ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR MONOMETHYLAMINE (CAS Reg. No. 74-89-5)

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 toxicologic 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

Methylamine (monomethylamine; MMA) is a primary aliphatic amine which has an offensive fishy odor. It is a degradation product of alkaloids and proteins in many species, and is an endogenous metabolite of epinephrine, sarcosine, and creatine in humans. MMA is a high production volume chemical in the U.S. with a wide range of industrial applications as a compressed gas and as a 40% aqueous solution. MMA is a potent eye and mucous membrane irritant, which largely determines the clinical picture of MMA vapor intoxication. In both humans and animals, MMA causes respiratory system toxicity (impaired breathing, lung congestion and edema) that can lead to death, as well as corneal opacity. Animal studies have also shown MMA-induced toxicity to the liver, brain, and hematopoietic and nervous systems.

MMA is metabolized in mammals by semicarbazide-sensitive amine oxidase (SSAO), to form formaldehyde, hydrogen peroxide, and ammonia. Elevated levels of endogenous MMA and/or increased SSAO activity, and the increased levels of the MMA metabolites, are believed to cause vascular endothelial damage, and are associated with a number of disease states (diabetes, heart disease, non-diabetic obesity, Alzheimer's disease, cerebral arteriopathy, inflammatory liver disease, atherosclerosis, and congestive heart failure). Individuals with increased SSAO activity may therefore be a sensitive sub-population. Several studies indicate that SSAO activity is greater in human than rodent tissues (Lewinsohn et al. 1978; Boomsma et al. 2000).

The level of distinct odor awareness (LOA) for MMA is 0.56 ppm. 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 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 is based on two studies. The point of departure in the Kinney et al. (1990) study was a single 6-hour exposure of male CD rats to 75 ppm. Exposures were actually repeated for two-weeks (10 exposures) and resulted in mild irritation of the nasal turbinates. Repeat exposure to higher concentrations (250 and/or 750 ppm) caused more severe nasal lesions and /or systemic toxicity and mortality. A single 6-hour exposure to 75 ppm is expected to cause no more than mild sensory irritation. In the second study, exposure of male Wistar rats to 465 ppm for 30 minutes was a NOAEL for notable signs of discomfort, but resulted in interstitial pneumonitis progressing to fibrosis (Jeevaratnam and Sriramachari 1994; Sriramachari and Jeevaratnam 1994). A total UF of 10 was applied to the point of departure in both studies, including 3 for interspecies uncertainty and 3 for human variability, because mild 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 the well-conducted study of Kinney et al. (1990) was a repeat exposure study and the effect was essentially a NOAEL, a modifying factor of 0.5 was applied. The study of Sriramachari and Jeevaratnam (1994) used only one exposure, the description of the study results lacked details, and the endpoint was above the definition of an AEGL-1. In the absence of robustness and in light of the seriousness of the endpoint, a modifying factor of 3 was applied to the 465 ppm value for a combined uncertainty and modifying factor of 30. Application of these uncertainty and modifying factors to the respective studies yields an AEGL-1 value of 15 ppm. The resulting AEGL-1 value of 15 ppm was adopted for 10 minutes to 8 hours because mild sensory irritation is not expected to vary greatly over time.

AEGL-2 values were derived from the Kinney et al. (1990) repeat exposure study. Ten exposures of male CD rats to 250 ppm, 6 hours/day, caused reversible lesions of the anterior respiratory tract. The severity of the lesions (focal erosion and ulceration of the nasal turbinate mucosa) was attributed to the repeat exposure scenario, i.e., repeated local irritation. Lesions did not extend into the trachea or lungs. Lesions following a single exposure would be less severe and also reversible. 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). Time scaling, $C^n \times t = k$ where $n = 1.9$, was based on rat lethality data ranging from 6 to 60 minutes (data set of IRDC 1992a). Lethality data were used to time-scale the AEGL-2 values because local irritation is considered the first step leading to pulmonary irritation and death.

The AEGL-3 was based on the study provided by the International Research and Development Corporation (IRDC 1992a) in which rats were exposed to concentrations of 17,600-35,300 ppm for 6 minutes, 10,600-17,400 ppm for 20 minutes, or 4100-8670 ppm for 60 minutes. The mortality response data of IRDC (1992a) were used in the probit-analysis based dose-response program of ten Berge (2006) to calculate the LC_{01} at each AEGL-3 exposure duration. The program incorporated all of the data at the 6-, 20-, and 60-minute time points. The data indicated a time-scaling value of 1.9 ($C^{1.9} \times t = k$). A total uncertainty factor of 10 was applied, including 3 for interspecies uncertainty and 3 for human variability, because lethality 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).

AEGL values for MMA are presented in Table 1.

TABLE 1.Summary of AEGL Values for Monomethylamine

Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL–1[1] (Non-disabling)	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)	Mild sensory (nasal) irritation in rats (Kinney et al. 1990; Sriramachari and Jeevaratnam and 1994)
AEGL–2 (Disabling)	160 ppm (200 mg/m^3)	92 ppm (120 mg/m^3)	64 ppm (80 mg/m^3)	31 ppm (39 mg/m^3)	21 ppm (27 mg/m^3)	Reversible nasal lesions in rats (Kinney et al. 1990)
AEGL–3 (Lethal)	910 ppm (1200 mg/m^3)	510 ppm (650 mg/m^3)	350 ppm (440 mg/m^3)	170 ppm (220 mg/m^3)	110 ppm (140 mg/m^3)	LC_{01} in rats (IRDC 1992a)

[1] A Level of Distinct Odor Awareness (LOA) of 0.56 ppm was calculated for MMA based on the odor threshold of 0.035 ppm provided by Ruijten (2005). 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

Methylamine (monomethylamine; MMA) is a primary aliphatic amine which has an offensive fishy odor. It is a natural degradation product of alkaloids and proteins in many vegetable and animal species. Human endogenous sources of MMA also include epinephrine, sarcosine, and creatine (Dar et al. 1985). MMA is a potent eye and mucous membrane irritant, which largely determines the clinical picture of MMA vapor intoxication. In both humans and animals, MMA at sufficiently high concentrations has caused severe toxicity to the respiratory system (impaired breathing, lung congestion and edema) leading to death, as well as corneal opacity. Animal studies have also shown MMA-induced toxicity to the liver, brain, and hematopoietic system, as well as behavioral changes.

MMA is a colorless, easily liquefiable gas that is soluble in water, alcohol, acetone, and benzene. It has a wide range of industrial applications as a compressed gas and as a 40% aqueous solution. MMA is used in organic synthesis, as a fuel additive, in manufacture of pharmaceutical preparations, insecticides, surfactants, explosives, plastic monomers, ion exchange resins, rubber accelerates, cellulose acetate, rayon, photographic developers, and in the tanning and dyeing industries (HSDB 2006). MMA is manufactured by several methods, including heating methanol, ammonium chloride, and zinc chloride to approximately 300°C; reacting ammonia and methanol at high temperature and pressure in the presence of silica-alumina catalyst; and by the reductive amination of formaldehyde (Cavender 2001). In the U.S., MMA is a high production volume chemical with an annual production volume of over 50 million pounds in 1985 (HSDB 2006). In 1997, the demand for the methylamines (MMA, dimethylamine [DMA], and trimethylamine [TMA]) was estimated as 318 million lbs (Chemical Marketing Reporter 1997). Selected physical and chemical properties of MMA are listed in Table 2.

TABLE 2. Physical and Chemical Properties of Monomethylamine

Parameter	Value	Reference
Synonyms	Monomethylamine; MMA; amino-methane; methanamine;	O'Neil et al. 2001
Chemical Formula	CH_3NH_2	NIOSH 2006a
Molecular Weight	31.06	O'Neil et al. 2001
CAS Registration Number	74-89-5	O'Neil et al. 2001
Physical State	Colorless gas	NIOSH 2006a
Water Solubility	Very soluble	Cavender 2001
Acid ionization constant, pK_a	10.65 at 25°C	Cavender 2001
Vapor Pressure	2 atm at 25°C	Cavender 2001
Vapor Density (Air =1)	1.07	Cavender 2001
Liquid Density (water =1)	0.7691	Cavender 2001
Melting Point	-93.5°C	O'Neil et al. 2001
Boiling Point	-6.3°C at 760 torr	O'Neil et al. 2001
Explosive Limits	4.9 to 20.7 vol% in air	NIOSH 2006a
Conversion Factors	1 ppm = 1.27 mg/m^3; 1 mg/l=783 ppm	NIOSH 2006a

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No quantitative human acute exposure studies were located. Yang et al. (1995) described the care and treatment of 35 people accidentally exposed to MMA vapor that leaked from an overturned truck carrying liquid MMA through a residential area in China. The exposure duration was unknown, but was certainly no more than a few hours. The exposed group of 18 males and 17 females were 7-71 years old, and were hospitalized within 7-8 hours of exposure. All had varying degrees of respiratory toxicity, including difficulty breathing, hoarse voice, dry hurting throat, pink saliva, and chemical burns that led to edema and tissue damage of the nose, mouth, and lungs. Many had lesions of the eyes (lids stuck together and painful, cloudy cornea, impaired eyesight) and painful burns on exposed skin, with drainage and bleeding. Other symptoms included coma, fainting, dizziness, headache, nausea, vomiting, stomach ache, black stool, high body temperature (up to 39.5°C), rapid heart rate, circulatory failure, and seizures. The patients were treated with oxygen and various antibiotics and rinses (boric acid, sodium bicarbonate, hydrogen peroxide), and every effort was made to keep their respiratory systems clear of the viscous mucous lumps of tissue that obstructed breathing. No one lost their eyesight, but 6 of the 35 people died within 10 days of exposure. The period of highest mortality was 1-4 days after exposure, the major cause being chemical burns and tissue death of the lungs.

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold/ Odor Awareness

MMA has a pungent, fishy odor. The MMA odor awareness threshold in humans was reported as 0.021 ppm (Leonardos et al. 1969), 0.02-9.4 ppm (Ruth 1986), 0.0009-4.7 ppm (AIHA 1989), and 3.2 ppm (Amoore and Hautala 1983). An odor awareness threshold (Lim_{olf}) of 0.008 ppm was determined in 31 volunteers aged 18 to 50 by Dabaev (1981). Olfactory fatigue to MA occurs readily (Sutton 1963).

A level of distinct odor awareness (LOA) of 0.56 ppm was calculated for MMA based on an odor threshold of 0.035 ppm (Ruijten 2005). 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. Calculations for the LOA are in Appendix A.

2.2.2. Incidental or Occupational Exposure

No studies were located in which the MMA air concentration, duration of exposure, and resulting effects were all quantified. The concentration of MMA, DMA (dimethylamine), and ammonia 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 MMA levels of 0.55-29 ppm (13/14 were <3 ppm), DMA levels of 0.65-18 ppm (10/14 were <7 ppm), and ammonia levels of 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.

Secondary sources reported the irritation threshold of MMA as 7.9 ppm (Izmerov et al. 1982) and 18 ppm (Ruth 1986). Exposure to 10 ppm MMA for a prolonged period was reportedly not irritating, possibly due to olfactory fatigue, which is caused by aliphatic amines (Sutton 1963). A worker exposed to 25 ppm MA reported "some irritation," whereas 2-60 ppm caused "allergic or chemical bronchitis," but no other exposure details were provided (ACGIH 1992).

A secondary source reports that "methylamines" (defined as MMA, TMA, and DMA) 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). Short exposures (unknown duration) to 20-100 ppm MMA were reported to cause irritation of the eyes, nose, and throat, whereas at >100 ppm, MMA vapors are "intolerably ammoniacal," and caused irritation of the nose and throat, violent sneezing, coughing, a burning sensation of the throat, larynx constriction, difficulty breathing, pulmonary congestion, and lung edema (Sutton 1963; Deichmann and Gerarde 1969).

2.3. Neurotoxicity

The only report of MMA neurotoxic effects to humans was made by Yang et al. (1995) in their description of the accidental exposure to MMA vapor of 35 people who were hospitalized. In addition to severe respiratory and ocular effects, symptoms included coma, fainting, dizziness, headache, nausea, vomiting, and seizures. The exposure concentration and duration were not reported but were certainly a small fraction of a day.

2.4. Developmental and Reproductive Toxicity

No human data regarding MMA reproductive or developmental toxicity were located.

2.5. Genotoxicity

No data were found on the genotoxic potential of MMA in humans.

2.6. Carcinogenicity

No human carcinogenicity studies were found for MMA, and no regulatory bodies have evaluated its carcinogenic potential.

2.7. Summary

MMA has a pungent, fishy odor with an odor awareness threshold of 0.0009-4.7 ppm and an irritation threshold of 7.9-18 ppm. Olfactory fatigue to MMA occurs readily. Secondary source reports indicate that exposure to 20-100 ppm irritates the eyes, nose, and throat, and concentrations >100 ppm are "intolerably ammoniacal," causing irritation of the nose and throat, burning throat, larynx constriction, difficulty breathing, pulmonary congestion, and lung edema. No studies were located that evaluated MMA developmental or reproductive toxicity, genotoxicity, or carcinogenicity to humans. The accidental poisoning (undefined exposure time or concentration) of 35 people was described in which six people died within 10 days of exposure, mainly due to lung chemical burns and tissue death. Other effects included difficulty

breathing, chemical burns of the nose, mouth, eyes, and exposed skin, coma, dizziness, headache, nausea, black stool, high body temperature, rapid heart rate, and circulatory failure.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

The available acute lethality animal studies are presented in Table 3.

TABLE 3. Monoethylamine Acute Lethality Animal Studies

Species	Exposure Time	Concentration (ppm)	Mortality	Effects (Reference)
Rat	6 min 20 min 60 min	17,600-35,300 10,600-17,400 4100-8670	LC_{50}=24,400 ppm LC_{50}=9600 ppm LC_{50}=7110 ppm	Labored breathing, rales, gasping, corneal opacity, lung lesions (IRDC 1992a)
	60 min	1500 3000 6000 12,000 24,000	0/10 2/10 6/10 10/10, 10/10 LC_{50}=4830 ppm	Rats huddled during exposure; necropsy of decedents showed congestion of the upper respiratory mucosa, lungs, and liver (Air Products 1976)
	150 min	100, 200, 300, 400, 500	LC_{50}=448 ppm (24-hour)	24-hour observation, static exposure; labored breathing, dyspnea, lacrimation, excitement, facial skin necrosis; lung hemorrhage; increased lung lipid peroxidation at 400 and 500 ppm (Sarkar and Sastry 1992)
	4 hrs	1865 – 10469	LC_{50}=4800 ppm	Dyspnea, restlessness, apathy, convulsions, redness and/or hemorrhage of mouth, nose, and eyes, copious salivation, spasmodic eye closures, bronchopneumonia; signs persisted for 8-14 days after exposure (Koch et al. 1980)
	4 hrs	517 1465 2063 3213	2/20 5/20 17/20 20/20 LC_{50}=1740 ppm	Lethality as noted; at unspecified concentrations: respiratory irritation, difficult breathing, nasal lesions, corneal opacity, lung congestion, emphysema, gastric bleeding, gum and tongue cyanosis, facial skin damage, renal cortex necrosis in females (Klimisch et al. 1983)
	6 hr/d, 5 d/wk, for 2 wk	75 250 750	0/10 0/10 5/10	All had red nasal discharge, severe at ≥250 ppm; at 75 ppm had mild irritation of nasal turbinates; at ≥250 ppm had nasal lesions; at 750 ppm rats were hyperactive, aggressive, and had lung noise, labored breathing, salivation, ocular opacity, diarrhea, altered blood chemistry; pathology of bone marrow, lungs, liver; 5/10 died at ≥ day 8 (Kinney et al. 1990)
Mouse	2 hrs	unknown	LC_{50}=1890 ppm	Agitation, nasal blood discharge, labored breathing, cyanosis, head tremors, shaky gait, clonic spasms, death; pulmonary hemorrhage, pathology in blood vessels of internal organs and brain, liver, kidneys (Gorbachev 1957)

3.1.1. Rats

Incomplete details are available from a secondary source (IUCLID 2004) of a one-hour LC_{50} study in which male rats were exposed to 1500, 3000, 6000, 12,000, or 24,000 ppm MMA (Air Products 1976). Exposure was whole-body in a 70-liter chamber with an airflow of 16.7 L/minute. The only reported clinical signs were that all rats huddled during exposure. The incidence of mortality was 0/10, 2/10, 6/10, 10/10, and 10/10, respectively at exposure concentrations of 1500, 3000, 6000, 12,000, and 24,000 ppm. The LC_{50} was approximated as 5000 ppm; an LC_{50} of 4830 ppm was subsequently obtained using EPA BenchMark dose software (version 1.3.2). All deaths occurred within four days of exposure. Necropsy, only performed on decedents, revealed congestion of the upper respiratory mucosa, lungs, and liver. No other study details were available.

Koch et al. (1980) exposed 8-week-old female Wistar rats (10/group) for 4 hours to 1865-10,469 ppm at 22.3°C (experiment V), to 2778-6912 ppm at 22.2°C (experiment VIIIa), or to 2778-6912 ppm at 29.1°C (experiment VIIIb). The actual concentrations tested were not stated, but only that they were monitored by gas chromatography and were a geometric progression series using a factor of 1.25. A control group was included. Animals were exposed and observed in colorless transparent cages. The post-exposure period was two weeks. The chamber humidity, temperature, and CO_2 content (<0.2 vol %) were controlled. Inspiratory dyspnea was observed in all animals within the first exposure hour, sooner at the higher temperature. During the first hour of treatment, at least half the animals (at unspecified concentrations) displayed restlessness, apathy, convulsions, rough unkempt fur, and severe irritation of the eyes and respiratory tract (mucous membrane redness and/or hemorrhage of the mouth, nose, and eyes, 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. Lethality occurred in a few animals during exposure, was most frequent during days 1-6 after exposure, and was seen last on day 12 (temperature not specified). The incidence of lethality at specific concentrations was not stated, but a text figure suggested that mortality increased proportionately to test concentration. LC_{50} values were calculated using the statistical method of Spearman and Kärber and by probit analysis as approximately 4800 ppm at 22°C and 4400 ppm at 29°C. The mean survival time was 7.3 days at 22°C and 4.4 days at 29°C.

Groups of Wistar rats (10/sex/group) were exposed for 4 hours to 517, 1465, 2063, or 3213 ppm MMA, as determined by gas chromatography (Klimisch et al. 1983). During exposure, the primary effect was ocular and nasal irritation and respiratory difficulty. Difficulty breathing persisted after exposure, and was accompanied by ocular and nasal mucosal lesions, with one case of corneal opacity. The concentrations at which these effects occurred, incidence, and duration were not specified. Mortality over the 14-day observation period was 2/20, 5/20, 17/20, and 20/20, respectively, at 517, 1465, 2063, or 3213 ppm. Several animals died during treatment at 2063 and 3213 ppm, but most deaths occurred 24-48 hours after exposure. Necropsy revealed lung congestion, emphysema, decrease of mucus amount in the trachea, gastric bleeding, cyanosis of the gums and the tongue, facial skin damage, and necrosis in the renal cortex of some females. The mean lethal MMA concentration was determined to be between 1465 and 2,063 ppm. Using BenchMark dose software (Version 1.3.2), the calculated LC_{50}, $BMCL_{05}$, and BMC_{01} are 1740, 1020, and 1150 ppm, respectively. The validity of the $BMCL_{05}$ and BMC_{01} values is questionable, since they are inconsistent with the study's finding of 10% mortality at 517 ppm and 25% mortality at 1465 ppm.

Sarkar and Sastry (1992) exposed 2-month old female albino rats (number not stated) to 0, 100, 200, 300, 400, or 500 ppm MMA for 2.5 hours. Exposure was in a 12.5 L bell jar in which a 40% aqueous MMA solution had been placed for 3 hours prior to the exposure. The concentrations were not verified analytically. Animals were observed for 24 hours after exposure, at which time survivors were sacrificed and the following samples collected: blood for enzyme activity analysis (serum glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, lactate dehydrogenase and alkaline phosphatase); muscle to evaluate MMA levels; and lungs to measure lipid peroxidation. The rats (not stated if some or all) exhibited labored breathing, dyspnea, lacrimation, excitement, and facial skin necrosis. Necropsy showed lung hemorrhage (did not state which organs were examined at necropsy) and skin necrosis. The number of rats that died at a given concentration was not stated, only that the LC_{50} was 448 mL/L (i.e., 448 ppm) by the method of Litchfield and Wilcoxon (1949). Serum enzyme levels and muscle MMA content did not differ from controls, but there were 58% and 78% increases in lung lipid peroxidation at 400 and 500 ppm, respectively, consistent with the lung being a target organ.

In an inhalation LC_{50} study (IRDC 1992a; Ulrich et al. 1994), CD Sprague-Dawley rats (5/sex/dose; 49-65 days old) were exposed whole-body to anhydrous MMA for 6 minutes (17,600-35,300 ppm), 20 minutes (10,600-17,400 ppm), or 60 minutes (4100-8670 ppm). Exposure concentrations were generated by diluting MMA 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. The study results are summarized in Table 4. Observations in all groups included labored breathing, rales, and corneal opacity that persisted throughout the study. Body weight gains were decreased during the first week in both sexes, and in some cases during the second week. Almost all deaths occurred during the first 3 days after exposure. Necropsy revealed eye abnormalities (primarily corneal opacity) and lung congestion (red, discolored lungs) at almost all test concentrations. The incidence of lung congestion was correlated with lethality and was generally dose-related, particularly for the 60-minute exposure. Lethality was clearly dose-related for the 60-minute exposure, but less so for the 6 and 20 minute exposures. The LC_{50} values were 24,400 ppm for 6 minutes, 9600 ppm for 20 minutes, and 7110 ppm for 60 minutes, as calculated by the method of C.I. Bliss (1938). The mortality data were subsequently re-evaluated using EPA BenchMark dose software (Version 1.3.2.), which yielded LC_{50} values for 6, 20, and 60 minutes of 24,439, 9600, and 7108 ppm, respectively, and $BMCL_{05}$ values of 14,067 ppm, 489 ppm, and 4485 ppm, respectively. However, confidence in the values was good for only the 60-minute mortality data ($p=0.89$), but poor for the 6- and 20-minute data ($p= 0.15$ and 0.06, respectively), which lacked a clear dose-response.

In a range-finding study, presumably with young adult male Crl:CD rats, the approximate 4-hour LC_{50} was 4300 ppm (DuPont Company 1985). This study preceded the repeat-dose study by Kinney et al. (1990) described below.

TABLE 4. Summary of Lethality Data in Rats Following Exposure to Monomethylamine

Exposure duration	MMA concentration (ppm)	Lethality	Observations; calculated LC_{50}	Necropsy gross findings	
				Eye abnormalities	Congested or red lungs
6 minutes	17,600	0/10	Labored breathing, rales, gasping, corneal opacity; LC_{50}=24,400 ppm	10/10	0/10
	22,500	3/10		10/10	3/10
	26,200	9/10		7/10	9/10
	26,500	6/10		10/10	4/10
	35,300	9/10		9/10	8/10
20 minutes	10,600	3/10	Labored breathing, rales, gasping, corneal opacity; one 10,800 ppm female had abnormal gait immediately after exposure; LC_{50}=9600 ppm	7/10	2/10
	10,800	7/10		10/10	6/10
	11,000	6/10		10/10	7/10
	11,600	10/10		10/10	8/10
	13,900	8/10		10/10	8/10
	17,400	9/10		10/10	9/10
60 minutes	4100	0/10	Labored breathing, rales, gasping, corneal opacity; LC_{50}=7110 ppm	4/10	0/10
	6370	2/10		8/10	2/10
	7000	4/10		5/10	4/10
	7100	6/10		7/10	6/10
	8670	9/10		10/10	8/10

Source: IRDC 1992a.

Kinney et al. (1990) exposed groups of eight-week old male CD rats (10/group) nose-only to 0 (air only), 75, 250, or 750 ppm MMA for 6 hours a day, 5 days a week for 2 weeks (2-day rest after 5th day). The concentrations were generated by diluting pure MMA gas with 15 L/min air, and were confirmed analytically by IR spectroscopy at 30-minute intervals. Rats were weighed and observed daily, and blood and urine were collected from all animals at the end of exposure (10/group), and at the end of a two-week recovery period (5/group) for evaluation of clinical pathology parameters. Half of the rats were sacrificed immediately after the last exposure, and the other five after the recovery period, except for the 750 ppm group. Four rats in the 750-ppm group died or were sacrificed *in extremis* during exposures 8 or 10 and one died on the 12th day of the recovery period. Of the five survivors, three were sacrificed after the 10th exposure, and two after the 2-week recovery. All animals were necropsied and tissues examined by light microscopy, and selected organs were weighed (heart, lungs, liver, spleen, kidneys, testes, thymus).

All groups exhibited red nasal discharge, which was most severe at 250 and 750 ppm. Rats in the 750-ppm group were hyperactive, aggressive, and had hunched posture, lung noise, labored breathing, gasping, dry red nasal and ocular discharge, salivation, wet perineum, diarrhea, ruffled fur, and facial hair loss. During the exposures, no adverse clinical signs were observed in the control, 75 ppm, or 250 ppm exposure groups. During the recovery period, the group exposed to 750 ppm continued to have lung noise, clear or dry red nasal discharge, ocular opacity, diarrhea and discolored fur (and one died on day 12). Body weight and weight gain were decreased at only 750 ppm, starting on day 2, the decrease being significant (6-30%; $p<0.05$) from exposure day 3 through the 2-week recovery period. Rats in the 750-ppm group also had significantly ($p<0.05$) increased erythrocyte, neutrophil, and monocyte counts, hemoglobin, hematocrit, serum alanine and aspartate aminotransferase, blood urea nitrogen and cholesterol, decreased serum total protein, and acidic urine (also seen at 250 ppm). The most notable organ weight changes were decreased absolute and relative weight of the spleen and

thymus at 750 ppm. After the 14-day recovery period, the clinical chemistry and organ weights either returned to normal or improved. Pathomorphological changes at 750 ppm consisted of distended gastrointestinal tract, small spleen and thymus (due to depletion of lymphocytes), bone marrow hypocellularity, focal hepatic necrosis, dark or dull red lungs, red nasal discharge, congested brain, and nasal lesions (degeneration, severe necrosis leading to atrophy, and septal perforation in the nasal turbinate mucosa). At 250 ppm, the nasal mucosa was the primary target, lesions consisting of focal erosions and/or ulcerations, blood clots, and degeneration and/or necrosis. Blood clots were still visible after the two-week recovery period, but the lesions (necrosis/ulceration) were not detected following the two-week recovery period. With the exception of elevated BUN values, the clinical chemistry and hematologic findings in the 250-ppm group were normal. Animals exposed to 75 ppm had "only a mild irritation of the nasal turbinate mucosa," which was not observed following the two-week recovery period.

3.1.2. Mice

Gorbachev (1957) determined an LC_{50} of 1890 ppm for mice exposed for 2 hours to MMA. No further method details, including the test concentrations, were available. MMA intoxication was characterized by agitation, nasal blood discharge, labored breathing, cyanosis, head tremors, shaky gait, heightened reflexes, clonic spasms, and death from respiratory standstill. Pathomorphological study of dead animals revealed pulmonary hemorrhage, necrotic tracheobronchitis, and hyperemia in blood vessels of internal organs and of the brain. Animals that died later had dystrophic changes in the liver and kidneys.

3.2. Non-Lethal Toxicity

The available non-lethal MMA inhalation toxicity animal data are presented in Table 5.

TABLE 5. Non-lethal Inhalation Toxicity Studies for Monomethylamine

Species	Exposure Time	Concentration (ppm)	Effect (Reference)
Rat	30 min	465	Sacrificed after 24 hrs.; no visible respiratory distress but had thoracic cavity filled with a blood clot and serosanguinous fluid, marked interstitial pneumonitis, splitting of blood vessel coats (Jeevaratnam and Sriramachari 1994)
Rat	30 min	465	Sacrificed after 1, 4, or 10 wks.; after 1 wk lungs were pale with extensive edema and monocyte and histiocyte infiltration; after 4 wks had mild interstitial edema and severe interstitial pneumonitis that progressed to fibrosis after 10 wks (Sriramachari and Jeevaratnam 1994)
Mouse	15 min	85-192	RD_{50} = 141 ppm (calculated 50% decrease in breathing rate) (Gagnaire et al. 1989)
Rabbit	40 min	102 39	Threshold of irritation, manifested as decreased respiratory rate (Izmerov et al. 1982; Gorbachev 1957) Disrupted conditional and reflex activity (Gorbachev 1957)
Cat	30 min	157	Threshold of irritation, manifested as increased salivation (Izmerov et al. 1982; Gorbachev 1957)

3.2.1. Rats

Jeevaratnam and Sriramachari (1994) exposed four male Wistar rats for 30 minutes to 19 umol/L MA (465 ppm). The atmosphere was generated from a 40% aqueous solution that was heated in a static exposure chamber and the air concentration was calculated and not measured analytically. The animals were sacrificed after 24 hours and examined histologically, although only the results for the lungs were reported. The animals showed no visible signs of respiratory distress and none died. Histopathological examination showed the thoracic cavity of almost all animals (not specified) was "filled with a blood clot and serosanguinous fluid. The lungs were moderately heavy but there was no obvious evidence of hemorrhages." The lungs displayed marked interstitial pneumonitis (cellular elements included mononuclears, macrophages, and lymphocytes) and perivascular edema without interstitial damage or intra-alveolar edema. Some of the larger blood vessels had splitting or widening of the muscular coats without endothelial damage.

A follow-up study was conducted by the same laboratory, using the same experimental set-up, in which male Wistar rats were exposed for 30 minutes to 19 umol/L MA (465 ppm) (Sriramachari and Jeevaratnam 1994). However, instead of being sacrificed 24 hours after exposure, four rats were sacrificed at 1, 4, and 10 weeks after exposure and their lungs examined histologically. The appearance and behavior of the rats were not reported. After one week, the lungs were pale and translucent and there was extensive edema. The lung parenchyma and perivascular areas were filled with a clear aqueous liquid with widespread tissue separation that extended to the walls of the blood vessels. The interstitial spaces were infiltrated with mononuclear cells and histiocytes without foamy cells. Four weeks after exposure, the lungs showed severe interstitial pneumonitis but only mild interstitial edema, and reticulin staining revealed fibrillogenesis in the interstitial septa. After 10 weeks, the lungs had severe interstitial pneumonitis that extended into peribronchial and perivascular areas, and was accompanied by an abundance of collagen fibers. Thus, although pulmonary edema was seen primarily after one week, the interstitial pneumonitis progressed to fibrosis over time.

3.2.2. Mice

The RD_{50} (i.e., concentration of MMA causing a 50% decrease in the breathing rate) of male OF_1 Swiss mice was determined to be 141 ppm by Gagnaire et al. (1989) in an oronasal exposure study. Exposure was for a total of 15 minutes to 85-192 ppm MA, which was delivered to the 200 liter stainless steel exposure chamber by bubbling air through the liquid amine. The effect on breathing rate was seen within 30-60 seconds, and recovery after the 15-minute exposure occurred within one minute.

3.2.3. Rabbits

The irritating properties from a single inhalation exposure of MMA in rabbits were most vividly observed as breathing inhibition (Gorbachev 1957; Izmerov et al. 1982). The threshold for irritation for a 40-minute exposure, manifest as a decreased respiratory rate, was 102 ppm. However, exposure to 39 ppm MMA for 40 minutes disrupted the conditional and reflex activity in the animals. No further study details were available.

3.2.4. Cats

In cats, the threshold for MMA irritation, manifested as an increase in salivation, was 157 ppm for a single 30-minute exposure (Gorbachev 1957; Izmerov et al. 1982). No further study details were available.

3.3. Subchronic and Chronic Toxicity

A chronic experiment tested the effects of continuous exposure for six months to 0 (control), 0.213, 0.042, 0.008, or 0.003 ppm MMA on 800 male and female white rats (Dabaev 1981). Parameters monitored included the general status and activity of the animals, body mass, routine biochemical and immunological studies, the mass of internal organs, and histological analysis. MMA inhalation caused adverse effects on the nervous system (decreased orientational activity, summation threshold index, cholinesterase activity), and decreased levels of erythrocytes, and the activity of blood peroxidase and catalase activity. Neurological effects were seen earliest (second test week) and were the most pronounced in the 0.213 ppm group. At 0.042 ppm, neurological effects were seen by test day 48-49, at 0.008 ppm after 159-180 days, and no changes occurred at 0.003 ppm. The high-dose animals had adverse histopathological changes in the liver (marked hepatocyte protein and lipid dystrophy, lipdosis, decreased glycogen content), kidneys (lymphoid follicle dystrophy), lungs (inflammation), and heart (myocardial dystrophy). Less marked changes were seen in the liver and lungs of the 0.042 and 0.008 ppm groups, whereas none were found at 0.003 ppm.

3.4 Neurotoxicity

Neurotoxic signs were reported in several animal studies at concentrations that caused marked respiratory and ocular irritation and lesions, and in some cases death. Female Wistar rats exposed for 4 hours to 1865-10,469 ppm displayed restlessness or excitement, apathy, convulsions, rough unkempt fur, and severe irritation of the eyes and respiratory tract, and some died (at unspecified concentrations) (Koch et al. 1980). The symptoms increased in severity with dose and persisted for 8-14 days after exposure. Male CD rats exposed nose-only to 750 ppm MMA for 6 hours a day, 5 days a week for 2 weeks, were hyperactive, aggressive, and had hunched posture, labored breathing, nasal and ocular discharge, salivation, wet perineum, diarrhea, ruffled fur, and 5/10 died starting on day 8 of exposure (Kinney et al. 1990). During the recovery period, the rats continued to have respiratory and ocular signs, diarrhea, and discolored fur. Mice exposed for 2 hours to MMA (concentrations not specified but the LC_{50} was 1890 ppm) showed agitation, nasal blood discharge, labored breathing, cyanosis, head tremors, shaky gait, heightened reflexes, clonic spasms, and death from respiratory standstill (Gorbachev 1957). Microscopic findings included lung lesions and hyperemia in blood vessels of the internal organs and of the brain. Gorbachev (1957) reported that exposure to 39 ppm MMA for 40 minutes disrupted the conditional and reflex activity of rats, and exposure to 157 ppm for 30 minutes caused increased salivation in cats, but no other study details were available.

Pirisino et al. (2005) has proposed that MMA, like ammonia, may modulate neuron firing (see Section 4.2.) by targeting the voltage-operated neuronal potassium channels. MMA also stimulated nitric oxide (NO) release from the rat hypothalamus, suggesting a role in neurodegenerative diseases. Like ammonia, MMA was hypophagic in mice (causing them to eat abnormally small amounts of food) without having amphetamine-like effects (no induction of dopamine or serotonin release).

3.5. Developmental and Reproductive Toxicity

Guest and Varma (1991) conducted *in vivo* and *in vitro* studies to investigate the developmental toxicity of MMA in mice. Pregnant CD-1 mice were injected intraperitoneally (*ip*) with 0.25, 1, 2.5, or 5 mmol/kg MMA daily, from gestational day (GD) 1 to 17. Dams were killed on GD 18. Parameters examined included maternal body weight and mortality, fetal and placental weight, resorptions, and fetal death. Half of the embryos were used for visceral examination and half for skeletal examination. For the *in vitro* experiments, dams were sacrificed on the morning of day 8 and the embryos cultured 48 hours in 0.5 to 2.0 mM MMA. On day 10, embryo development was scored by the method of Brown and Fabro (1981). The embryos were frozen at -80°C, homogenized, and used to determine levels of DNA (diphenylamine method), RNA (orcinol reaction), and protein (Coomassie staining). There was a decrease in fetal body weight *in vivo* but no effect on maternal body weight. MMA did not cause maternal toxicity or adversely affect pregnancy outcome or the incidence of external, visceral, or skeletal abnormalities. The cultured mouse embryos, however, had concentration-dependent decreases in the yolk sac diameter, crown-rump length, head length, fetal survival, developmental score, somite number, and content of DNA, RNA, and protein. At ≥0.5 mM, there was retardation in forelimb and branchial bar development relative to other organs, and the embryos were dorsally convex at 1 mM.

Male white rats exposed by inhalation continuously to 0.008, 0.042, or 0.213 ppm MMA for 6 months had decreased total spermatozoid count and motility, atrophy of spermatogenic epithelium, and decreased relative and absolute mass of the testicles at 0.213 ppm (Dabaev 1981). Testicular changes were similar but less pronounced at 0.042 ppm, were seen only occasionally at 0.008 ppm, and were not seen at 0.003 ppm. Similarly exposed females had a prolonged diestrous phase of the estrous cycle after four months at 0.042 and 0.213 ppm (Dabaev 1981). Male and female rats were mated (3 females to one male), but details of the exposure, mating, and embryonic evaluation protocol were not provided. Treatment resulted in a dose-dependent increase in post-implantation embryonic deaths (3% in controls; 7%, 17%, and 62% at 0.008, 0.042, or 0.213 ppm, respectively) and considerable enlargement of post implantation embryos, although the progeny were not examined for developmental anomalies.

Groups of six female rats 12-13 weeks of age with regular estrous cycles were administered 5 mg/kg/day MMA by stomach tube and mated with non-treated rats with proven fertility (Sarkar and Sastry, 1990). Treatment did not cause changes in the estrous cycle, reproductive indices of fertility, gestation, live birth, lactation, average weight of pups at birth or weaning, although the average litter size was significantly decreased (6.33 vs. 8.83 in control group, $p<0.05$). Many experimental details (e.g., treatment duration of dams), were absent in the study report.

3.6. Genotoxicity

MMA was tested in the *Salmonella*/microsome preincubation assay at 0.033, 0.10, 0.33, 1.0, 3.3, and 10 mg/plate in strains TA98, TA100, TA1535, and TA1537, in the presence and absence of metabolic activation (Mortelmans et al. 1986; NTP 1986). The tests produced negative results and toxicity was seen at only 10 mg/plate (total clearing of background lawn). Meshram et al. (1992) tested 0.08-64 mg/plate MMA hydrochloride (0.04-29 mg/plate MMA) by liquid preincubation using strains TA98, TA100, and TA104 in the presence and absence of rat liver S9 mixture. A mutagenic response was not seen in any of the tested strains, and

cytotoxicity occurred at 64 mg/plate. Hussain and Ehrenberg (1974) found that *Escherichia coli* SD-4 incubated with 0.25 or 0.50 M MMA for 1 hour did not mutate to become streptomycin-resistant, whereas cells incubated with 1.00 M MMA had a slight increase in the number of mutants (historical control ranges were not provided, however).

In contrast, MMA was mutagenic at the *tk* locus in the L5178Y mouse lymphoma cell forward mutation assay, in the absence of exogenous metabolic activation (Caspary and Myhr 1986). Duplicate assays tested concentrations of 0-5 mM. Mutation frequency was increased at ≥2.5 mM in one assay and at ≥3.8 mM in the second assay, and cytotoxicity occurred at 400 nL/mL in both assays.

3.7. Carcinogenicity

No studies were found that examined the carcinogenic potential of MMA in animals. Under acidic (e.g. stomach) conditions, the related compounds DMA and TMA, but not MMA, can react with nitrite to form dialkylnitrosamines, which are known carcinogens. However, neither DMA nor TMA have shown carcinogenic activity in long-term animal studies. Lijinsky and Taylor (1977) found that chronic dietary administration to rats of the TMA metabolite TMAO did not increase tumor formation. A 2-year inhalation study with DMA found no increase in neoplasia in rats or mice exposed to 10, 50, or 175 ppm 6 hours/day, 5 days/week (CIIT 1990).

3.8. Summary

Rat and mouse MMA inhalation studies found signs consistent with severe irritation of the respiratory tract and eyes (labored breathing, rales, lacrimation, nasal and ocular discharge) and neurotoxicity (hyperactivity, apathy, head tremors, shaky gait, convulsions, salivation, and diarrhea). The symptoms generally increased in severity with test concentration and persisted for one to two weeks after exposure. Macroscopic and/or microscopic lesions occurred consistently in the eyes (corneal opacity) and lungs (congestion, hemorrhage, emphysema, interstitial pneumonitis, perivascular edema, and blood vessel damage that progressed to pulmonary fibrosis). Some studies also found facial skin necrosis, gastric bleeding, cyanosis of the gums and the tongue, renal cortex necrosis, nasal lesions, and hematological alterations. Rat LC_{50} studies obtained values of 4300 ppm and 1740 ppm for 4 hours (Koch et al. 1980; Klimisch et al. 1983), 448 ppm for 2.5 hours (Sarkar and Sastry 1992), 24,400 ppm for 6 minutes, 9600 ppm for 20 minutes, and 4830 ppm and 7110 ppm for 60 minutes (Air Products 1976; IRDC 1992a), and a mouse 2-hour LC_{50} of 1890 ppm was obtained by Gorbachev (1957). The reasons for the inconsistencies among some of the data are unclear; it is possible that the rat 2.5-hour LC_{50} of 448 ppm was a poor estimate of the actual test concentration as this was a static exposure and analytical concentrations were not determined. Gagnaire et al. (1989) determined an RD_{50} of 141 ppm for male OF_1 Swiss mice exposed to MMA for 15 minutes. An irritation threshold study found that rabbits exposed for 40 minutes to 102 ppm had a decreased the respiratory rate and at 39 ppm had disrupted conditional and reflex activity, whereas a 30-minute exposure to 157 ppm caused increased salivation in cats (Gorbachev 1957; Izmerov et al. 1982).

MMA neurotoxic potential was shown in several animal studies, at concentrations that caused marked respiratory and ocular irritation and lesions, and in some cases death. A recent study has suggested that MMA may modulate neuron firing. Effects on development and reproduction were not evaluated after an acute inhalation exposure, although male rats exposed

for 6 months to 0.042 or 0.213 ppm had adverse effects on spermatogenesis and decreased testicular weight (Dabaev 1981). MMA oral or intraperitoneal administration caused decreased fetal body weight in mice and decreased litter size in rats (Guest and Varma 1991; Sarkar and Sastry 1990). MMA and MMA-HCl were generally negative in bacterial mutagenicity studies, but induced mutations in mouse lymphoma cells in the absence of metabolic activation (Caspary and Myhr 1986). There was no evidence of MMA carcinogenic potential in animals.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Distribution

MMA is metabolized in mammals by semicarbazide-sensitive amine oxidase (SSAO; EC 1.4.3.6), to form formaldehyde, hydrogen peroxide, and ammonia (Yu 1990). The SSAO responsible for MMA metabolism has benzylamine oxidase activity. SSAO is believed to be involved in the regulation of leukocyte trafficking to sites of inflammation, glucose transport signaling in adipocytes, and adhesive events between leukocytes and vascular walls (Yu et al. 2006). SSAO was found to be highly homologous to vascular adhesion protein-1 (VAP-1) cloned from human gut smooth muscle, and is likely the same protein (Smith et al. 1998). Plasma membrane-bound SSAO is found in a variety of tissues in animals, the highest concentrations being in vascular endothelial cells, smooth muscle cells, and adipocytes, but a soluble form is also present in blood (Lyles 1996; Stolen et al. 2004). Rodents and humans have high lung SSAO activity, which was found to be greater in humans than rats (Lewinsohn et al. 1978; Boomsma et al. 2000; see Section 4.4.1.).

The fate of MMA following inhalation exposure was examined in only one study, where MMA, DMA, 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 amine levels measured at 14 locations in the factory were 0.55-29 ppm MMA (13/14 were <3 ppm), 0.65-18 ppm DMA (10/14 were <7 ppm), and 1.4-50 ppm ammonia (9/14 ≤12 ppm). DMA excretion increased in parallel with DMA exposure during the work day, whereas urinary MMA levels remained relatively constant, being about 10 to 30-fold lower than urinary DMA levels.

Rechenberger (1940) reported that a human subject who ingested 2, 4, or 10 g MMA-HCl did not experience any adverse effects, and his urine contained 1.74-1.93% of the ingested (unchanged) MMA within 24 hours of exposure.

The toxicokinetics of [^{14}C]-MMA-HCl (75 μg/kg) was studied after *ip* injection of female Wistar rats and female Dutch rabbits (Dar et al. 1985; Dar and Bowman 1985). Urine and expired air were collected for 24 hours in metabolism cages; feces were not collected due to expected low radioactivity. The majority of the administered radioactivity was excreted as $^{14}CO_2$ in both species. At 2, 6, and 24 hours after treatment, rats exhaled 36, 46, and 53%, respectively, of the given dose, and rabbits exhaled 11, 32, and 46% of the given dose as $^{14}CO_2$. The 24-hour urine contained 14% and 6% of the given radioactivity of rats and rabbits, respectively, of which approximately 2% and 6%, respectively, was [^{14}C]-methylurea labeled in the methyl and carbonyl positions. A group of similarly MMA-treated rats that was pretreated with antibiotics to sterilize the gut had total 24-hour $^{14}CO_2$ and urinary excretion similar to a non-pretreated group. This indicated that intestinal microorganisms do not play a major role in MMA metabolism (Dar et al 1985).

Streeter et al. (1990) examined the disposition of MMA in male Fischer-F344/NCr-rats (53 days old) administered 18 µm/kg ^{14}C-MMA or 3 µm/kg ^{14}C-MMA-d_3 (deuterated) intravenously (*iv*). Twenty blood samples were collected over a period 50 minutes and their MMA and total radioactivity content measured. Urine samples were collected from a separate group of MMA-treated rats over 0-24, 24-48, and 48-72 hours after dosing. To determine bioavailability of MMA, rats were also gavaged with 0.08 mmol/kg ^{14}C-MMA or 0.09 mmol/kg ^{14}C-MMA-d_3. Following *iv* administration, the elimination of MMA from the blood was biphasic first-order for both compounds, with a terminal half-life [$t_{½}$ (β)] of 19.1 minutes for ^{14}C-MMA and 40.0 minutes for ^{14}C-MMA-d_3. Calculation using the AUC (area under the curve) for unmetabolized MMA and the total radioactivity after *iv* and oral dosing indicated that MMA systemic bioavailability and total absorption from the gut were, respectively, 69% and 93% for MMA and 121% and 120% for MMA-d_3. The latter values were considered erroneous and due to the incomplete elimination of the compound during the experimental timeframe (for blood collection). The vast majority of the radioactivity in the 0-72-hour urine of *iv*-treated rats consisted of unchanged MMA, which represented 11% and 48% of the given dose for ^{14}C-MMA and ^{14}C-MMA-d_3, respectively, and corresponded to renal blood clearances of 6 and 12 mL/minute/kilogram. The remainder of the urinary radioactivity had HPLC peaks with retention times consistent with those of formaldehyde, monomethylurea, and formate. Deuterium isotope effects were calculated to be 1.9 for the terminal half-life after an *iv* dose, 2.2 for systemic bioavailability, and 1.8 for systemic blood clearance. The magnitude of the deuterium isotope effects suggests that C-H bond breakage may be the rate-determining step in MMA biotransformation (Klinman 1978).

4.2. Toxicity Mechanisms

The mechanism of MMA toxicity has not been defined, although its irritant properties are likely related to its high alkalinity (pK_a of 10.65 at 25°C) and corrosiveness to exposed tissues such as skin, eyes, and the respiratory mucosa. Thus, MMA has been reported to cause respiratory and ocular irritation in both humans and animals and at sufficiently high concentrations causes breathing difficulties, lesions of the eyes and lungs, and death associated with lung lesions. MMA vapor is also associated with systemic effects in exposed animals (e.g., neurotoxicity, pathological alterations of the liver, thymus, spleen, and brain), the etiology of which is less clear.

Since SSAO has high activity in vascular tissue, it was proposed that elevated levels of formaldehyde-protein cross-links may cause vascular disease. Consistent with this theory, MMA was toxic to cultured human and rat aortic smooth muscle cells when incubated with soluble bovine SSAO, as determined by the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide)] reduction cell viability assay (Hernandez et al. 2006). Co-incubation with the SSAO-specific inhibitor MDL72974A completely eliminated the cytotoxic effect. The rat cells (A7r5) also showed evidence of apoptosis, which appeared to be primarily mediated by formaldehyde. Protein-formaldehyde crosslinking was also shown *in vitro* after incubation of the bipeptide lysine-leucine or bovine serum albumin with formaldehyde (Gubisne-Haberle et al. 2004).

Neurotoxicity may be related to the ability of MMA, like ammonia, to modulate neuron firing, as proposed by Pirisino et al. (2005). Both MMA and ammonia target the voltage-operated neuronal potassium channels, probably inducing release of transmitter, although the two appear to interact with different Kv1.6 channels. Like ammonia, MMA is hypophagic in mice (i.e. causing them to eat abnormally little) without inducing dopamine or serotonin release. MMA also

stimulated nitric oxide (NO) release from the rat hypothalamus, which has been associated with some neurodegenerative diseases.

Yu et al. (2006) examined the role of SSAO-mediated deamination in pulmonary inflammation using transgenic (Tg) mice. The Tg mice overexpressed human SSAO (referred to as VAP-1) targeted to endothelial cells. SSAO levels were an order of magnitude greater in the lungs than in other examined Tg mouse tissues (heart, liver, spleen, and pancreas). Inhalation of MMA vapor (1 hour/day for 2 days, examined on day 3; MMA concentration undefined) significantly increased the cell counts in bronchiolar lavage (BAL) fluid of Tg mice, but not of non-Tg mice. Pretreatment with the SSAO inhibitor MDL-72974A significantly reduced the MMA-induced BAL cell numbers. Tg mice injected *ip* with MMA had increased protein-formaldehyde deposits in tissues including the lungs after 72 hours (primarily at the lysine residues), which were significantly reduced by the SSAO inhibitor MDL-72974A. Yu et al. (2006) concluded that SSAO-catalyzed deamination to form formaldehyde plays an important role in MMA-induced acute lung inflammation.

4.3. Structure-Activity Relationship

The upper respiratory irritation (i.e., RD_{50}) of a series of aliphatic amines including MMA, DMA, TMA, and EA (ethylamine) were determined by Gagnaire et al. (1989). Male Swiss-OF_1 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. The results indicate that TMA and DMA (RD_{50} of 61 and 70 ppm) are stronger upper respiratory irritants than MMA and EA (RD_{50} of 141 and 151 ppm). 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 picture 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, but 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) found somewhat different relative potencies (LC_{50} values) than Koch et al. (1980) for MMA, DMA, and TMA 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; 7,110 5,290 7,910 and 5,540 ppm for 60 minutes. Thus the relative acute toxicities (causing lethality) for all exposure durations were DMA>EA>MMA>TMA, although the differences in LC_{50} values were not great (within approximately 40% for a given exposure time).

4.4. Other Relevant Information

4.4.1. Species Variability

Acute toxicity data were available for only rats and mice, which both had primarily respiratory and neurological effects from MMA, but the data were insufficient to define which of the two species was more sensitive. Mice were exposed for only 2 hours, whereas rats were exposed for 6, 20, 60, and 240 minutes [results of the 2.5-hour exposure experiment by Sarkar and Sastry (1992) were inconsistent with the other rat data]. The mouse 2-hour LC_{50} of 1890 ppm (Gorbachev 1957) was lower than the rat 1-hour LC_{50} of 7110 ppm (IRDC 1992a) and the rat 4-hour LC_{50} of 4800 ppm obtained by Koch (1980), but was comparable to the 4-hour LC_{50} of 1740 ppm obtained by Klimisch et al. (1983). Therefore, there did not appear to be a great deal of variability in MMA acute toxicity between rats and mice.

Lewinsohn et al. (1978) found that the aorta and lung had the highest SSAO activity among examined tissues in rats and humans, using benzylamine as the substrate. SSAO activity in the aorta was comparable between rats and humans, but humans had an approximately 2-fold greater SSAO activity in the lungs than rats. For both rats and humans, serum SSAO activity was >100-fold lower than in the aorta or lung. Boomsma et al. (2000) evaluated SSAO activity in tissues from rats, pigs, and humans, and found that it was highest in humans in almost all tissues examined, followed by rat and pig. All three species had relatively high SSAO activity in artery and vein tissue, and low activity (on a per gram basis) in the plasma. Humans and rats also had high lung SSAO activity, which was highest in humans (14-fold greater than in rats, and 52-fold greater than in pigs). Boomsma et al. (2000) also examined plasma SSAO activity in a number of mammalian species and found that the V_{max} was approximately 20 to 300-fold higher in goats, sheep, cows, horses, pigs, rabbits, and dogs than in humans, but the V_{max} for rat and guinea pig SSAO was approximately 10 to 20-fold lower than of humans. Thus, if SSAO activity is positively correlated with sensitivity to MMA toxicity, especially in the lungs and vascular system, humans appear to be more sensitive than the other tested species.

4.4.2. Susceptible Populations

Humans with elevated levels of endogenous MMA and/or those with elevated SSAO activity may be more susceptible to toxicity from MMA vapor than the general population. SSAO has been implicated as having a role in vascular endothelial damage via metabolism of MMA to formaldehyde, ammonia and hydrogen peroxide, thus contributing to a number of disease states (Yu et al. 2003). These include diabetes, heart disease, obesity (non-diabetic),

Alzheimer's disease, cerebral arteriopathy, inflammatory liver disease, atherosclerosis, and congestive heart failure.

4.4.3. Concentration-Exposure Duration Relationship

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, and n ranged from 1 to 3 for 90% of the chemicals examined. Bisson et al. (2003) examined the value of n in $C^n \times t = k$ for time scaling MMA exposure concentrations from 1 to 60 minutes. They obtained n = 1.88 (rounded to 1.9) by probit analysis of the IRDC (1992a) 6, 20, and 60-minute LC_{50} values for MMA.

A computer program, developed by ten Berge (2006) and based on probit analysis according to Finney (1971), integrates all concentration and time information for a range of lethality data. Concentration, time, and response (including number of animals responding) are considered simultaneously in a linear regression equation, with the Maximum Likelihood statistical method used to find the closest estimates of the regression coefficients for each parameter. The probit-analysis dose-response program of ten Berge was used to estimate the LC_{01}, considered the threshold for lethality, at each AEGL exposure duration (with confidence limits of 95%). The full data set on lethality was used. The calculated n value was 1.87 (rounded to 1.9).

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

The available published data on MMA toxicity in humans is inappropriate for derivation of AEGLs due to lack of information on concentrations and exposure times correlated with observed effects. Secondary sources (see Section 2.2.2.), none of which gave the exposure duration, have reported that the MMA irritation threshold was 7.9 and 18 ppm; "prolonged" inhalation of 10 ppm was not irritating; 25 ppm caused "some irritation;" 2-60 ppm caused "allergic or chemical bronchitis;" "short" exposure to 20-100 ppm MMA was irritating to the eyes, nose, and throat; and that >100 ppm was "intolerably ammoniacal," and caused irritation of the nose and throat, violent sneezing, coughing, burning throat, larynx constriction, difficulty breathing, pulmonary congestion, and lung edema. Defining concentrations that cause irritation is confounded by the fact that olfactory fatigue to MMA occurs readily (Sutton 1963).

5.2. Summary of Animal Data Relevant to AEGL-1

Animal studies potentially useful for derivation of AEGL-1 values include:

(1) the 2-week Kinney et al. (1990) study in which male CD rats were exposed nose-only to 0, 75, 250, or 750 ppm MMA 6 hours/day, 5 days/week for 2 weeks. Animals exposed to 75 ppm had "mild irritation of the nasal turbinates," whereas more pronounced nasal lesions occurred at 250 and 750 ppm; the latter group had 50% mortality with severe respiratory and neurological effects. A single exposure to 75 ppm could be the AEGL-1 point of departure (POD);

(2) the static exposure studies in which male rats inhaled 465 ppm (nominally) for 30 minutes and were sacrificed after 24 hours (Jeevaratnam and Sriramachari 1994) or

after 1, 4, and 10 weeks (Sriramachari and Jeevaratnam 1994), and their lungs were examined histologically. After 24 hours, the animals had no signs of respiratory distress but had thoracic cavities "filled with a blood clot and serosanguinous fluid," lungs with marked interstitial pneumonitis and perivascular edema, and splitting or widening of the muscular coats of some large blood vessels. After one week, there was extensive edema that extended to the walls of the blood vessels, whereas at later time points, the main lesion was severe interstitial pneumonitis that progressed to fibrosis. Because the pulmonary lesions were severe and irreversible, an adjustment factor of 3 could be applied to 465 ppm to obtain a 30-minute POD of 155 ppm.

(3) the RD_{50} study in which 141 ppm was calculated to cause a 50% decrease in the breathing rate of male OF_1 Swiss mice exposed to 85-192 ppm for 15 minutes (Gagnaire et al. 1989); and

(4) the irritation threshold studies in which a 40-minute exposure to 102 ppm decreased the respiratory rate of rabbits, a 40-minute exposure to 39 ppm disrupted the conditional and reflex activity of rabbits, and a 30-minute exposure to 157 ppm caused increased salivation in cats (Gorbachev 1957; Izmerov et al. 1982). Few study details were available.

5.3. Derivation of AEGL-1

The AEGL-1 is based on two studies. The point of departure in the Kinney et al. (1990) study was a single 6-hour exposure of male CD rats to 75 ppm. Exposures were actually repeated for two-weeks (10 exposures) and resulted in mild irritation of the nasal turbinates. Repeat exposure to higher concentrations (250 and/or 750 ppm) caused more severe nasal lesions and /or systemic toxicity and mortality. A single 6-hour exposure to 75 ppm is expected to cause no more than mild sensory irritation. In the second study (Jeevaratnam and Sriramachari1994), exposure of male Wistar rats to 465 ppm for 30 minutes was a NOAEL for notable signs of discomfort, but caused interstitial pneumonitis progressing to fibrosis (Sriramachari and Jeevaratnam 1994). A total UF of 10 was applied, including 3 for interspecies uncertainty and 3 for human variability, because mild 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 the well-conducted study of Kinney et al. (1990) was a repeat exposure study and the effect was essentially a NOAEL, a modifying factor of 0.5 was applied. The study of Jeevaratnam and Sriramachari (1994) used only one exposure, the description of the study results lacked details, and the endpoint was more serious than that defined by an AEGL-1. In the absence of robustness and due to lung histopathology, a modifying factor of 3 was applied. Application of these uncertainty and modifying factors to the respective studies yields an AEGL-1 value of 15 ppm. Because there is adaptation to the mild irritation that defines the AEGL-1, the value was used for all exposure durations. Additionally, Sutton (1963) notes that olfactory fatigue to amines occurs readily.

The AEGL-1 of 15 ppm is consistent with the mouse respiratory inhibition study that determined an RD_{50} of 141 ppm for MMA (Gagnaire et al. 1989). According to Alarie (1981), exposure to the RD_{50} is intolerable to humans, 0.1 of the RD_{50} (i.e., 14 ppm) for several hours-days causes sensory irritation in humans, 0.01 x RD_{50} (1.4 ppm) should cause no sensory irritation, and 0.03 x RD_{50} (4.2 ppm) is an estimate of an occupational exposure threshold limit

value (TLV). The resulting AEGL-1 value is shown in Table 6 and calculations are detailed in Appendix B. A category graph of the AEGL values in relation to the data is in Appendix C.

TABLE 6. AEGL-1 Values for Monomethylamine

10-min	30-min	1-h	4-h	8-h
15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data were found appropriate for derivation of AEGL-2 values. Secondary sources possibly useful as supporting evidence state that short exposure (unknown duration) to 20-100 ppm MMA was irritating to the eyes, nose, and throat, whereas >100 ppm (unknown duration) was "intolerably ammoniacal," and caused irritation of the nose and throat, violent sneezing, coughing, burning throat, larynx constriction, difficulty breathing, pulmonary congestion, and lung edema (Sutton 1963; Deichmann and Gerarde 1969).

6.2. Animal Data Relevant to AEGL-2

Animal studies potentially useful for derivation of AEGL-2 values include:

(1) the 2-week Kinney et al. (1990) study in which male CD rats were exposed nose-only to 0, 75, 250, or 750 ppm MMA 6 hours/day, 5 days/week for 2 weeks. Animals exposed to 75 ppm had mild irritation of the nasal turbinates; 250 ppm caused marked red nasal discharge, nasal mucosa focal erosions and/or ulcerations, blood clots, degeneration and/or necrosis, which were reversible following a 2-week recovery period; rats in the 750 ppm group had 50% mortality and were hyperactive, aggressive, salivated, had labored breathing, ocular opacity, hematotoxicity, and pathological alterations of the nasal passages, lungs, liver, thymus, spleen, and brain. A single exposure to 250 ppm could be the point of departure (POD) for AEGL-2 development;

(2) the static exposure studies in which male rats inhaled 465 ppm (nominal) for 30 minutes and were sacrificed after 24 hours (Jeevaratnam and Sriramachari 1994) or after 1, 4, and 10 weeks (Sriramachari and Jeevaratnam 1994), and their lungs were examined histologically. After 24 hours, the animals had no signs of respiratory distress but had thoracic cavities "filled with a blood clot and serosanguinous fluid," lungs with marked interstitial pneumonitis and perivascular edema, and splitting or widening of the muscular coats of some large blood vessels. After one week, there was extensive edema that extended to the walls of the blood vessels, whereas at later time points, the main lesion was severe interstitial pneumonitis that progressed to fibrosis. Because the pulmonary lesions were severe and irreversible, an adjustment factor of 3 could be applied to 465 ppm to obtain a 30-minute POD of 155 ppm.

(3) the RD_{50} study in which 141 ppm was the RD_{50} (50% decrease in the breathing rate) of male OF_1 Swiss mice exposed to 85-192 ppm for 15 minutes (Gagnaire et al. 1989); and

(4) the IRDC (1992a) LC_{50} study in which CD Sprague-Dawley rats were exposed whole-body to MMA for 60 minutes (4100-8670 ppm). All groups of rats exhibited labored breathing, rales, and corneal opacity throughout the 14-day study. Mortality and reddened lungs were found in all but the 4100 ppm group, although microscopic evaluation was not conducted. Because corneal opacity exceeds the severity of AEGL-2, and the presence of lung lesions was not excluded microscopically, this endpoint is above the definition of an AEGL-2.

6.3. Derivation of AEGL-2

AEGL-2 values were derived from the Kinney et al. (1990) repeat exposure study. Ten exposures of male CD rats to 250 ppm, 6 hours/day, caused reversible lesions of the anterior respiratory tract. The severity of the lesions (focal erosion and ulceration of the nasal turbinate mucosa) was attributed to the repeat exposure scenario, i.e., repeated local irritation. Lesions did not extend into the trachea or lungs. Lesions following a single exposure would be less severe and also reversible. 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). Time scaling, $C^n \times t = k$ where $n = 1.9$, was based on rat lethality data ranging from 6 to 60 minutes (data set of IRDC 1992a). Lethality data were used to time-scale the AEGL-2 values because local irritation is considered the first step leading to pulmonary irritation and death. The derived AEGL-2 values are presented in Table 7, and the calculations are shown in Appendix B.

TABLE 7. AEGL-2 Values for Monomethylamine

10-min	30-min	1-h	4-h	8-h
160 ppm (200 mg/m^3)	92 ppm (120 mg/m^3)	64 ppm (80 mg/m^3)	31 ppm (39 mg/m^3)	21 ppm (27 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

The only available MMA human lethality study described in detail the symptoms experienced by a group of 35 people accidentally exposed to MMA, but did not quantitate exposure concentration or duration (Yang et al. 1995).

7.2. Summary of Animal Data Relevant to AEGL-3

The acute lethality studies consistently found that MMA caused severe respiratory system toxicity, and many also reported eye irritation and neurotoxicity. The studies considered for derivation of AEGL-3 values were:

(1) the inhalation LC_{50} study of IRDC (1992a), where rats were exposed for 6, 20, or 60 minutes yielding LC_{50} values of 24,400 ppm, 9600 ppm, and 7110 ppm, respectively; the highest non-lethal value at 60 minutes was 4100 ppm;

(2) the one-hour LC_{50} study in which male rats exposed to 1500-24,000 ppm MMA (Air Products 1976) had an LC_{50} of 4830 ppm, but the unpublished study report and many experimental details were unavailable;

(3) the Koch et al. (1980) study in which rats exposed for 4 hours to 865-10,469 ppm at approximately 22°C had an LC_{50} of 4800 ppm, but individual dose-response data were not provided;

(4) the study of Klimisch et al. (1983), where rats exposed for 4 hours to 517-3213 ppm MMA had a calculated $BMCL_{05}$ value of 1020 ppm, which was inconsistent with 2/20 deaths seen at 517 ppm;

(5) the Sarkar and Sastry (1992) 150-minute static exposure study in which an LC_{50} of 448 ppm was determined in rats exposed to 0, 100, 200, 300, 400, or 500 ppm MMA, but the test concentrations were not verified analytically;

(6) the repeat-exposure study of Kinney et al. (1990), in which rats inhaled 75, 250, or 750 ppm 6 hours/day, 5 days/week for 2 weeks and 5/10 of the 750 ppm rats died, starting on day 8; and

(7) the 2-hour exposure mouse study by Gorbachev (1957), which determined an LC_{50} of 1,890 ppm, but many study details (such as all test concentrations) were unavailable.

7.3. Derivation of AEGL-3

Using the rat data of IRDC (1992a), the probit-analysis based dose-response program of ten Berge (2006) was used to calculate the LC_{01} at each AEGL-3 exposure duration. The program incorporated all of the data at the 6-, 20-, and 60-minute time points in Table 4. The data indicated a time-scaling value of 1.9 ($C^{1.9} \times t = k$). A total uncertainty factor of 10 was applied, including 3 for interspecies uncertainty and 3 for human variability, because lethality 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). The derived AEGL-3 values are presented in Table 8, and the calculations are shown in Appendix B.

TABLE 8. AEGL-3 Values for Monomethylamine

10-min	30-min	1-h	4-h	8-h
910 ppm (1200 mg/m^3)	510 ppm (650 mg/m^3)	350 ppm (440 mg/m^3)	170 ppm (220 mg/m^3)	110 ppm (140 mg/m^3)

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

The AEGL-1 is based on two studies with the rat: Kinney et al. (1990) and Sriramachari and Jeevaratnam (1994). The repeat dose study of Kinney et al. (1990) was also used to derive AEGL-2 values. The point of departure for the AEGL-1 was the mild nasal irritation observed in rats following 10 exposures to 75 ppm for 6 hours/day. In the second study (Sriramachari and Jeevaratnam 1994), exposure of male Wistar rats to 465 ppm for 30 minutes was a NOAEL for notable signs of discomfort, but the thorax showed signs of hemorrhage; lung fibrosis was present after several weeks. Inter- and intraspecies uncertainty factors of 3 each for a total of 10 were applied because the mechanism of action is direct contact irritation. Because exposures were repeated in the Kinney et al. study and the lesions was mild, essentially below the definition of an AEGL-1, a modifying factor of 0.5 was applied. Because the lesions in the second study were above the definition of an AEGL-1, a modifying factor of 3 was applied. Both sets of adjustments result in a value of 15 ppm. Because there is adaptation to the slight sensory irritation that defines the AEGL-1, the 15 ppm value was set across all exposure durations.

The point of departure for the AEGL-2 was the 250 ppm repeat exposure of rats that resulted in reversible lesions of the anterior nasal cavity; there were no effects on the lungs (Kinney et al. 1990). 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. Time scaling, $C^n \times t = k$ where $n = 1.9$, was based on rat lethality data ranging from 6 to 60 minutes (data set of IRDC 1992a). Lethality data were used to time-scale the AEGL-2 values because local irritation is considered the first step in a continuum leading to pulmonary irritation and death.

Using the full rat data set on lethality, the probit-analysis based dose-response program of ten Berge (2006) was used to calculate the LC_{01} at each AEGL-3 exposure duration. The program incorporated all of the data at the 6-, 20-, and 60-minute time points in Table 4. The data indicated a time-scaling value of 1.9 ($C^{1.9} \times t = k$). A total uncertainty factor of 10 was applied, including 3 for interspecies uncertainty and 3 for human variability, because lethality 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

A summary of the AEGL values for MMA and their relationship to one another are shown in Table 9. Summary derivations are in Appendix D.

TABLE 9. Summary of AEGL Values for Monomethylamine

Classification	Exposure Duration				
	10 min	30-min	1-h	4-h	8-h
AEGL-1 (Non-disabling)	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)
AEGL-2 (Disabling)	160 ppm (200 mg/m^3)	92 ppm (120 mg/m^3)	64 ppm (80 mg/m^3)	31 ppm (39 mg/m^3)	21 ppm (27 mg/m^3)
AEGL-3 (Lethal)	910 ppm (1200 mg/m^3)	510 ppm (650 mg/m^3)	350 ppm (440 mg/m^3)	170 ppm (220 mg/m^3)	110 ppm (140 mg/m^3)

8.2. Comparison with Other Standards and Guidelines

The existing standards and guidelines for MMA are shown in Table 10. The 1-hour ERPG-1 of 10 ppm was based on a clearly defined objectionable odor. Although different endpoints were used, the AEGL-1 and ERPG-1 values are similar. The 1-hour ERPG-2 of 100 ppm was based on worker reports of sensory irritation at 100 ppm and the repeat-dose rat study of Kinney et al. (1990) in which 75 ppm was shown to have no effect. The 1-hour AEGL-2 of 64 ppm was based on the next highest concentration in the study of Kinney et al. (250 ppm), but with addition of several uncertainty factors. The ERPG-3 was based on several mortality studies including the data set of IRDC (1992a). Based on the 60-minute data, AIHA calculated an LC_{10} of 5771 ppm. The 1-hour AEGL-3 is 1.4-fold lower.

The ACGIH (1992) TLV-TWA of 5 ppm and STEL of 15 ppm are intended to protect workers from MMA irritation of the eyes, skin, and respiratory tract. The ACGIH noted that repeated exposure to 75 ppm caused marginal respiratory tract pathology in rats but a NOEL was not determined, and that transient exposure to <10 ppm was not associated with irritation in workers (the referred to data are from Kinney et al. 1990, and Sutton 1963). The NIOSH IDLH of 100 ppm was based on the report by Deichmann and Gerarde (1969) that short exposures (unknown duration) to 20-100 ppm MMA caused transient irritation of the eyes, nose, and throat, whereas >100 ppm MMA caused irritation of the nose and throat, violent sneezing, coughing, a burning sensation of the throat, larynx constriction, difficulty breathing, pulmonary congestion, and lung edema (NIOSH 2006b).

TABLE 10. Extant Standards and Guidelines for Monomethylamine

Standard	Exposure Duration				
	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-1	15	15	15	15	15
AEGL-2	160	92	64	31	21
AEGL-3	910	510	350	170	110
ERPG-1 (AIHA) [a]			10		
ERPG-2 (AIHA)			100		
ERPG-3 (AIHA)			500		
PEL-TWA (OSHA) [b]					10
IDLH (NIOSH) [c]		100 ppm			
REL-TWA (NIOSH) [d]					10
TLV-TWA (ACGIH) [e]					5
TLV-STEL (ACGIH) [f]	15 (15 min)				
MAK (Germany) [g]					10
MAK Peak Limit (Germany) [h]	10 (15 min and momentary)				
MAC (Netherlands) [i]	15 (15 min)				5
LLV (Swedish)[j]					10
STV (Swedish)[k]	(15 min)				

[a] **ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association** (AIHA 2004)

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 2006) 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 1992; 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 1992; 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] 2005) is defined analogous to the ACGIH-TLV-TWA.

[h] **MAK Spitzenbegrenzung (Peak Limit [Category I, excursion factor 1])** (Deutsche Forschungsgemeinschaft [German Research Association] 2005) 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. A momentary value of 10 ppm should not be exceeded.

[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.

[j] **LLV (Level Limit Value)** Swedish Occupational Exposure Limits. 2000. Swedish National Board of Occupational Safety and Health. Defined analogous to the ACGIH-TLV-TWA.

[k] **STV (Short-Term Value)** Swedish Occupational Exposure Limits. 2000. Swedish National Board of Occupational Safety and Health. Defined as a recommended value consisting of a time-weighed average for exposure during a reference period of 15 minutes.

8.3. Data Adequacy and Research Needs

The clinical picture of MMA toxicity is defined by its irritant properties, although no quantitative single exposure irritation data were available for humans or animals. This type of data should be collected to confirm the validity of the developed AEGL-1 and AEGL-2 values.

There were no quantitative human data for MMA exposures that caused systemic effects, although a fairly consistent picture of MMA-induced toxicity was seen from the tested animal species, and the accidental human exposure report of Yang et al. (1995). A shortcoming of the animal data, however, was the lack of a study that examined the toxicity of a range of exposure durations, i.e., >4 hours and <4 hours. This is a concern because there was some inconsistency between LC_{50} values obtained among laboratories [e.g. if we compare 60-minute rat LC_{50} of 7110 ppm (IRDC 1992a) and 2-hour mouse LC_{50} of 1890 ppm (Gorbachev 1957) to the 4-hour rat LC_{50} of 4800 ppm (Koch et al. 1980), 4300 ppm (DuPont Company 1985), or 1740 ppm (Klimisch et al. 1983)]. If one study had been conducted that tested over a period of ≥4 hours, it would have added confidence to the choice of studies used for AEGL derivation, and for the calculation of n in $C^n \times t = k$.

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APPENDIX A: Derivation of the Level of Distinct Odor Awareness (LOA)

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, 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 methylamine was reported to be 0.035 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:

$3 = 2.33 \times \log (C / 0.035) + 0.5$, which can be rearranged to
$\log (C / 0.035) = (3 - 0.5) / 2.33 = 1.07$, and results in
$C = (10^{1.07}) \times 0.035 = 0.41$ 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 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 = 0.41 ppm x 1.33 = 0.56 ppm

The LOA for methylamine is 0.56 ppm.

APPENDIX B: Derivation of AEGL Values

Derivation of AEGL-1

Key studies: Kinney at al. (1990). Male rats were exposed to 0, 75, 250, or 750 ppm MMA for 6 hours/day, 5 days/week for 2 weeks. Rats exposed to 75 ppm had mild irritation of the nasal turbinates, whereas 250 ppm caused marked red nasal discharge and nasal mucosa lesions, and 750 ppm caused 50% mortality (starting on day 8) and lesions of the lungs, eyes, and other organs. Although a no-effect level for mild irritation of the nasal turbinates was not determined, mild irritation after 10 exposures, and a single 6-hour exposure to 75 ppm is expected to cause no more than mild sensory irritation and is the AEGL-1 POD.

Sriramachari and Jeevaratnam (1994). Male rats were exposed to 465 ppm for 30 minutes. Rats showed no visible signs of respiratory distress, but the thorax showed edema and hemorrhage. The lungs showed pneumonitis and perivascular edema, but no edema of the alveolar spaces. The interstitial pneumonitis progressed to fibrosis over time.

Toxicity endpoint: Mild sensory (nasal) irritation

Scaling: None: The same AEGL-1 value was used for 10 minutes to 8 hours because mild nasal sensory irritation does not vary greatly over time

Uncertainty Factors: Total uncertainty factor: 10
Interspecies: 3: Mild nasal irritation from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and not likely to vary greatly between species.
Intraspecies: 3: Mild nasal irritation from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and not likely to vary greatly among humans.

Modifying Factor: A modifying factor of 0.5 was applied to the Kinney et al. (1990) study because the exposures were repeated and the effect was essentially a NOAEL. A modifying factor of 3 was applied to the Sriramachari and Jeevaratnam (1994) study because the study was not robust and the endpoint was beyond that defined by an AEGL-1.

Calculations:

10-minute through 8-hour AEGL-1: 75 ppm/10 x 0.5 = 15 ppm (19 mg/m^3)
465 ppm/30 = 15 ppm (19 mg/m^3)

Derivation of AEGL-2

Key study: Kinney at al. (1990). Male rats were exposed to 0, 75, 250, or 750 ppm MMA for 6 hours/day, 5 days/week for 2 weeks. Rats exposed to 75 ppm had mild irritation of the nasal turbinates, whereas 250 ppm caused marked red nasal discharge and nasal mucosa lesions, and 750 ppm caused 50% mortality (starting on day 8) and lesions of the lungs, eyes, and other organs. At 250 ppm, lesions did not extend into the lungs. After a two week recovery period, the lesions observed at 250 ppm were largely reversible. Reversible nasal lesions are within the scope of AEGL-2 and were used as the point of departure.

Toxicity endpoint: Reversible nasal cavity lesions following repeat exposure of rats to 250 ppm, 6 hours/day for two weeks.

Scaling: Time scaling, $C^n \times t = k$, where n = 1.9 was calculated from both the LC_{50} data of IRDC (1992a) and the full data set on lethality of IRDC (1992a), the latter using the ten Berge (2006) computer program.

Uncertainty Factors: Total uncertainty factor: 10
Interspecies: 3. Nasal irritation from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and not likely to vary greatly between species.
Intraspecies: 3: Nasal irritation from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and not likely to vary greatly among humans.

Modifying Factor: None

Calculations: $(C/UF)^{1.9} \times t = k$
$(250\ ppm/10)^{1.9} \times 360\ minutes = 1.631 \times 10^5\ ppm^{1.9}\cdot min = k$

10-min AEGL-2 $C = (1.631 \times 10^5\ ppm^{1.9}\cdot min/10\ min)^{1/1.9}$
$C = 160\ ppm$

30-min AEGL-2 $C = (1.631 \times 10^5\ ppm^{1.9}\cdot min/30\ min)^{1/1.9}$
$C = 92\ ppm$

1-hour AEGL-2 $C = (1.631 \times 10^5\ ppm^{1.9}\cdot min/60\ min)^{1/1.9}$
$C = 64\ ppm$

4-hour AEGL-2 $C = (1.631 \times 10^5\ ppm^{1.9}\cdot min/240\ min)^{1/1.9}$
$C = 31\ ppm$

8-hour AEGL-2 $C = (1.631 \times 10^5\ ppm^{1.9}\cdot min/480\ min)^{1/1.9}$
$C = 21\ ppm$

Derivation of AEGL-3

Key study: IRDC (1992a). Sprague-Dawley rats (5/sex/dose) exposed whole-body to 4100, 6370, 7000, 7100 or 8670 ppm MMA for 60 minutes had 14-day mortalities of 0/10, 2/10, 4/10, 6/10, and 9/10, respectively. An LC_{50} of 7110 was obtained.

Toxicity endpoint: LC_{01} (lethality threshold) in rats

Scaling: The probit-analysis dose-response program of ten Berge was used to estimate the LC_{01} at each AEGL exposure duration. The full data set on lethality was used (see table below). The calculated n value was 1.87 (rounded to 1.9). A linear regression of the LC_{50} values at each of the exposure durations in the key study (6, 20, and 60 minutes) results in the same value of n.

Uncertainty Factors: Total uncertainty factor: 10
Interspecies: 3. Extreme pulmonary irritation from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and not likely to vary greatly between species.
Intraspecies: 3: Extreme pulmonary irritation from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and not likely to vary greatly among humans.

Modifying Factor: None

Data for calculations:

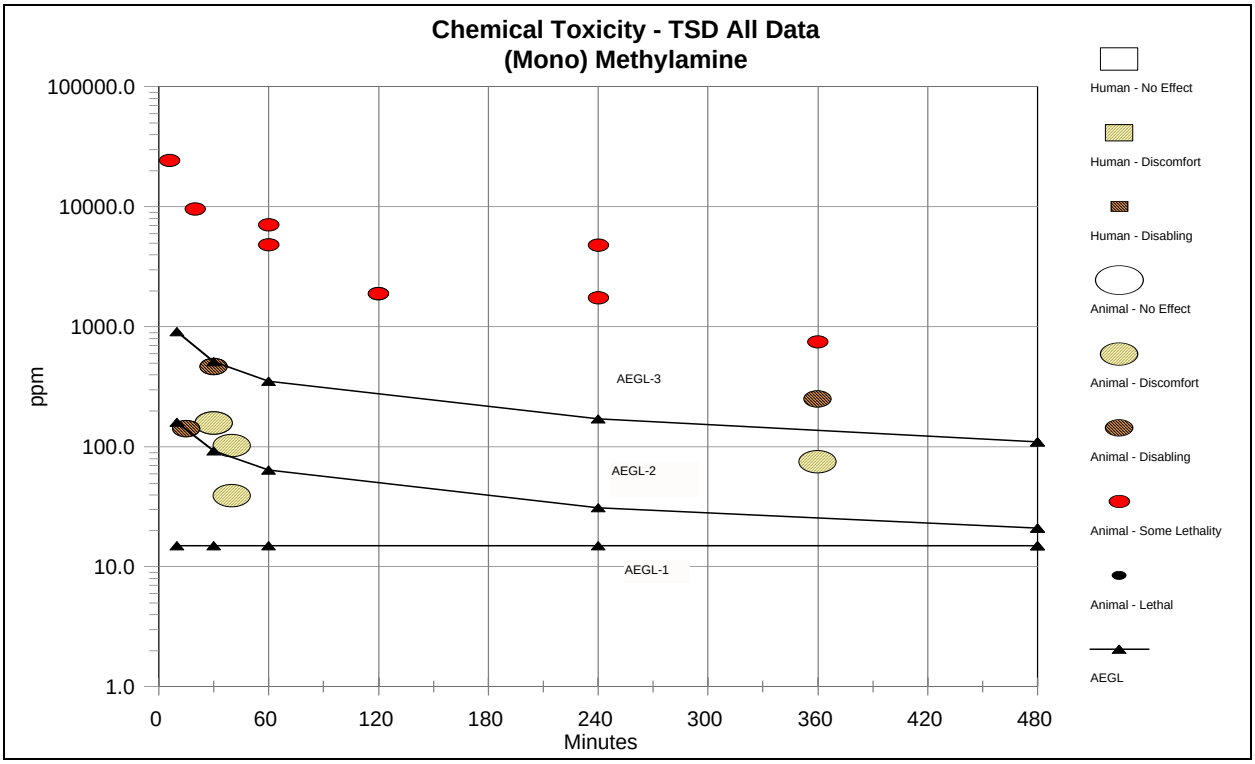
Exposure duration	MMA concentration (ppm)	Lethality	Necropsy gross findings	
			Eye abnormalities	Congested or red lungs
6 minutes	17,600	0/10	10/10	0/10
	22,500	3/10	10/10	3/10
	26,200	9/10	7/10	9/10
	26,500	6/10	10/10	4/10
	35,300	9/10	9/10	8/10
20 minutes	10,600	3/10	7/10	2/10
	10,800	7/10	10/10	6/10
	11,000	6/10	10/10	7/10
	11,600	10/10	10/10	8/10
	13,900	8/10	10/10	8/10
	17,400	9/10	10/10	9/10
60 minutes	4100	0/10	4/10	0/10
	6370	2/10	8/10	2/10
	7000	4/10	5/10	4/10
	7100	6/10	7/10	6/10
	8670	9/10	10/10	8/10

Program output:

Exposure Duration	AEGL-3 Value
10 minutes	910 ppm
30 minutes	510 ppm
60 minutes	350 ppm
4 hours	170 ppm
8 hours	110 ppm

n = 1.87

APPENDIX C: Category Plot for Methylamine (MMA)



The data included in this plot are shown below. The only study with reported exposure durations and concentrations that was omitted from the plot was Sarkar and Sastry (1992), because its 2.5-hour LC_{50} value of 448 ppm (24-hour observation) was grossly inconsistent with the other rat studies. This study used static exposure (in 12 L jar) and the analytical concentration was not determined.

For Category, 0 = No effect, 1 = Discomfort, 2 = Disabling, SL = Some Lethality, 3 = Lethal							
Source	Species	Sex	# Expo-sures	ppm	Minutes	Cate-gory	Comments
NAC/AEGL-1	rat	m	10	15	10	AEGL	Kinney et al 1990; 6 hr/day for 10 days
NAC/AEGL-1				15	30	AEGL	Sriramachari and Jeevaratnam 1994, 465 ppm for 30 minutes
NAC/AEGL-1				15	60	AEGL	
NAC/AEGL-1				15	240	AEGL	
NAC/AEGL-1				15	480	AEGL	
NAC/AEGL-2	rat	m, f	1	160	10	AEGL	Kinney et al 1990; 6 hr/day for 10 days
NAC/AEGL-2				92	30	AEGL	
NAC/AEGL-2				64	60	AEGL	
NAC/AEGL-2				31	240	AEGL	
NAC/AEGL-2				21	480	AEGL	
NAC/AEGL-3	rat	m, f	1	910	10	AEGL	IRDC 1992a; LC_{01} (threshold for lethality)

NAC/AEGL-3				510	30	AEGL	
NAC/AEGL-3				350	60	AEGL	
NAC/AEGL-3				170	240	AEGL	
NAC/AEGL-3				110	480	AEGL	
IRDC 1992a	rat	m, f	1	24400	6	sl	LC_{50} in rats; exposed to 16,600 - 35,300 ppm
			1	9600	20	sl	LC_{50} in rats; exposed to 10,600 - 17,400 ppm
			1	7110	60.0	sl	LC_{50} in rats; exposed to 4100 - 8670 ppm
Air Products 1976	rat	m, f	1	4830	60	sl	LC_{50} in rats; exposed to 1500 - 24,000 ppm
Koch et al. 1980	rat	f	1	4800	240.0	sl	LC_{50} in rats; exposed to 1865 - 10,469 ppm
Klimisch et al. 1983	rat	m, f	1	1740	240	sl	LC_{50} in rats; exposed to 517 - 3213 ppm
Kinney et al. 1990	rat	m	10	75	360	1	Mild irritation & discharge of nasal turbinates,
			10	250	360	2	Nasal lesions, severe discharge
			10	750	360	sl	Nasal lesions & discharge, mortality, ocular opacity, respiratory and neuro toxicity
Gorbachev 1957	mouse	?	1	1890	120	sl	LC_{50} in mice; actual exposure concentrations. Unknown
Jeevaratnam & Sriramachari 1994	rat	m	1	465	30	2	24-hr observation; lung hemorrhage, pneumonitis, split blood vessels
Sriramachari & Jeevaratnam 1994	rat	m	1	465	30	2	10-week observation; lung edema, pneumonitis progressing to fibrosis
Gagnaire et al. 1989	mouse	m	1	141	15	2	RD_{50} in mice; tested 85-192 ppm
Gorbachev 1957	rabbit	?	1	102	40	1	Threshold for irritation, manifested as decreased breathing rate
			1	39	40	1	Disrupted conditional and reflex activity
Gorbachev 1957	cat	?	1	157	30	1	Threshold for irritation, manifested as increased salivation

APPENDIX D: Derivation Summary of Acute Exposure Guideline Levels for Methylamine

AEGL-1 Values				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)	15 ppm (19 mg/m^3)

Key References:
(1) Kinney, L.A., R. Valentine, H.C. Chen et al. 1990. Inhalation Toxicology of Methylamine. Inhal. Toxicol. 2: 29-39.
(2) Sriramachari, S. and K. Jeevaratnam. 1994. Comparative toxicity of methyl isocyanate and its hydrolytic derivatives in rats. II. Pulmonary histopathology in the subacute and chronic phases. Arch. Toxicol. 69: 45-51.

Test species/Strain/Sex/Number: (1) Male CD rats, 10/group; (2) Male Wistar rats, four total

Exposure Route/Concentrations/Duration: (1) Inhalation, nose-only to 0, 75, 250, or 750 ppm MMA 6 hours/day, 5 days/week for 2 weeks; (2) Inhalation, 465 ppm for 30 minutes

Effects:
(1) Rats exposed to 75 ppm had mild irritation of the nasal turbinates, whereas 250 ppm caused marked red nasal discharge and nasal mucosa lesions (focal erosions, ulcerations, blood clots, degeneration, necrosis) which in some cases persisted through the 2-week recovery period. Rats exposed to 750 ppm had 50% mortality (starting on day 8) and additionally had lesions of the lungs, eyes, liver, thymus, spleen, and brain;
(2) No clinical signs; pulmonary edema was observed after one week with progression to fibrosis after 10 weeks.

Endpoint/Concentration/Rationale: (1) Mild sensory (nasal) irritation from a single 30-minute exposure to 75 ppm; (2) Pulmonary congestion after a single exposure

Uncertainty Factors/Rationale: Total uncertainty factor: 10
Interspecies:
3: Mild sensory irritation from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and not likely to vary greatly between species.
Intraspecies:
3: Mild sensory irritation from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and not likely to vary greatly among humans.

Modifying Factor: (1) 0.5 based on the mild endpoint;
(2) 3 based on the lack of robustness of the study and the lung histopathology

Animal to Human Dosimetric Adjustment: Not applied

Time Scaling: None; using the same value for 10 minutes to 8 hours was considered appropriate because mild irritant effects do not vary greatly over time

Data Adequacy: The data are considered sufficient. The AEGL-1 falls in the concentration range expected to cause some sensory irritation (14 ppm) per methodology proposed by Alarie (1981), and the mouse respiratory inhibition study of Gagnaire et al. (1989).

1

AEGL-2 Values				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
160 ppm (200 mg/m^3)	92 ppm (120 mg/m^3)	64 ppm (80 mg/m^3)	31 ppm (39 mg/m^3)	21 ppm (27 mg/m^3)
Key reference: Kinney, L.A., R. Valentine, H.C. Chen et al. 1990. Inhalation Toxicology of Methylamine. Inhal. Toxicol. 2: 29-39.				
Tested species/Strains/Number: Male CD rats, 10/group				
Exposure Route/Concentrations/Duration: Inhalation, nose-only to 0, 75, 250, or 750 ppm MMA 6 hours/day, 5 days/week for 2 weeks				
Effects: Rats exposed to 75 ppm had mild irritation of the nasal turbinates, whereas 250 ppm caused marked red nasal discharge and nasal mucosa lesions (focal erosions, ulcerations, blood clots, degeneration, necrosis) which in some cases persisted through the 2-week recovery period. Rats exposed to 750 ppm had 50% mortality (starting on day 8) and additionally had lesions of the lungs, eyes, liver, thymus, spleen, and brain				
Endpoint/Concentration/Rationale: Reversible nasal lesions (NOAEL for irreversible nasal lesions) following repeat exposure to 250 ppm for 6 hours.				
Uncertainty Factors/Rationale: Total uncertainty factor: 10 Interspecies: 3: Irritation from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and not likely to vary greatly between species. Intraspecies: 3: Irritation from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and not likely to vary greatly among humans.				
Modifying Factor: None				
Animal to Human Dosimetric Adjustment: Not applied				
Time Scaling: $C^n \times t = k$, where the same n value of 1.9 was calculated from the three LC_{50} values of IRDC (1992a) or the whole IRDC data set, the latter using the ten Berge (2006) probit analysis computer program.				
Data Adequacy: The data were considered adequate to derive AEGL-2 values. The developed AEGL-2 values are consistent with secondary source human reports that short exposures (unknown duration) to 20-100 ppm MMA caused irritation of the eyes, nose, and throat, whereas above 100 ppm, MMA vapors were "intolerably ammoniacal," and caused larynx constriction, difficulty breathing, pulmonary congestion, and lung edema (Sutton 1963; Deichmann and Gerarde 1969). Using the IRDC (1992a) highest non-lethal value at 60 minutes (4100 ppm) and applying a modifying factor of 3 (a conservative approach) along with the total uncertainty factor of 10 yields values that are two-fold higher.				

1

AEGL-3 Values				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
910 ppm (1200 mg/m^3)	510 ppm (650 mg/m^3)	350 ppm (440 mg/m^3)	170 ppm (220 mg/m^3)	110 ppm (140 mg/m^3)

Key reference: IRDC (International Research and Development Corporation). 1992a. Acute inhalation toxicity evaluation on monomethylamine in rats. Study sponsored by Air Products and Chemicals, Inc., Allentown, PA.

Tested species/Strains/Number: CD Sprague-Dawley rats, 5/group/sex

Exposure Route/Concentrations/Duration: Inhalation of 17,600, 22,500, 26,200, 26,500, or 35,300 ppm for 6 minutes; 10,600, 10,800, 11,000, 11,600, 13,900, or 17,400 ppm for 20 minutes; 4100, 6370, 7000, 7100, 8670 ppm for 60 minutes

Effects: Labored breathing, rales, and corneal opacity persisted throughout the study. Body weight gains were decreased primarily during the first week. Necropsy revealed eye abnormalities (primarily corneal opacity) and lung congestion (red, discolored lungs). Mortalities for the respective 6-minute exposure duration were 0/10, 3/10, 9/10, 6/10, and 9/10. Mortalities for the respective 20-minute exposure duration were 3/10, 7/10, 6/10, 10/10, 8/10, and 9/10. Mortalities for the respective 60-minute exposure duration were 0/10, 2/10, 4/10, 6/10, and 9/10.

Endpoint/Concentration/Rationale: LC_{01} (lethality thresholds) at each exposure duration as calculated by the ten Berge (2006) probit analysis software program

Uncertainty Factors/Rationale: Total uncertainty factor: 10

Interspecies:

3: Pulmonary congestion from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and not likely to vary greatly between species.

Intraspecies:

3: Pulmonary congestion from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and not likely to vary greatly among humans.

Modifying factor: None

Animal to Human Dosimetric Adjustment: Not applied

Time Scaling: $C^n \times t = k$, where the same n value of 1.9 was calculated from the three LC_{50} values of IRDC (1992a) or the whole IRDC data set, the latter using the ten Berge (2006) probit analysis computer program.

Data Adequacy: The key study was consistent with the overall MMA data set, showed a clear dose-response, and was the best of the seven available acute lethality studies.

2

3