanitariya (Hygiene and Sanitation) 21:47-49.

Toxicity Endpoint: Threshold for lethality in rats; calculated 2-hour $BMCL_{05}$ of 1978 ppm

Time scaling: $C^n \times t = k$ (ten Berge et al. 1986) where n = 2.8 was calculated from a linear regression of three LC_{50} studies with lethality data at five exposure durations, ranging from 6 minutes to 4 hours. Scaling was used for 10 minutes to 8 hours.

Uncertainty Factors: Total uncertainty factor: 10
Interspecies: 3: Very similar LC_{50} values, and a similar mode of toxicity, were found for two species (rats and mice).
Intraspecies: 3: Little human variability is expected in the response to a direct-acting very basic irritant gas (lethality due to lung injury), and there is no evidence that metabolism in involved in DMA toxicity.

Modifying Factor: None

Calculations:

$$C^{2.8} \times t = k$$

$$(1978 \text{ ppm})^{2.8} \times 120 \text{ minutes} = 2.035 \times 10^{11} \text{ ppm}^{2.8}\text{-min}$$

10-min AEGL-3: $C^{2.8} \times 10 \text{ min} = 2.035 \times 10^{11} \text{ ppm}^{2.8}\text{-min}$; C = 4804 ppm
4804/10 = 480 ppm (880 mg/m^3)

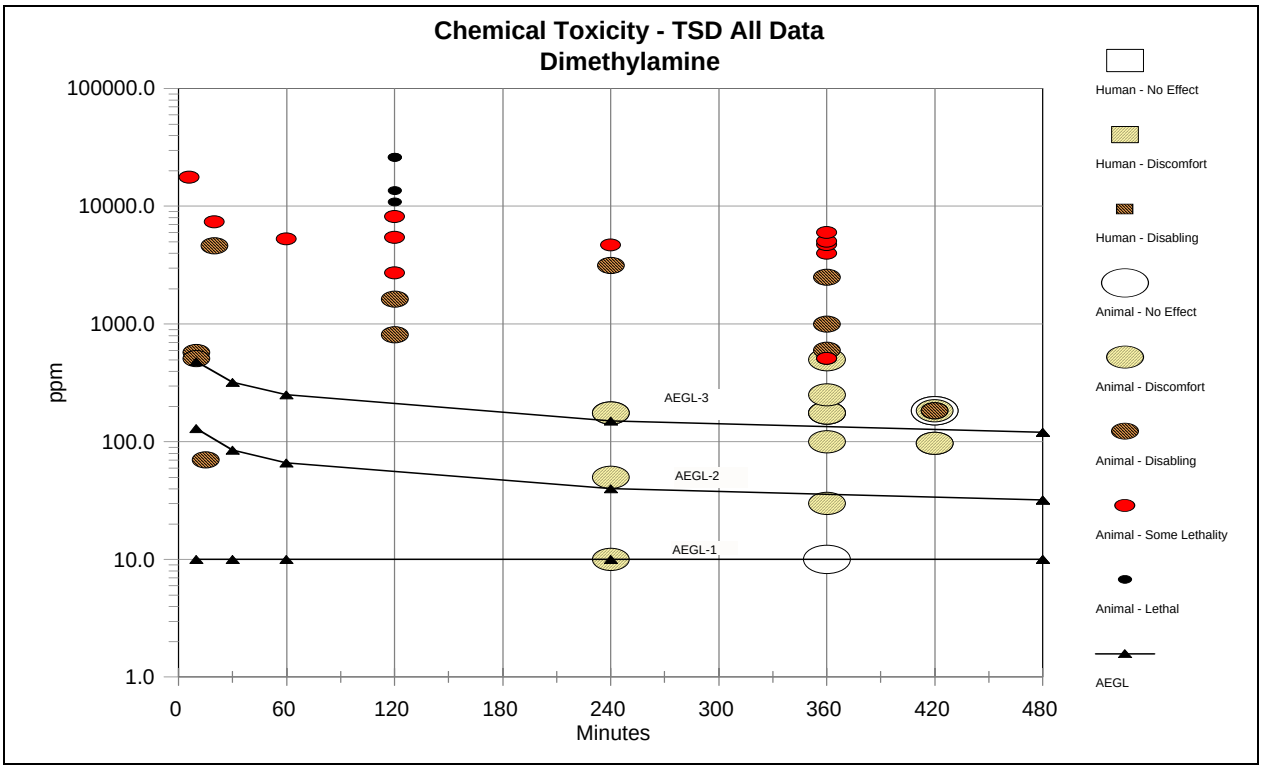
30-min AEGL-3: $C^{2.8} \times 30 \text{ min} = 2.035 \times 10^{11} \text{ ppm}^{2.8}\text{-min}$; C = 3245 ppm
3245/10 = 320 ppm (590 mg/m^3)

1-hour AEGL-3: $C^{2.8} \times 60 \text{ min} = 1.08 \times 10^{11} \text{ ppm}^{2.8}\text{-min}$; C = 2533 ppm
2533/10 = 250 ppm (460 mg/m^3)

4-hour AEGL-3: $C^{2.8} \times 240 \text{ min} = 1.08 \times 10^{11} \text{ ppm}^{2.8}\text{-min}$; C = 1544 ppm
1544/10 = 150 ppm (280 mg/m^3)

8-hour AEGL-3: $C^{2.8} \times 480 \text{ min} = 1.08 \times 10^{11} \text{ ppm}^{2.8}\text{-min}$; C = 1205 ppm
1205/10 = 120 ppm (220 mg/m^3)

APPENDIX D: Category Plot for Dimethylamine



The data included in this plot are shown below, and consist of the single and multiple-exposure data for DMA. For the Hollingsworth et al. (1959) study, the only results shown are those of the eye examination conducted after 9 days in rats, guinea pigs, and rabbits.

For Category, 0 = No effect, 1 = Discomfort, 2 = Disabling, SL = Some Lethality, 3 = Lethal							
Source	**Species**	**Sex**	**# Exposures**	**ppm**	**Minutes**	**Category**	**Comments**
NAC/AEGL-1				10	10	AEGL	NOAEL for nasal inflammation/lesions
NAC/AEGL-1				10	30	AEGL	(Mitchell et al. 1982)
NAC/AEGL-1				10	60	AEGL	
NAC/AEGL-1				10	240	AEGL	
NAC/AEGL-1				10	480	AEGL	
NAC/AEGL-2				130	10	AEGL	Nasal lesions (Gross et al. 1987)
NAC/AEGL-2				85	30	AEGL	
NAC/AEGL-2				66	60	AEGL	
NAC/AEGL-2				40	240	AEGL	
NAC/AEGL-2				32	480	AEGL	
NAC/AEGL-3				480	10	AEGL	2-hour $BMCL_{05}$ in mice (Mezentseva 1956)
NAC/AEGL-3				320	30	AEGL	
NAC/AEGL-3				250	60	AEGL	
NAC/AEGL-3				150	240	AEGL	
NAC/AEGL-3				120	480	AEGL	
IRDC 1992a	rat	m,f	1	4620	20	2	4/10 had corneal opacity; gasping, lacrimation, decreased body weight gain
	rat	m,f	1	17600	6	sl	LC_{50} in rats; exposures to 13,700-19,900 ppm
	rat	m,f	1	7340	20	sl	LC_{50} in rats; exposures to 4620-8860 ppm
	rat	m,f	1	5290	60.0	sl	LC_{50} in rats; exposures to 4100 - 8670 ppm
Steinhagen et al. 1982	rat	m	1	600	360	2	Severe eye irritation, nasal and lung lesions at 48-hour observation
	rat	m	1	1000	360.0	2	Severe eye irritation, nasal, lung and eye lesions
	rat	m	1	2500	360.0	2	Severe eye irritation, nasal, lung, eye, and liver lesions
	rat	m	1	4000	360.0	sl	Severe eye irritation; nasal, lung, eye, and liver lesions, death
	rat	m	1	4740	360	sl	Severe eye irritation; nasal, lung, eye, and liver lesions, death
	rat	m	1	5058	360	sl	Severe eye irritation; nasal, lung, eye, and liver lesions, death

For Category, 0 = No effect, 1 = Discomfort, 2 = Disabling, SL = Some Lethality, 3 = Lethal							
Source	**Species**	**Sex**	**# Exposures**	**ppm**	**Minutes**	**Category**	**Comments**
	rat	m	1	6000	360	sl	Severe eye irritation; nasal, lung, eye, and liver lesions, death
Koch et al. 1980	rat	f	1	4700	240	sl	LC_{50} in female Wistar rats; exposure concentrations unknown
Mezentseva 1956	mouse	?	1	815	120	2	Lacrimation, scattered lung hemorrhage
	mouse	?	1	1630	120	2	Lacrimation, scattered lung hemorrhage
	mouse	?	1	2720	120	sl	Lacrimation, severe lung hemorrhage, gasping, death
	mouse	?	1	5440	120	sl	Lacrimation, severe lung hemorrhage, gasping, death
	mouse	?	1	8150	120	sl	Lacrimation, severe lung hemorrhage, gasping, death
	mouse	?	1	10900	120	3	Lacrimation, severe lung hemorrhage, gasping, 100% mortality
	mouse	?	1	13600	120	3	Lacrimation, severe lung hemorrhage, gasping, 100% mortality
	mouse	?	1	26100	120	3	Lacrimation, severe lung hemorrhage, gasping, 100% mortality
Buckley et al. 1984	mouse	m	5	510	360	sl	Severe nasal lesions, 3/24 died during exposure
Steinhagen et al. 1982	rat	m	1	573	10	2	RD_{50} for F-344 rats exposed to 49-1576 ppm
Steinhagen et al. 1982	mouse	m	1	511	10	2	RD_{50} for Swiss-Webster mice exposed to 49-1576 ppm
Gagnaire et al. 1989	mouse	m	1	70	15	2	RD_{50} for OF-1 mice exposed to 45-98 ppm
BASF 1979	rat	m	1	3140	240	2	Eye and nose irritation, dyspnea, hunched posture, abnormal gait; study is inconsistent with body of data
Gross et al. 1987	rat	m	1	175	360	1	Extensive nasal lesions and altered mucus flow; only nasal tissues examined
Gross et al. 1987	rat	m	2, 4, 9	175	360	1	Extensive nasal lesions and altered mucus flow; only nasal

For Category, 0 = No effect, 1 = Discomfort, 2 = Disabling, SL = Some Lethality, 3 = Lethal							
Source	**Species**	**Sex**	**# Exposures**	**ppm**	**Minutes**	**Category**	**Comments**
							tissues examined
Buckley et al. 1985	rat	?	3	500	360	1	Severe congestion and nasal lesions; limited study data
	rat	?	5	175	360	1	Severe congestion and nasal lesions; limited study data
	rat	?	5	250	360	1	Severe congestion and nasal lesions; limited study data
Mitchell et al. 1982	rat	m,f	65	10	360	0	No effects found from 90-day exposure
		m,f	65	30	360	1	Decreased initial body weight gain, altered organ weights
		m,f	65	100	360	1	Decreased initial body weight gain, altered organ weights, no histopathology
Hollingsworth et al. 1959	g. pig	m,f	9	97	420	1	Very slight corneal "injury" seen by fluorescein staining after exposure 9
		m,f	9	183	420	2	Moderate corneal "injury" after exposure 9
Hollingsworth et al. 1959	rabbit	m,f	9	97	420	1	Slight corneal "injury" seen by fluorescein staining after exposure 9
		m,f	9	183	420	1	Slight corneal "injury" after exposure 9
Hollingsworth et al. 1959	rat	m,f	9	183	420	0	No corneal "injury" seen by fluorescein staining after 9 exposures
CIIT 1990	rat	m,f	130	10	240	1	Minimal nasal lesions after 6 months exposure
	rat	m,f	130	50	240	1	Minimal to moderate nasal lesions after 6 months exposure
	rat	m,f	130	175	240	1	Severe nasal lesions, decreased body weight gain after 6 months

APPENDIX E: Derivation Summary of Acute Exposure Guideline Levels for Dimethylamine (CAS Reg. No. 124-40-3)

AEGL-1 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
10 ppm (18 mg/m³)	10 ppm (18 mg/m³)	10 ppm (18 mg/m³)	10 ppm (18 mg/m³)	10 ppm (18 mg/m³)

Key Reference: Mitchell, R.I., K.L. Pavkov, W.D. Kerns, and M.M. Connell. 1982. Final Report on a 90-day inhalation toxicology study in rats exposed to dimethylamine. Conducted by Battelle Laboratories, Columbus OH, for the CIIT.

Test Species/Strain/Number: Rat/F-344/10 per sex per group

Exposure Route/Concentrations/Durations: Inhalation/0, 10, 30, 100 ppm/6 hours/day, 5 days/week, 13 weeks

Effects: No clinical signs, no histopathological lesions at any treatment concentration

Endpoint/Concentration/Rationale: NOAEL for irritation of the nasal passages

Uncertainty Factors: Total uncertainty factor: 10

Interspecies:

3: Sensory irritation from an alkaline, direct-acting contact irritant is not expected to differ greatly among species

Intraspecies:

3: Mild sensory irritation or discomfort is a direct surface-contact effect, not subject to pharmacokinetic differences between individuals; in addition, the key study was a multiple-exposure study.

Modifying Factor: None

Animal to Human Dosimetric Adjustment: Not applied

Time Scaling and Scaling Process: None; using the same value for 10 minutes to 8 hours was considered appropriate because there is adaptation to the mild sensory irritation that defines the AEGL-1.

Data Adequacy: Several studies, including Steinhagen et al. (1982) addressed sensory irritation. The key endpoint of sensory irritation was considered relevant to an AEGL-1 effect in humans. The next higher tested concentration, 175 ppm for 6 hours (Gross et al. [1987]) caused nasal lesions, an effect above the definition of an AEGL-1.

AEGL-2 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
130 ppm (240 mg/m³)	85 ppm (160 mg/m³)	66 ppm (120 mg/m³)	40 ppm (74 mg/m³)	32 ppm (59 mg/m³)

Key Reference: Gross, E.A., D.L. Patterson, and K.T. Morgan. 1987. Effects of acute and chronic dimethylamine exposure on mucociliary apparatus in the nose of the F-344 rat. Toxicol. Appl. Pharmacol. 90: 359-376.

Test Species/Strain/Number: Male F-344 rats/ 6 per group.

Exposure Route/Concentrations/Durations: Inhalation/175 ppm/6 hours per day for 1, 2, 4, or 9 days

Effects: Focal degeneration of squamous epithelium in the nasal vestibule and extensive vacuolation of both the respiratory and olfactory epithelia in the anterior nasal passages; squamous metaplasia, repair, and some resolution following chronic exposure.

Endpoint/Concentration/Rationale: 175 ppm for 6 hours; lesions considered reversible/repairable

Uncertainty Factors: Total uncertainty factor: 10

Interspecies:

3: Interspecies variability was small, based on the similar response (nasal, eye, and lung lesions) at comparable concentrations for several animal species.

Intraspecies:

3: The critical endpoint nasal irritation form a direct-acting very basic irritant gas is not expected to vary greatly among humans.

Modifying Factor: 0.5; the endpoint was considered below the definition of an AEGL-2

Animal to Human Dosimetric Adjustment: Not applied

Time Scaling: $C^n \times t = k$ (ten Berge et al. 1986) where n = 2.8 was calculated from a linear regression of three LC_{50} studies with lethality data at 5 exposure durations, ranging from 6 minutes to 4 hours. Scaling was used for 10 minutes to 8 hours.

Data Adequacy: The values are supported by acute and chronic sensory irritation studies including those of Steinhagen et al. (mouse RD_{50}; 1982) and Mitchell et al. (1982), respectively. The developed AEGL-2 values, which range from 32 to 130 ppm, are, with the exception of the 10-minute value, below levels of "methylamines" (i.e. >100 ppm) reported by secondary sources to cause irritation of the nose and throat, difficulty breathing, pulmonary congestion, and lung edema in humans (Deichmann and Gerarde 1969).

AEGL-3 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
480 ppm (880 mg/m³)	320 ppm (590 mg/m³)	250 ppm (460 mg/m³)	150 ppm (280 mg/m³)	120 ppm (220 mg/m³)

Key Reference: Mezentseva, N.V. 1956. Data on the Toxicity of Dimethylamine. Gigiyena i Sanitariya (Hygiene and Sanitary) 21: 47-49.

Test Species/Strain/Number: White mice/strain not reported/10-16 per group

Exposure Route/Concentrations/Durations: Inhalation/815, 1630, 2720, 5440, 8150, 10,900, 13,600, 26,100 ppm/2 hours

Effects:

Concentration	Mortality
815 ppm	0% mortality
1630 ppm	0% mortality
2720 ppm	0% mortality
5440 ppm	20% mortality
8150 ppm	40% mortality
10,900 ppm	83% mortality
13,600 ppm	80% mortality
4725 ppm	Calculated LC_{50}

Lacrimation, hunched posture, gasping; survivors had scattered lung hemorrhages

Endpoint/Concentration/Rationale: The calculated $BMCL_{05}$ of 1978 ppm (EPA BenchMark dose software, v. 1.3.2) was used as an estimate of the 2-hour lethality threshold in mice

Uncertainty Factors: Total uncertainty factor: 10

Interspecies:

3: Very similar LC_{50} values, and a similar mode of toxicity, were found for two species (rats and mice).

Intraspecies:

3: Little human variability is expected in the response to a direct-acting very basic irritant gas (lethality due to lung injury), and there is no evidence that metabolism is involved in DMA toxicity.

Modifying Factor: None

Animal to Human Dosimetric Adjustment: Not applied

Time Scaling: $C^n \times t = k$ (ten Berge et al. 1986) where n = 2.8 was calculated from a linear regression of three LC_{50} studies with lethality data at 5 exposure durations, ranging from 6 minutes to 4 hours. Scaling was used for 10 minutes to 8 hours.

Data Adequacy: The available acute lethality studies were adequate for deriving AEGL-3. The developed AEGL-3 values are supported by a lethality study with rats (IRDC 1992a).