ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
TRIMETHYLAMINE
(CAS Reg. No. 75-50-3)

INTERIM

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) was 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

Trimethylamine (TMA) is a basic ($pK_a = 9.80$) aliphatic tertiary amine gas at room temperature with a pungent, fishy, ammonia-like odor. It is very soluble in water and in organic solvents. TMA is present in the plasma and urine of humans, and is ingested in foods such as fish; it is also formed following ingestion of foods containing TMA precursors (e.g., trimethylamine oxide, choline, and L-carnitine) after metabolism by enterobacteria. TMA vapor has caused respiratory and eye irritation leading to respiratory tract and corneal lesions, as well as neurotoxic effects, and in some cases pathological changes in the liver, spleen, and kidneys.

The level of distinct odor awareness (LOA) for TMA is 0.00051 ppm (see Appendix A for LOA derivation). 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 was based on human occupational exposure data (AIHA 2005). The AIHA report indicated that TMA concentrations ranging from 0.1 to 8 ppm did not cause toxic effects in workers exposed to 8-hour periods. The point of departure is the 8-hour exposure to 8 ppm. An intraspecies uncertainty factor of 1 was applied for intraspecies variability because the effect was below the definition of an AEGL-1, and the healthy worker population is thought to encompass a range of variability in response to an irritant. AEGL-1 values were set equal for all exposure durations from 10 minutes to 8 hours because the irritating effects of TMA at low concentrations are considered to be concentration related, and the there is adaptation to the mild irritation that defines the AEGL-1. The value is supported by the relative toxicity to dimethylamine for which there were sufficient animal data that addressed AEGL-1 level effects.

AEGL-2 values were derived from an acute inhalation study in which 0/6 male CD rats died after a 4-hour exposure to 2000 ppm; whereas, 3/6 died at 3500 ppm (Kinney et al. 1990). During exposure, rats at both concentrations had difficulty breathing, showed nasal and oral discharge, were immobile, and did not react to sound. Because the severity of these effects exceeds the scope of AEGL-2, the non-lethal concentration of 2000 ppm was divided by 3 to obtain 670 ppm as an estimate of the threshold for lung lesions and neurotoxicity. The 4-hour 670 ppm concentration was used as the point of departure for the AEGL-2. An interspecies uncertainty factor of 3 was applied because animal lethality data showed little interspecies differences, and the irritating effect from a direct-acting alkaline chemical is not expected to vary greatly between species. An intraspecies uncertainty factor of 3 was applied because the effect of a direct-acting irritant is unlikely to vary greatly among humans (NRC 2001). Following adjustment by 1/3, a total uncertainty factor of 10 was applied. Time-concentration scaling for was performed using the ten Berge et al. (1986) relationship, $C^n \times t = k$, where $n = 2.5$. This relationship was calculated from rat lethality data ranging from 20 minutes to 4 hours.

AEGL-3 values were derived from a study in which CD Sprague-Dawley rats were exposed to 11,200-18,200 ppm for 20 minutes or 6150-8170 ppm TMA for 60 minutes (IRDC 1992a). The rats exhibited gasping, labored breathing, salivation, corneal opacity, congested or reddened lungs, and mortality. Similar effects were seen in the rat and mouse acute lethality studies. The data allowed calculation of LC_{50}, $BMCL_{05}$ and BMC_{01} values for

both time points. The 20- and 60-minute $BMCL_{05}$ values of 5719 and 3841 ppm, respectively were used as points of departure for deriving AEGL-3 values. Interspecies and intraspecies uncertainty factors of 3 each for a total of 10 were applied because lethality data from mice and rats suggested little interspecies variability, and the effects of an alkaline, direct-acting irritant are unlikely to vary greatly between species or among humans (NRC 2001). Time-concentration scaling was performed using the ten Berge et al. (1986) relationship $C^n \times t = k$, where $n = 2.5$ was calculated from a linear regression of three LC_{50} values with exposure durations of 20 minutes to 4 hours. The 20-minute $BMCL_{05}$ was time-scaled to the 10- and 30-minute AEGL-3 exposure durations, and the 60-minute $BMCL_{05}$ was time-scaled to the 4- and 8-hour exposure durations.

AEGL values are listed in Table 1.

TABLE 1. Summary of AEGL Values for Trimethylamine

Classification	10-min	30-min	1-h	4-h	8-h	Endpoints (Reference)
AEGL–1[1] (Nondisabling)	8.0 ppm (19 mg/m³)	8.0 ppm (19 mg/m³)	8.0 ppm (19 mg/m³)	8.0 ppm (19 mg/m³)	8.0 ppm (19 mg/m³)	No-effect level in occupational exposures (AIHA 2005)
AEGL–2 (Disabling)	240 ppm (580 mg/m³)	150 ppm (360 mg/m³)	120 ppm (290 mg/m³)	67 ppm (160 mg/m³)	51 ppm (120 mg/m³)	Estimated threshold for lung toxicity and neurotoxicity in rats (Kinney et al. 1990)
AEGL–3 (Lethal)	750 ppm (1800 mg/m³)	490 ppm (1200 mg/m³)	380 ppm (920 mg/m³)	220 ppm (530 mg/m³)	170 ppm (410 mg/m³)	$BMCL_{05}$ in rats (IRDC 1992a)

[1]A Level of Distinct Odor Awareness (LOA) of 0.00051 ppm was calculated for TMA, as shown in Appendix A. The LOA is defined as the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, and about 10% of the population will experience a strong odor intensity (Van Doorn et al. 2002).

1. INTRODUCTION

Trimethylamine (TMA), a basic ($pK_a = 9.80$) aliphatic tertiary amine, is a gas at room temperature with a pungent, fishy, ammonia-like odor. TMA is formed naturally from the biodegradation of plants, fish and animal products, and is ingested in foods such as fish, or from foods containing TMA precursors [e.g. trimethylamine oxide (TMAO), choline, and L-carnitine], which are metabolized to TMA by enterobacteria (Bain et al. 2005). Human exposure to TMA vapor has caused respiratory and eye irritation and corneal lesions. Effects in laboratory animals consisted of respiratory tract toxicity (gasping, labored breathing, lung lesions), eye lesions, neurotoxicity (apathy, splayed hind- or forelimbs, uncoordinated movements, convulsions, brain lesions), and some studies also found pathological changes of the liver, spleen, and kidneys.

TMA is very soluble in water and in organic solvents. TMA is used as a warning agent for natural gas, a synthetic flavor (fish) ingredient, and in the synthesis of photochemicals, choline salts, flotation agents, dyes, pesticides, ion-exchange resins, cationic starches, and intense sweeteners (HSDB 2006). TMA can be synthesized from paraformaldehyde and ammonium chloride, by the reaction of formic acid, formaldehyde, and ammonia, and by interaction of methanol and ammonia with a catalyst at high temperature. The U.S. production capacity of TMA was 170,000 tons in 1990 (HSDB 2006). Selected physical and chemical properties of TMA are presented in Table 2.

TABLE 2. Chemical and Physical Properties of Trimethylamine		
Parameter	**Value**	**Reference**
Synonyms	N,N-dimethylmethanamine; TMA	NIOSH 2005
Chemical formula	$(CH_3)_3N$; C_3H_9N	NIOSH 2005; HSDB 2006
Molecular weight	59.11	O'Neil et al. 2001
CAS Reg. No.	75-50-3	O'Neil et al. 2001
Physical state	Gas (colorless); liquid below 2.8°C	O'Neil et al. 2001
Water solubility	Very soluble in water (and organic solvents)	O'Neil et al. 2001; HSDB 2006
Dissociation constant (pKa)	9.80	HSDB 2006
Density	0.627 g/mL at 25°C	HSDB 2006
Boiling point	2.87°C (1atm)	O'Neil et al. 2001
Melting point	- 117.08°C	O'Neil et al. 2001
Vapor Density (air =1)	2.04	Cavender 2001
Vapor Pressure	1610 mm Hg at 25°C	Daubert and Danner 1989
Flammability limits in air	2.0 – 11.6% (by volume)	NIOSH 2005
Conversion factors	1ppm = 2.42 mg/m³; 1 mg/m³ =0.4136 ppm	NIOSH 2005

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data concerning lethal TMA concentrations in humans were located.

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold/Odor Awareness

TMA has a pungent, fishy ammonia-like odor. A secondary source reports that "methylamines" [defined as TMA, DMA (dimethylamine), and MMA (monomethylamine)] have a pungent, fishy odor below 100 ppm, but at air concentration "somewhere in the range of 100-500 ppm," their odor is indistinguishable from that of ammonia (Deichmann and Gerarde 1969).

The TMA odor threshold has been reported as 0.00021 ppm (Leonardos et al. 1969), 0.00033 ppm (Ruth 1986), 0.00044 ppm (Amoore and Hautala 1983), 0.00058 ppm (Stephens 1971), and 0.000032 ppm (Ruijten 2005) in sources considered credible. Rejected/unreviewed sources give a range of odor thresholds as 0.00011-0.87 ppm (AIHA 1995).

Using human volunteers, Rotenberg and Mashbits (1967) determined a TMA odor awareness threshold of 0.8 ppm, which produced a fishy odor. The chemical and analytical detection was performed with colorimetric methodology, based on the occurrence of yellow coloration when a TMA aqueous solution is in the presence of ortho-nitrophenol.

A level of distinct odor awareness (LOA) of 0.00051 ppm was calculated for TMA using the method of van Doorn et al. (2002), and the odor detection threshold of 0.000032 ppm provided by Ruijten (2005). The calculation is shown in Appendix A. The LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, and about 10% of the population will experience a strong odor intensity.

2.2.2. Clinical Studies

A number of human oral exposure studies were conducted to investigate the metabolism and toxicokinetics of TMA, as described in Section 4.1.

2.2.3. Occupational Exposure

The AIHA (2005) reported that TMA concentrations ranging from 0.1-8 ppm, with most 8-hour TWAs of <5 ppm, were measured in industrial rooms during 8-hour workdays. "Routine medical and biological monitoring" (not described) revealed no toxic effects in these workers. This limited report did not state whether any irritation occurred at 0.1-8 ppm, but did state that "moderate" upper respiratory irritation occurred at ≥ 20 ppm (exposure time not specified). No additional details were provided.

A secondary source (Deichmann and Gerarde 1969) reports that "methylamines" (defined as TMA, DMA and MMA) at >100 ppm cause irritation of the nose and throat, violent sneezing, coughing, a burning sensation of the throat, larynx constriction, difficulty breathing, pulmonary congestion, and lung edema. Since the authors do not attribute these effects to "monomethylamine," they are assumed to be applicable for all three methylamines.

2.2.4. Accidental Exposure

A sealed glass vial containing TMA exploded when a chemistry student was trying to open it, sending TMA vapor to one of his eyes (Grant 1974). The student was wearing glasses and no mechanical injuries were observed, but the vapor triggered epithelium loss from the cornea. The epithelium healed and 4-5 days after the exposure the eye looked normal with no edema of the corneal stroma. The TMA concentration and exposure duration were not provided.

2.3. Neurotoxicity

The limited human TMA inhalation data reported no neurotoxic effects.

2.4. Developmental/Reproductive Toxicity

No data concerning potential reproductive or developmental toxicity of TMA in humans were found in the available literature.

2.5. Genotoxicity

No human genotoxicity data were found for TMA in the available literature.

2.6. Carcinogenicity

No studies were found that examined the carcinogenicity of TMA in humans. Because mechanisms have been proposed by which the known carcinogen N-nitrosodimethylamine can be formed from TMA and TMAO (Bain 2005) in the presence of nitrosating agents, there is some concern about the neoplastic potential of TMA. Thus, the German exposure guidelines warn that co-exposure to TMA and nitrosating agents should be minimized (see Section 8.2.). However, a 2-year mouse and rat inhalation study with the

related amine DMA, which can also potentially form N-nitrosodimethylamine, showed no tumor formation despite severe chronic nasal lesions (CIIT 1990).

2.7. Summary

Reported human TMA odor thresholds ranged from 0.00011- 0.87 ppm, with most of the values between 0.0011 and 0.0058 ppm. The AIHA (2005) reported that exposure to ≥20 ppm TMA caused respiratory irritation in humans, and that 0.1 to 8 ppm TMA did not cause any toxic effects in workers exposed for 8-hour workdays, but no were provided. A secondary source (Deichmann and Gerarde 1969) reports that "methylamines" at >100 ppm cause irritation of the nose and throat, larynx constriction, difficulty breathing, and lung edema. The level of distinct odor awareness (LOA) for TMA was calculated to be 0.00051 ppm.

Accidental exposure of a chemistry student's eye to TMA vapor caused epithelium loss from the cornea that resolved in 4-5 days, but the exposure concentration was unknown (Grant 1974). No human studies were located that evaluated TMA acute lethality, neurotoxicity, developmental or reproductive toxicity, genotoxicity, or carcinogenicity.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Table 3 summarizes the available TMA acute lethality data in laboratory animals after a single inhalation exposure.

TABLE 3. Trimethylamine Acute Lethality Inhalation Studies in Animals

Species	Exposure Time	Concentration (ppm)	Mortality	Effects (Reference)
Rat	3 min	"substantially saturated"	6/6	All animals died within 3 minutes; no other information was provided (BASF AG 1979a)
	6 min 10 min 20 min 60 min	18,600 18,100 11,200–18,200 6150–8170	0/10 2/10 LC_{50} = 11,870 ppm LC_{50} = 8010 ppm	Clinical signs included gasping, labored breathing, rales, salivation, decreased body weight gain, corneal opacity, congested or reddened lungs (IRDC 1992a)
	4 hr	2000 3500 ppm	0/6 3/6	During exposure rats were immobile, did not react to sound, had difficulty breathing, and showed nasal and oral discharge. Rats had weight loss for days 1-2 and lung noise for days 1-9. Animals were not necropsied (Kinney et al. 1990)
	4 hr	3243–5750 (at 22°C)	LC_{50} = 4350 ppm	Rats were restless, then apathetic, had splayed limbs, inspirational dyspnea, uncoordinated movements, convulsions, excessive sweating, lacrimation, nasal hemorrhage; lung, liver, kidney, heart lesions (Koch et al. 1980; Johannsen et al. 1980)
Mouse	2 hr	Unknown	LC_{16} = 5910 ppm LC_{50} = 7850 ppm LC_{84} = 10,250 ppm	During exposure, agitation progressed to decreased movement and no response to external stimuli, loss of motor coordination, and clonic spasms lasting for 2-3 minutes. (Rotenberg and Mashbits 1967)

3.1.1. Rats

Rats (6/sex) exposed to a "substantially saturated" atmosphere of TMA at 20°C all died within 3 minutes (BASF AG 1979a). The TMA concentration was not measured. No further study details were provided except to state that the study was performed using the range-finding method of Smyth et al. (1962).

Koch et al. (1980) exposed female Wistar rats (8 weeks old) to 3040-7455 ppm TMA for 4 hours at 21.8 – 29.4°C in a series of five experiments using 44 groups of 10 rats. The test concentrations were not stated, but were a geometric progression series using a factor of 1.05-1.15. A control group was included. The chamber humidity, temperature, and CO_2 content (<0.2 vol %) were controlled and TMA concentration was monitored by gas chromatography. Animals were observed during exposure and for 14 days post-exposure. During exposure, the rats were initially restless but within a half hour appeared apathetic, had splayed hind- or forelimbs, inspirational dyspnea, and occasional uncoordinated movements and convulsions. During the second half-hour of exposure, the rats had marked hyperhidrosis (excessive sweating) and increased apathy and intensity of central nervous system effects, which consisted of sudden convulsions or muscle tremors that interrupted the somnolent state of the animals. The rats also had prolific nasal secretions, lacrimation, hemorrhage from the corners of the eyes and nasal orifices, and cyanosis of the ears. The first deaths occurred after 2 hours of exposure, and most animals died during the 4th exposure hour, typically following convulsions; the last animal died on day 4. Post-exposure signs included severe apathy, swelling of nasal orifices, dried bloody excretions, anorexia, and general ill health. These signs disappeared rapidly in the surviving animals. The calculated LC_{50} values (method of Spearman and Kärber and probit analysis) decreased as temperature increased, and were approximately 4350 ppm at 21.8EC, 3910 ppm at 25.7EC, 3840 ppm at 27.0EC, and 3380 ppm at 29EC.

Johannsen et al. (1980) histologically examined 82 of the rats exposed to TMA in the experiment of Koch et al. (1980). The 82 rats consisted of 63 rats that died during or after exposure (mean survival time of 3.3 hours), and 19 rats that survived 28 days (until sacrifice). The study authors did not state the exposure concentration of TMA or the room temperature; per Koch et al. (1980), TMA was in the range of 3040-7455 ppm, and the temperature was 21.8-29.4°C. The animals were examined macroscopically and the lungs, liver, kidneys, heart, skeletal muscle, and brain were examined microscopically. In the premature decedents, macroscopic abnormalities included marked blood profusion of the liver, spleen, and kidneys, and lung lobular hyperemia. Microscopic lung changes consisted of lobular red areas, bronchial inflammation with desquamation of the bronchial epithelium, bronchopneumonia in a few cases, and perivascular and peribronchial edema. Liver lesions included perilobular fatty liver, liver cell degeneration, and hyperemia. Most animals had lower nephron necrosis and vascular hyperemia of the kidneys, heart muscle, and many had brain edema and hyperemia. The surviving rats had few pathological changes, including one case of bronchopneumonia and three of lower nephron necrosis.

In an inhalation LC_{50} study (IRDC 1992a), CD Sprague-Dawley rats (5/sex/dose; 49-82 days old) were exposed whole-body to anhydrous TMA for 6 minutes (18,600 ppm), 10 minutes (18,100 ppm), 20 minutes (11,200-18,200 ppm), or 60 minutes (6150-8170 ppm). The study is summarized in Table 4. Exposure concentrations were generated by diluting TMA gas with air, and were quantitated by IR spectroscopy. Animals were observed daily for 14 days, weighed on days 0, 7, and 14, and survivors sacrificed on day 14. All animals were necropsied. The rats had decreased body weight gain primarily during the 1st week, and

all groups exhibited gasping, labored breathing, rales, increased salivation, and corneal opacity immediately after exposure. The respiratory changes persisted throughout the study in only the 20 and 60 minute exposure groups, whereas corneal opacity persisted in all groups. Necropsy revealed eye lesions (cloudy cornea) in a few animals with no dose-response, and dose-related increases in the incidence of lung congestion (red, discolored lungs), which generally correlated with lethality. Lethality occurred in all groups treated for ≥ 10 minutes, was generally dose-related, and primarily occurred immediately after exposure. The LC_{50} values [and 95% confidence limits] were 12,000 ppm [10,800-13,100 ppm] for 20 minutes and 7910 ppm [7300-8560 ppm] for 60 minutes, as calculated by the method of C.I. Bliss (1938). Subsequent analysis of the mortality data using EPA BenchMark dose software (Version 1.3.2.) yielded 20-minute values of LC_{50}= 11,870 ppm, BMC_{01}= 7420 ppm, and $BMCL_{05}$= 5720 ppm; and 60-minute values of LC_{50}= 8010 ppm, BMC_{01}= 6330 ppm, and $BMCL_{05}$= 4100 ppm. The statistical confidence was greater for the 60-minute values (p = 0.50) than for the 20-minute values (p = 0.069).

TABLE 4. Summary of Lethality Data in Rats following Exposure to TMA

Exposure duration	Concentration (ppm)	Lethality	Observations	Necropsy findings	
				Cloudy cornea	Congested or red lungs
6 min	18,600	0/10	Labored breathing, corneal opacity, inc. salivation	0/10	0/10
10 min	18,100	2/10	Death, gasping, rales, labored breathing, corneal opacity, decreased body weight gain throughout study	2/10	4/10
20 min	11,200 12,700 12,700 14,100 16,200 18,200	2/10 6/10 9/10 9/10 8/10 10/10	LC_{50}= 12,000 ppm[1]; gasping, labored breathing, salivation, corneal opacity, decreased. Body weight gain during week 1 for males and both weeks for females at 11,200 and 12,700 ppm	4/10 0/10 0/10 2/10 1/10 1/10	1/10 6/10 4/10 7/10 8/10 10/10
60 min	6150 7100 7680 7720 8170	1/10 3/10 4/10 3/10 7/10	LC_{50}= 7910 ppm[2]; gasping, labored breathing, rales, corneal opacity, decreased body weight gain during week 1 for all males and for females at >7100 ppm	0/10 0/10 1/10 0/10 1/10	1/10 2/10 3/10 3/10 6/10

[1]BenchMark dose software yields LC_{50}= 11,870 ppm; BMC_{01}= 7420 ppm; and $BMCL_{05}$= 5720 ppm.
[2]BenchMark dose software yields LC_{50}= 8010 ppm; BMC_{01}= 6330 ppm; and $BMCL_{05}$= 4100 ppm.
Source: IRDC 1992a.

Kinney et al. (1990) studied TMA acute toxicity in 7-8 week old male CD (SD)BR rats. The TMA atmosphere was generated by dilution of TMA gas with 15 L/min air, and TMA air concentration was measured every 30 minutes with a Miran 1A infrared spectrometer. Rats (6/group) were exposed to 2000 or 3500 ppm TMA for 4 hrs, observed and weighed daily for two weeks, and the survivors sacrificed. Neither gross nor microscopic pathology were evaluated. No animals died in the 2000 ppm group, whereas at 3500 ppm TMA 3/6 animals died during exposure. During the exposure, all rats were immobile and did not react to sound, and exhibited difficulty breathing, and nasal and oral discharge. After exposure, survivors had moderate to severe (unspecified) weight loss for days 1-2, and lung noise for days 1-9. At 3500 ppm, rats also had dry red nasal and ocular discharge at the beginning of the post-exposure period.

3.1.2. Mice

Rotenberg and Mashbits (1967) exposed male white mice to TMA for 2 hours. A total of 114 animals were used, but the number of animals/concentration and the concentrations tested were not provided. A colorimetric assay using ortho-nitrophenol was used for chemical and analytical measurements of TMA. The lethality values obtained were LC_{16} = 5910 ppm, LC_{50} = 7850 ppm, and LC_{84} = 10,250 ppm. During exposure, the animals were initially agitated but this symptom gradually progressed to decreased movement. The animals did not respond to external stimuli. By the beginning of the 2nd hour of exposure, animals experienced loss of motor coordination and exhibited clonic spasms lasting for 2-3 minutes before death. It was not stated whether the animals were necropsied.

3.2. Nonlethal Toxicity

The available TMA nonlethal toxicity animal studies are summarized in Table 5.

TABLE 5. Trimethylamine Non-lethal Exposure Inhalation Studies in Animals

Species	Exposure Time	Concentration tested (ppm)	Effect (Reference)
Rat	4 hr	2440	Irregular respiration and nasal discharge during and one day after treatment. Incomplete report (BASF AG 1979b)
Rat	6 h/d, 5 d/wk for 2 wks	74 240 760	All groups had microscopic lesions in the nose, and 760 ppm group also in trachea and lungs; nasal lesions were minimal at 74 ppm and moderate or severe at 760 ppm, and still present after the recovery period; 760 ppm rats also had decreased response to auditory stimuli during exposure and decreased mean BW from 2nd exposure day through the 7th recovery day (Kinney et al. 1990)
Rat	5 hr/d for 7 months	10.4 31.0	Rats were excited and aggressive during first month, had diarrhea during exposure; at 31 ppm had lung lesions (bronchopneumonia, hemorrhage, necrosis) and hemorrhage in the liver, kidneys and spleen, and inc. adrenal gland weight; 10 ppm group had similar but less pronounced changes (Rotenberg and Mashbits 1967)
Mouse	15 min	17 – 70	The concentration that reduced the respiratory rate by 50% (RD_{50}) was calculated to be 61 ppm (Gagnaire et al. 1989)

3.2.1. Rats

Groups of Sprague-Dawley rats (10/sex) exposed whole-body for 4 hours to 2440 ppm TMA (2570 ppm nominal) had irregular respiration and nasal discharge during and one day after treatment (BASF AG 1979b). None died during the 14-day study. No effects were seen on animal body weight, taken on study days 0, 7, and 14, and necropsy of all animals revealed no toxic effects. Further study details were not available. These study results were inconsistent with the body of the TMA data, i.e., much lower toxicity was seen at the given test concentration than in other studies.

Kinney et al. (1990) exposed 8-week old male CD rats (10/group) by nose-only inhalation to either 0 (air-only control), 74, 240, or 760 ppm TMA for 6 hours/day, 5 days/week for 2 weeks (10 exposures). The chamber atmosphere was analyzed with a Miran 1A infrared spectrometer every 30 minutes during exposure. Animals were observed and weighed daily. Rats were sacrificed either immediately following exposure (5/group) or after a 14-day recovery period (5/group); organs and tissues were examined macroscopically

and microscopically. The heart, lungs, liver, spleen, kidneys, testes, and thymus were weighed. Urinalysis, hematology of whole blood, and serum chemistry were evaluated prior to sacrifice after the 10-day exposure (10 rats/group), and after the 2-week recovery period (5 rats/group). Only the 760 ppm group had clinical signs, consisting of decreased response to auditory stimuli during exposure, and decreased mean body weight from the second exposure day through the seventh day of recovery. Small increases were seen in the erythrocyte count at 250 and 760 ppm, and in hemoglobin concentration, hematocrit, platelet count, the absolute number of neutrophils, and serum concentrations of urea nitrogen, protein and creatinine at 760 ppm. These changes were not present following the 14-day recovery period, and may have been due to dehydration at 760 ppm. All groups had histopathological alterations in the nose, trachea and lungs, which were the most severe in the nose, although only the 760 ppm rats had an increased incidence of tracheal and lung lesions relative to the control group (Table 6). The nasal lesions consisted of hyperemia and congestion with edema of the nasal mucosa, epithelial degeneration and necrosis of the nasal mucosa, focal regeneration or squamous metaplasia of the nasal mucosa, as well as bloody clots or inflammatory secretion in the nasal lumen. The irritation severity was dose-related, being minimal at 75 ppm and moderate or severe at 760 ppm, and was still evident at the end of the 14-day recovery period. The 760 ppm rats had increased lung weights and mildly distended alveoli and inflamed or necrotic tracheas after the tenth exposure only.

TABLE 6. Incidence [and Severity] of Clinical Pathology Findings in Rats Exposed to TMA for 6 Hours/Day, 5 Days/Week for 2 Weeks

Finding **(n=5)**	0 ppm		74 ppm		240 ppm		760 ppm	
Organ: Lesion	d 10[1]	d 14r[1]	d 10	d 14r	d 10	d 14r	d 10	d 14r
Nasal cavity and turbinates:								
Hyperemia, congestion with edema	0 [0]	0 [0]	4 [P]	4 [P]	5 [P]	3 [P]	5 [P]	5 [P]
Epithelial degeneration, necrosis, atrophy	0 [0]	0 [0]	5 [1]	5 [1]	4 [1]	4 [1]	5 [2]	5 [1]
Regeneration, focal squamous metaplasia	0 [0]	0 [0]	1 [P]	1 [P]	3 [P]	2 [P]	1 [P]	2 [P]
Blood clots, bloody inflammatory secretion	0 [0]	0 [0]	2 [P]	3 [P]	0 [0]	2 [P]	4 [P]	3 [P]
Trachea: Squamous metaplasia, focal	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	3 [P]	0 [0]
Tracheitis, necrosis	0 [0]	0 [0]	1 [1]	0 [0]	0 [0]	1 [1]	3 [2]	0 [0]
Lung: Focal interstitial pneumonitis	1 [1]	3 [1]	1 [1]	4 [1]	0 [0]	1 [1]	3 [2]	0 [0]
Emphysematous alveoli	0 [0]	0 [0]	0 [0]	0 [0]	1 [1]	0 [0]	4 [1]	0 [0]

[1]Animals were evaluated immediately after the 10th exposure (d 10) and after the 2-week recovery period, i.e., 14 d after the 10th exposure (d 14R).
Severity: 1 = slight; 2 = moderate; P = present.
Source: Kinney et al. 1990.

Rotenberg and Mashbits (1967) studied TMA inhalation exposure in a 7-month chronic experiment. Two groups of animals (12 male white rats/group) were exposed 5 hours/day to TMA at 10.4 ppm (25.0 mg/m^3) or 31.0 ppm (75.0 mg/m^3). Male rats from the third group were used as control. During exposure, air samples were taken 3-4 times a day and TMA levels determined (per method described in Section 2.2.1.). Excitation and aggressiveness were manifested for 3-4 weeks after the beginning of the experiment. For the first exposure month, diarrhea was observed during the first 2-3 hours of each exposure. Lymphocytes count decreased and the number of neutrophils increased in rats from the 31.0 ppm group beginning from the 4th exposure month onward. No statistically significant deviations between experimental and control groups were revealed when the following data were analyzed: body weight, oxygen consumption, emission of carbon dioxide, protein

fractions in the blood, antitoxic function of the liver (Quick's – Pytel's Test), and the threshold for nervous and muscular excitability. Pathomorphological studies showed animals from the 10.4 ppm group exhibited bronchopneumonia and hemorrhage in the pulmonary tissue with destruction of interalveolar layers, and isolated hemorrhage in the liver, kidneys and spleen. Rats from the 10 ppm group had similar changes but they were less pronounced. The only statistically significant change in relative organ weight was an increase of the adrenal gland weight of rats exposed to 31 ppm.

3.2.2. Mice

Gagnaire et al. (1989) exposed male Swiss-OF_1 mice oronasally to 17-70 ppm TMA for 15 minutes while measuring their respiratory rate by a plethysmographic technique. The mice were exposed in 200-liter steel inhalation chambers, the vapor was generated by running air through the liquid amine, and the ethylamine concentration was determined by HPLC. Decreased respiratory rate was considered to be an indicator of upper airway irritation, and occurred within 30-60 seconds of exposure. The respiratory rate returned to normal within one minute after cessation of exposure. The concentration that reduced the respiratory rate by 50% (RD_{50}) was calculated to be 61 ppm.

3.3. Neurotoxicity

Neurotoxic effects were seen in a number of the animal studies. Female Wistar rats exposed to 3040-7455 ppm TMA for 4 hours were initially restless during exposure, but within a half hour appeared increasingly apathetic, had splayed hind- or forelimbs, inspirational dyspnea, and occasional uncoordinated movements and convulsions (Koch et al. 1980). The animals had microscopic lesions in a number of organs, including brain edema and hyperemia, and most died during the 4^{th} exposure hour, typically following convulsions. In the IRDC (1992a) LC_{50} study, rats exposed for 6- 60 minutes to 6150 - 18,600 ppm had increased salivation in addition to dyspnea and eye lesions. Rats exposed to 2000 or 3500 ppm TMA for 4 hrs were immobile and did not react to sound, exhibited respiratory effects, and 3/6 died at 3500 ppm (Kinney et al. 1990). Male rats inhaling 74, 240, or 760 ppm TMA for 6 hr/day, 5 days/week for 2 weeks had a decreased response to auditory stimuli during exposure at 760 ppm, although it was not stated on which day(s) this occurred (Kinney et al. 1990). Rats exposed to 10.25 ppm TMA for 4 hours, or 10.4 or 31 ppm TMA 5 hours/day for 7 months were excited, aggressive, and had diarrhea during the first month, and the 31 ppm group had increased adrenal gland weight (Rotenberg and Mashbits 1967).

White mice exposed to 5910 - 10,250 ppm TMA for 2 hours were initially agitated but gradually became inactive, and by the second hour of exposure experienced a loss of motor coordination, did not respond to external stimuli, and exhibited clonic spasms lasting for 2-3 minutes prior to death (Rotenberg and Mashbits 1967).

3.4. Developmental/Reproductive Toxicity

Developmental or reproductive toxicity studies in which TMA was administered by inhalation were not available. The maternal and fetal toxicity of TMA in mice dosed intraperitoneally were evaluated in several studies. Pregnant Swiss mice given 18, 60, or 180 mg/kg TMA on gestation day (GD) 8 and sacrificed on GD 18 showed no maternal or fetal toxicity (Varma et al. 1990). Pregnant CD-1 mice given 14.8, 59, 148, or 296 mg/kg TMA from GD 1 to 17, and sacrificed on GD 18, had a transient increase in shallow breathing, tremors, loss of the righting reflex at 148 or 296 mg/kg TMA, and 5/11 died at

296 mg/kg (Guest and Varma 1991). Fetal body weight was decreased and fetal mortality increased at 148 and 296 mg/kg TMA. Pregnant Swiss CD-1 mice given 60, 150, 300, or 450 mg/kg/day TMA on GD 6-15 had decreased maternal weight and litter size at 450 mg/kg/day, and fetal weight was decreased at 300 and 450 mg/kg/day, more so for males than females (Guest and Varma 1993). Postnatal growth was inhibited at 450 mg/kg/day, and 8 weeks after birth, females had decreased kidney weight and males had decreased weight of the brain, kidneys, seminal vesicles, decreased brain protein and DNA content, and lower serum testosterone levels than age-matched controls.

Gavage administration of TMA (8, 40, or 200 mg/kg/day) to Sprague-Dawley rats from 2 weeks prior to breeding through day 4 of lactation caused no developmental or reproductive toxicity in a combined repeat dose and reproductive/developmental toxicity screening test (Takashima et al. 2003). Maternal toxicity was seen at only 200 mg/kg/day, consisting of excessive salivation, abnormal breathing noise, and one death on day 38 (pregnancy day 22).

3.5. Genotoxicity

TMA had no mutagenic activity in *Salmonella typhimurium* strains TA1535, TA1537, TA97, TA98 and TA100 with or without metabolic activation (Mortelmans et al., 1986). Concentrations of 0.010, 0.033, 0.10, 0.33, and 1.0 mg/plate were tested.

DuPont (1982) found no mutagenic activity in an Ames plate incorporation test using *S. typhimurium* strains TA1535, TA1537, TA98 and TA100, with or without liver metabolic activation. TMA was tested at 0.010, 0.050, 0.10, 0.50, 1.0, and 5.0 mg/plate, but due to cytotoxicity, in most cases results were only obtained for up to 1.0 mg/plate.

3.6. Carcinogenicity

No animal studies were found that examined the potential carcinogenicity of TMA. Mechanisms have been proposed by which TMA and TMAO can form the carcinogen N-nitrosodimethylamine and this has been accomplished *in vitro* (Bain 2005). 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 the related compound dimethylamine (DMA) found no increase in neoplasia in rats or mice exposed 6 hours/day, 5 days/week to up to 175 ppm (CIIT 1990).

3.7. Summary

TMA was toxic to the nervous and/or respiratory system in all of the conducted animal studies, which tested rats and mice. Koch et al. (1980) determined 4-hour LC_{50} values of approximately 4300 ppm at 22EC and approximately 3300 ppm at 29EC for female Wistar rats exposed to 3040-7455 ppm TMA. The animals had severe CNS effects and respiratory system toxicity, and microscopic evaluation (Johannsen et al. 1980) revealed pathological changes of the liver, spleen, and kidneys, lung, and brain. In the IRDC (1992a) LC_{50} study, rats were exposed for 6, 10, 20, or 60 minutes, but LC_{50} values were determined for only 20 minutes (12,000 ppm) and 60 minutes (7910 ppm) to avoid generating TMA concentrations in the explosive range (>20,000 ppm). The animals exhibited gasping, labored breathing, rales, increased salivation, corneal opacity, and lung lesions. Kinney et al. (1990) found that male rats that inhaled 2000 or 3500 ppm TMA for 4 hrs were immobile, did not react to sound, had difficult breathing, nasal and oral discharge, and 3/6 died at 3500 ppm. White

mice exposed to TMA for 2 hours were initially agitated but this symptom gradually progressed to decreased movement, loss of motor coordination, and clonic spasms that led to death (LC_{16} = 5910 ppm, LC_{50} = 7850 ppm, and LC_{84} = 10,250 ppm) (Rotenberg and Mashbits 1967).

Several non-lethal toxicity studies were available. CD rats exposed to 74, 240, or 760 ppm TMA for 6hr/day, 5 days/week for 2 weeks had decreased response to auditory stimuli during exposure and decreased body weight at 760 ppm, but all groups had histopathological alterations in the nose, trachea and lungs with dose-related severity that persisted through a 14-day recovery period. In a 7-month chronic experiment, rats exposed 5 hours/day to 10.4 ppm or 31.0 ppm TMA were excited, aggressive, and had diarrhea during exposure for the first month, and had a significant reduction in the threshold for nervous and muscular excitability (Rotenberg and Mashbits 1967). After 7 months, extensive lung lesions were found that were more pronounced in the 31 ppm group, which also had increased relative adrenal gland weight. Gagnaire et al. (1989) exposed male Swiss-OF_1 mice to 17-70 ppm TMA for 15 minutes, and determined that 61 ppm reduced the animals' respiratory rate by 50% (RD_{50}).

Developmental or reproductive toxicity studies using inhalation exposure were not available, although several rat and mouse studies found that TMA inhibited fetal growth and postnatal development at sufficiently high doses. TMA had no mutagenic activity in *Salmonella typhimurium* strains TA1535, TA1537, TA97, TA98 or TA100 with or without metabolic activation (Mortelmans et al., 1986; DuPont 1982). No studies examined the potential carcinogenicity of TMA, although it has been shown that TMA and its metabolite TMAO can form the carcinogen N-nitrosodimethylamine *in vitro*.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No studies were located evaluating the metabolism or disposition of TMA following inhalation exposure. TMA and its metabolites are present in the urine of humans due to metabolism of foods containing TMA precursors (Bain et al. 2005). In a group of five male volunteers, the plasma contained 6-15 µmol/L TMA and 4-97 µmol/L of the metabolite TMAO, and the median 24-hour urinary excretion was 0.2 mg TMA and 29 mg TMAO. Both human and animal studies have examined the metabolism and disposition of TMA after oral exposure, and showed that N-oxidation to TMAO is the major route of TMA metabolism, and little or no demethylation to form DMA occurs. Considerable variability exists in the ability of humans to metabolize TMA to TMAO.

4.1.1. Metabolism and Disposition of TMA in Humans

In humans, the metabolism of TMA to TMAO is mainly catalyzed by flavin-containing monooxygenase (FMO), which exists in several tissue-specific isoforms. Using an *in vitro* HPLC assay, Lang et al. (1998) showed that the human adult liver isoform FMO3 was at least 30-fold more active (i.e. greater turnover number) in metabolizing TMA to TMAO than human FMO variants FMO1, FMO2, FMO4, and FMO5, 11 heterologously expressed human P450 isoforms, and rabbit lung FMO2. FMO3 from adult liver was much more active than FMO3 from adult kidney or intestine, or human fetal liver, and was proposed to be responsible for TMA clearance in humans (Lang et al. 1998).

Four male volunteers ingested a capsule containing 300 mg TMA and a week later, 600 mg TMA as the hydrochloride salt (Al-Waiz et al. 1987a). Urine was collected the day before exposure (control) and for 8 hours after intake. The baseline pre-treatment urinary levels of 0.6 mg TMA and 23 mg TMAO increased 11-fold and 10-fold, respectively, after ingesting 300 mg, but increased 39-fold and 24-fold, respectively, after ingesting 600 mg, and gave the urine a fishy odor. Thus the capacity to metabolize TMA and/or to excrete TMAO was exceeded. Urinary levels of DMA were within 2-fold of control levels (4.4 mg TMA/8 hours) after either dose, indicating that demethylation was not a significant route of TMA metabolism.

TMA and TMAO were absorbed and eliminated rapidly in the urine of three healthy male volunteers who ingested 100 mg ^{14}C-TMA-HCl or ^{14}C-TMAO dihydrate, with ~95% of the radiolabel excreted in 24 hours (Al-Waiz et al. 1987b). Volatile exhaled amines or $^{14}CO_2$ were not detected after either treatment, and the feces contained only ~1% of the dose over the 3 days of sample collection. There was no evidence of TMA demethylation to DMA.

The plasma and urinary levels of TMA, TMAO, and DMA were evaluated by Lundh et al. (1995) in 5 healthy male non-smoking volunteers, age 25-55, who were given 300 or 600 mg TMA-HCl orally once a week for 6 weeks. Urine was collected before and for 24 hours after each dosing. Blood was taken before and one hour after dosing. The men were given a standardized diet during sample collection, and were asked to avoid eating fish and drinking alcohol during the study. Before dosing, the subjects' plasma contained 6-15 μmol/L TMA and 4-97 μmol/L TMAO. Treatment with 300 mg slightly increased plasma TMA levels in only one subject, whereas TMAO was increased to 155-253 μmol/L. Ingestion of 600 mg TMA increased plasma TMA to 14-59 μmol/L, with increases among the four subjects varying by up to 5-fold, and increased plasma TMAO to 222-407 μmol/L. The median 24-hour urinary excretion was 0.2 mg TMA and 29 mg TMAO before treatment, which increased to 3 mg TMA and 342 mg TMAO after treatment with the low dose, and to 23 mg TMA and 647 mg TMAO at the high dose, indicating that TMAO excretion was rate-limiting. DMA was not detected in plasma (<0.6 μmol/L), but small amounts were detected in the urine (1-2% of either dose).

4.1.2. Variation Among Humans in the Ability to N-oxidize TMA

It is known that some people have a decreased capacity to metabolize pungent TMA to non-odorous TMAO, and this hereditary autosomal recessive metabolic disorder is known as trimethylaminuria ("fish malodor syndrome") (Al-Waiz et al. 1987c; Zhang et al. 1995). This condition occurs much more frequently in women than men, and results in high concentrations of TMA in the plasma, urine, sweat, and breath. Affected individuals tend to have psychosocial problems such as depression and low self-esteem (Al-Waiz et al. 1987c). Whereas people with normal FMO3 activity excrete 0.5-1 mg TMA and 31-56 mg TMAO per 24 hours, trimethylaminuria patients excrete 12-36 mg TMA and 10 mg TMAO per 24 hours (Bain et al. 2005). Persons heterozygous for impaired N-oxidation can be identified when the individuals are challenged with 600 mg TMA, but not with lower doses (Al-Waiz et al. 1989). About 1% of the British Caucasian population is believed to be heterozygous carriers for impaired N-oxidation (Zhang et al. 1996a). A study of 82 Jordanian subjects found that 8 individuals had compromised ability to N-oxidize TMA to TMAO, suggesting that a significantly higher prevalence of this polymorphism in the Jordanian population (Hadidi et al. 1995). A smaller incidence of N-oxidation deficiency (2/116, 1.7%) was reported in a Jordanian population by Mitchell et al. (1997), who also reported a higher prevalence in subjects of Ecuadoran (3/80, 3.8%) and New Guinean (11/100, 11%) descent.

Toxic effects suggested, but not experimentally proven, as being caused by high but undefined TMA concentrations include abnormal neurological symptoms, teratogenic effects, altered rRNA synthesis, and an increased potential to form the carcinogen N-nitrosodimethylamine (Bain et al. 2005).

Cashman et al. (1997) and Dolphin et al. (1997) were among the first to identify FMO3 mutations in individuals with trimethylaminuria, and Cashman et al. (2000) identified two polymorphisms that are widely distributed in Canadian and Australian white populations. FMO3 DNA allele and genotype frequencies were evaluated at three polymorphic sites in 420 blood bank donors from California and Utah who were either non-Hispanic Caucasians, non-Hispanic African Americans, Hispanics, or Asians (Cashman et al. 2001). Significant heterogeneity was found among the ethnic subdivisions in the frequencies of alleles, haplotypes, and genotypes at the three sites, which may be correlated with differences in population susceptibility to chemicals metabolized by FMO3. The characterized human FMO3 gene variants have been catalogued in a database, which as of 2003 included 24 entries consisting of 12 missense, 3 nonsense, and one gross deletion mutation, as well as 8 variants not associated with trimethylaminuria (Hernandez et al. 2003).

A transient decrease in FMO3 activity resulting in secondary trimethylaminuria may be caused by an infection such as viral hepatitis, hormonal modulation of the enzyme during menstruation, or consuming large amounts of food high in TMA precursors such as choline or L-carnitine (Bain et al. 2005). Two cases of transient trimethylaminuria due to unknown causes were reported in children, in a two-month old girl and a four year-old boy (Mayatepek and Kohlmüller 1998). Analysis of their urine showed TMA levels more than 35-fold greater and TMAO levels up to 3-fold greater than healthy controls. The condition reversed itself spontaneously at 6 months of age for the infant and at 5 years of age for the boy.

Ten healthy male volunteers who ate 300 g/day brussell sprouts for 3 weeks had a 3-fold increase in their urinary TMA:TMAO ratio, indicating a significant reduction in FMO3 activity (Cashman 1999). The reduction of N-oxidation activity was proposed to be due to competitive enzyme inhibition by a metabolic intermediate formed during digestion of the sprouts, or to direct effects on regulation of the FMO3 gene.

A number of investigators have reported increased urinary excretion of TMA, often accompanied by body odor, in patients with liver disease. Mitchell et al. (1999) examined the 24-hour urine of 63 patients with various degrees of hepatocellular failure who had *foeter hepaticus*, or breath with a characteristic foul odor. Half of the patients had urinary TMA levels above the normal mean (0.08-1.84 µg/mL), of which 17 had urinary TMA levels >10 µg/mL. Wranne (1956) measured the urinary excretion of TMA and TMAO from 8 healthy people and 7 patients with liver disease at 1, 2, and 4 hours after ingesting 12 mg/kg TMA. The healthy subjects excreted ~95% of the ingested amine in the urine as TMAO after 4 hours, whereas TMAO was only ~40-75% of the total excreted TMA + TMAO in the 3 patients with the most severe liver disease. In a Japanese cohort of 24 male and 17 female patients (19-52 years old) with liver disease and trimethylaminuria, the urinary TMAO:TMA ratio was found to inversely correlate with their extent of liver damage, as determined by their plasma levels of lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase (Yamazaki et al. 2005).

4.1.3. Metabolism and Disposition of TMA in Animals

Several studies were available in which TMA was administered by ip, iv, oral, or intragastric routes. Al-Waiz and Mitchell (1991) showed that N-oxidation was the major pathway for TMA metabolism in 7 strains of rats (Wistar, Lewis, Fischer, A/GUS, PVG, DA, and BN; n=3) given a single, intragastric dose of 15 mg/kg body weight ^{14}C-TMA. During the first 24 hours after dosing, >75% of the radioactivity was excreted in the urine and ~3-9% in the feces. The urinary radioactivity consisted of ~52% TMA, ~45% TMAO, and ~3% DMA, and the feces contained >90% TMA and the rest TMAO, with no significant differences between the seven strains. In another study (Smith et al. 1994), 24 hours after iv dosing of Sprague-Dawley rats (n=5) with 0.2, 5.9, or 59 mg TMA, 96% of the radiolabel was present in the urine, and only minor amounts were in the feces (0.8%), in breath as CO_2 (0.8%), and in the blood and organs (each ≤ 0.04%). The fraction of unmetabolized TMA in the urine increased with dose: rats given 5.9 mg TMA excreted 17% of the dose as TMA and 39% as TMAO, but rats given 59 mg TMA excreted 42% of the dose as TMA and 17% as TMAO. The urine also contained substantial amounts of other unidentified metabolites, which were negligible in humans, albeit at a 20-fold lower dose of TMA (1-2% of dose; Al-Waiz et al. 1987b). TMA blood concentration decreased monoexponentially, as measured at 15 minutes, 30 minutes, and 1, 2, 4, and 8 hours after dosing, consistent with one-compartment kinetics. The TMA volume of distribution was high (725, 344, and 869 mL after dosing with 0.2, 5.9 and 59 mg TMA, respectively), suggesting that some tissues or regions outside the GI tract contained high TMA levels. The investigators noted that rapid administration (< 1 minute) of the high dose (59 mg) caused "respiratory distress" in the animals for 30 minutes, but this effect was reduced if the dose was given more slowly (3-5 minutes) or was given intraperitoneally.

The pharmacokinetics of TMA were examined in male Wistar rats (6/dose) given 10-40 mg/kg TMA intravenously (iv) as a bolus dose, or 20 mg/kg TMA orally (Nnane and Damani 2001). After iv dosing, TMA blood levels declined monoexponentially, and the TMA elimination half-life was 2-2.5 hours. The pharmacokinetics were linear at 10 and 20 mg/kg, but there was evidence of some saturation of TMA clearance and metabolism at 40 mg/kg. After oral dosing, TMA blood concentration peaked at 1 hour, and then declined monoexponentially with a half-life of 1.65 hours. TMAO blood levels were maximal 0.75-1 hour after iv dosing, and 0.75 hour after oral dosing. Blood TMAO concentrations declined roughly exponentially, albeit with a slope shallower than for TMA, after dosing by either route, indicating that TMAO elimination was rate-limiting. The large apparent volume of distribution after i.v. dosing (3.2-4.4 L/kg) indicated that TMA undergoes extensive distribution into rat tissues. The investigators also found that altering the composition of the animals' diet had a notable effect on TMA pharmacokinetics.

4.2. Mechanism of Toxicity

No studies were located that specifically addressed the mechanism of TMA toxicity. Its irritant properties are likely due to its alkalinity (pK_a of 9.80 at 25°C) and corrosiveness to exposed tissues such as eyes and the respiratory mucosa. Respiratory irritation, manifest as breathing difficulties and microscopic lesions of the nose, trachea, and lungs were seen in all TMA toxicity animal studies. The lesions were the most severe in the upper respiratory tract, consistent with the TMA high water-solubility.

Most of the TMA animal toxicity studies also reported neurotoxic effects, of which the mechanism is unknown, but which are consistent with the fact that TMA is lipid-soluble

as well as water-soluble. Neurotoxic effects in rats and mice were characterized as a decreased response to auditory stimuli, increased salivation, and as an initial restlessness or excitability followed by immobility, uncoordinated movements, and convulsions (Rotenberg and Mashbits 1967; Koch et al. 1980; Kinney et al. 1990; IRDC 1992a).

4.3. Structure-Activity Relationships

A comparison of the inhalation toxicity of TMA and its metabolite TMAO could not be made since TMAO is not a gas at room temperature. However, Dechezlepretre et al. (1967) found that TMA was considerably more toxic than TMAO in a series of intravenous injection experiments with mice. Groups of 6-12 male mice (strain Ardenay) were dosed with 6-8 unspecified doses (geometric progression) of either TMA, TMAO, TMA + TMAO, or TMA + water. For the co-exposure studies, varied amounts of TMA were added together with 300, 600, or 1200 mg/kg mg TMAO, or else TMA was injected 10 minutes after injection of 500 mg/kg TMAO or water. LD_{50} values (obtained by Litchfield and Wilcoxon (1949) log-probit method) for TMA varied from 90-148 mg/kg in four experiments, and for TMAO were 2240-3355 mg/kg in two experiments, indicating that TMA was 15 to 37-fold more toxic than TMAO. Co-dosing yielded LD_{50} values within ~30% of the TMA LD_{50} values, irrespective of TMAO dose or time of administration. This suggests that TMAO was not reduced to TMA to any appreciable extent in the animals, and did not appreciably affect the toxicity of TMA at the doses tested.

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 ~4800, 4600, and 4300 ppm, respectively, indicating relative toxicity of TMA>DMA>MMA.

The International Research and Development Corporation (IRDC 1992b;c 1993) found somewhat different relative potencies (LC_{50} values) than Koch et al. (1980) for MMA, DMA, TMA, and ethylamine (EA) when exposing Sprague-Dawley rats for 6, 20, or 60 minutes. All four amines caused gasping and/or labored breathing, rales, and corneal opacity during the exposure and recovery period, and decreased body weight primarily during the first week after exposure. Necropsy revealed eye abnormalities (corneal opacity) and lung congestion (red, discolored lungs) at almost all test concentrations, from treatment with each of the amines. The incidence of gross lung lesions generally correlated with lethality. Most deaths occurred within 3 days of exposure to MMA, within 2 days of exposure to DMA, during exposure to TMA, but the time of death was not specified for EA. LC_{50} values for MMA, DMA, TMA, and EA were, respectively 24,400, 17,600, not determined for TMA, and 22,200 ppm for 6 minutes; 9600, 7340, 12,000, and 9136 ppm for 20 minutes; 7110,

5290, 7910 and 5540 ppm for 60 minutes. Thus the relative acute toxicities (causing lethality) for all exposure durations were DMA>EA>MMA>TMA.

Gagnaire et al. (1989) exposed male Swiss-OF_1 mice to a series of aliphatic amines including TMA, MMA, DMA, and ethylamine. The mice were exposed oronasally for 15 minutes while their respiratory rates were measured by a plethysmographic technique. A decreased respiratory rate was considered to be an indicator of upper airway irritation. For these amines, 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 methylamine, and 151 ppm for ethylamine. This suggests that as upper respiratory irritants, TMA and DMA are more potent that methylamine and ethylamine. Gagnaire et al. (1989) also tested 16 other less closely structurally related aliphatic amines, which had RD_{50} values of 51-202 ppm, except two amines had much lower RD_{50} values (allylamine, 9 ppm; diallylamine, 4 ppm).

TMA is structurally related to the tertiary aliphatic amine dimethylethylamine (DMEA). Ståhlbom et al. (1991) evaluated the ability of known concentrations of DMEA to cause eye irritation and visual disturbances in a group of four male volunteers (age 33-53, non-smokers). The visual disturbances were characterized as “misty vision” or “halo vision” and thought to be due to corneal edema. Exposure for 8 hours to 3.3 or 6.7 ppm was without effect, whereas 13 ppm was irritating to eyes of 3/4 workers and caused reversible visual disturbances to one worker. Exposure for 15 minutes to 27 or 53 ppm was irritating to eyes of 3/4 workers but caused no visual disturbance.

4.4. Other Relevant Information

4.4.1. Species Variability

There were limited animal data on species variability, which involved only rats and mice. Rotenberg and Mashbits (1967) reported a 2-hour LC_{50} of 7790 ppm for white mice, whereas IRDC 1992a obtained a 60-minute LC_{50} of 7913 ppm, and Koch et al. (1980) determined a 4-hour LC_{50} value of approximately 4350 ppm (at 21.8°C). These data indicated that there was little variability in MMA acute toxicity between rats and mice.

Variability in the response to TMA among species can also be evaluated by comparing LD_{50} values obtained for four species in an intragastric study conducted by Trubko and Teplyakov (1981). The LD_{50} values were as follows: rabbits (240 mg/kg), guinea pigs (315 mg/kg), mice (460 mg/kg) and rats (535 mg/kg). The LD_{50} values showed little interspecies variability, being within approximately a factor of 2 of each other.

Protein sequence analysis showed that the amino acid sequence of the TMA-metabolizing enzyme FMO3 from mice was 79 and 82% identical to the human and rabbit FMO3 sequences, respectively (Falls et al. 1997).

4.4.2. Susceptible Populations

A potentially susceptible human population exists, consisting of people with a compromised ability to metabolize TMA to the less toxic metabolite TMAO (see Section 4.1.2). This can be due to a defective FMO3 gene, a transient decrease in FMO3 activity as the result of liver disease, modulation of the enzyme during menstruation,

or decreased enzyme activity levels in childhood. These conditions would presumably be exacerbated by consuming large amounts of food high in TMA or TMA precursors.

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. A value of n = 2.5 was calculated for the exponent n from a linear regression of the IRDC (1992a) 20 and 60-minute rat LC_{50} values and the 4-hour rat LC_{50} from Koch et al. (1980), as shown in Appendix B.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

AIHA (2005) reported that workers exposed for 8 hours to 0.1 to 8 ppm TMA, with most 8-hour TWAs of <5 ppm, had no toxic effects during "routine medical and biological monitoring." This limited report did not state whether any irritation occurred at 0.1-8 ppm, but did state that "moderate" upper respiratory irritation occurred at ≥ 20 ppm (exposure time not specified). Another secondary source (Deichmann and Gerarde 1969) reported that "methylamines" (defined as TMA, DMA and MMA) at >100 ppm cause irritation of the nose and throat, difficulty breathing, pulmonary congestion, and lung edema, which clearly exceed the scope of AEGL-1 effects.

As a point of comparison, four male volunteers exposed to the structurally similar tertiary amine DMEA found that exposure for 8 hours to 13 ppm, but not to 3.3 or 6.7 ppm, was irritating to the eyes and caused reversible visual disturbances, whereas a 15-minute exposure to 27 or 53 ppm was irritating to eyes but caused no visual disturbances (Ståhlbom et al. 1991; see section 4.3.).

5.2. Summary of Animal Data Relevant to AEGL-1

One rat study and one mouse study were potentially useful for AEGL-1 derivation. Kinney et al. (1990) exposed male CD rats to 0 (air-only control), 74, 240, or 760 ppm TMA for 6 hours/day, 5 days/week for 2 weeks (10 exposures). The rats were sacrificed either immediately after exposure or after a 14-day recovery period. All TMA-treated groups had histopathological alterations in the nose, and the 750 ppm group also had lesions in the trachea and lungs. The lesion severity was dose-related, being minimal at 75 ppm and moderate or severe at 760 ppm, and was still evident at the end of the 14-day recovery period. Because a no-effect level for nasal lesions was not established, and the lesions were still present after the recovery period, an adjustment factor of 3 could be applied to 74 ppm to obtain 25 ppm as a POD for AEGL-1.

Gagnaire et al. (1989) exposed male Swiss-OF_1 mice to 17-70 ppm TMA for 15 minutes in a respiratory inhibition (i.e., RD_{50}) study. Although responses to specific concentration were not provided, an RD_{50} of 61 ppm was calculated from the respiratory data. According to methodology proposed by Alarie (1981), exposure to the RD_{50} is intolerable to humans, exposure to 0.1 x RD_{50} (i.e., 6.1 ppm) for several hours-days causes sensory irritation, 0.01 x RD_{50} (0.61 ppm) should cause no sensory irritation, and 0.03 x RD_{50} (1.8 ppm) is an estimate for an occupational exposure threshold limit value (TLV).

5.3. Derivation of AEGL-1

The AEGL-1 was based human occupational exposure data (AIHA 2005). The AIHA report indicated that TMA concentrations ranging from 0.1 to 8 ppm did not cause toxic effects in workers exposed for 8-hour periods. The point of departure is the 8-hour exposure to 8 ppm. An intraspecies uncertainty factor of 1 was applied because the effect was below the definition of an AEGL-1, and the healthy worker population is thought to encompass a range of variability. AEGL-1 values were set equal for all exposure durations from 10 minutes to 8 hours because the irritating effects of TMA at low concentrations are considered to be concentration related, and there is adaptation to the mild irritation that defines the AEGL-1. The value is supported by the relative toxicity to dimethylamine for which there was sufficient animal data that addressed AEGL-1 level effects. The AEGL-1 is also consistent with a human study of the related tertiary amine DMEA. The DMEA study (Ståhlbom et al. 1991) found that the lowest concentration that caused reversible eye irritation and visual disturbance in four healthy men was between 6.7 and 13 ppm. The TMA AEGL-1 values are shown in Table 7. The calculations are detailed in Appendix C, and a category graph of the toxicity data in relation to the AEGL values is in Appendix D.

TABLE 7. AEGL-1 Values for Trimethylamine

10-min	30-min	1-h	4-h	8-h
8.0 ppm (19 mg/m³)	8.0 ppm (19 mg/m³)	8.0 ppm (19 mg/m³)	8.0 ppm (19 mg/m³)	8.0 ppm (19 mg/m³)

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Toxicity Data Relevant to AEGL-2

Some of the same data considered for the derivation of AEGL-1 are also relevant to developing AEGL-2 values. A secondary source reported that TMA caused upper airway irritation in humans exposed to ≥ 20 ppm for an unspecified duration (AIHA 2005), and that "methylamines" (defined as TMA, DMA and MMA) at >100 ppm cause irritation of the nose and throat, difficulty breathing, pulmonary congestion, and lung edema (Deichmann and Gerarde 1969). Four male volunteers exposed to the structurally similar amine DMEA found that exposure for 8 hours to 13 ppm, but not to 6.7 ppm, was irritating to the eyes and caused reversible visual disturbances, whereas a 15-minute exposure to 27 or 53 ppm was irritating to eyes but caused no visual disturbances (Ståhlbom et al. 1991).

6.2. Summary of Animal Data Relevant to AEGL-2

Two rat studies conducted by Kinney et al. (1990) were considered relevant to developing AEGL-2 values: the 4-hour single-exposure scenario, and the 6 hours/day 10-exposure study. The mouse RD_{50} study of Gagnaire et al. (1989) was not considered relevant because the exposure duration (15 minutes) was too short and only relevant to respiratory toxicity, but other animal studies have indicated that respiratory toxicity and neurotoxicity are relevant AEGL-2 endpoints.

In the Kinney et al. (1990) single-exposure study, male CD (SD)BR rats (6/group) were exposed to 2000 or 3500 ppm TMA for 4 hours and observed for two weeks, but neither gross nor microscopic pathology were evaluated. No lethality was observed at 2000 ppm, but 3 out of 6 animals died when exposed to 3500 ppm TMA. Difficult breathing, nasal and oral

discharge, immobilization, and lack of reaction to sound were displayed by rats at both concentrations during treatment. After treatment, surviving rats showed moderate to severe weight loss for days 1-2 and lung noise for days 1-9. Although the severity of these effects exceeds AEGL-2, the non-lethal concentration of 2000 ppm can be divided by 3 to obtain 670 ppm, which would be an estimate of the threshold for lung toxicity (based on "lung noise") and neurotoxicity, and be the AEGL-2 point of departure.

A second option was to use the multiple-exposure study of Kinney et al. (1990), in which male CD rats (10/group) were exposed to 0, 74, 240, or 760 ppm TMA for 6 hours/day, 5 days/week for 2 weeks (10 exposures), and sacrificed immediately or 14 days after the last treatment. The 760 ppm group had decreased response to auditory stimuli during exposure and decreased mean body weight through the seventh day of recovery. All groups had nasal lesions, the severity increasing with concentration. Nasal lesions still present after the recovery period. The 760 ppm rats also had tracheal and lung lesions. A single 6-hour exposure to 250 ppm could be treated as a no-effect level for lung lesions and neurotoxicity in rats, and be the AEGL-2 POD.

6.3. Derivation of AEGL-2

AEGL-2 values were derived from an acute inhalation study in which 0/6 male CD rats died after a 4-hour exposure to 2000 ppm; whereas, 3/6 died at 3500 ppm (Kinney et al. 1990). During exposure, rats at both concentrations had difficulty breathing, showed nasal and oral discharge, were immobile, and did not react to sound. Because the severity of these effects exceeds the scope of AEGL-2, the non-lethal concentration of 2000 ppm was divided by 3 to obtain 670 ppm as an estimate of the threshold for lung lesions and neurotoxicity. The 4-hour 670 ppm concentration was used as the point of departure for the AEGL-2. An interspecies uncertainty factor of 3 was applied because animal lethality data showed little interspecies variability, and the irritating effect from a direct-acting alkaline chemical is not expected to vary greatly between species. An intraspecies uncertainty factor of 3 was applied because the effect of a direct-acting irritant is unlikely to vary greatly among humans (NRC 2001). Following adjustment by 1/3, a total uncertainty factor of 10 was applied. Time-concentration scaling for 10 minutes to 8 hours was performed using the ten Berge et al. (1986) relationship, $C^n \times t = k$, where $n = 2.5$. This relationship was calculated from rat lethality data ranging from 20 minutes to 4 hours as detailed in Section 4.3.3. The derived values for AEGL-2 are presented in Table 8, and the calculations are provided in Appendix C. A category graph of the toxicity data in relation to the AEGL values is in Appendix D.

TABLE 8. AEGL-2 Values for Trimethylamine

10-min	30-min	1-h	4-h	8-h
240 ppm (580 mg/m³)	150 ppm (360 mg/m³)	120 ppm (290 mg/m³)	67 ppm (160 mg/m³)	51 ppm (120 mg/m³)

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human data consistent with the definition of AEGL-3 were available.

7.2. Summary of Animal Data Relevant to AEGL-3

Five acute lethality studies were considered for AEGL-3 derivation. These consisted of the 20-minute and 60-minute CD Sprague-Dawley rat studies conducted by IRDC (1992a), the 4-hour female Wistar rat study of Koch et al. (1980), the 4-hour CD rat study of Kinney et al (1990), and the 2-hour white mouse study of Rotenberg and Mashbits (1967). All of the studies found similar effects upon treatment, which consisted of neurological, respiratory system, and ocular toxicity. For the IRDC (1992a) studies, the point of departure could be the calculated 20-minute and 60-minute $BMCL_{05}$ values. The other studies lacked data allowing the calculation of $BMCL_{05}$ values. A lethality threshold could be estimated as 1/3 of the LC_{50} for the Koch et al. (1980) rat study and the Rotenberg and Mashbits (1967) mouse study, and the non-lethal concentration of 2000 ppm could be used as the lethality threshold for the Kinney et al. (1990) study.

7.3. Derivation of AEGL-3

AEGL-3 values were derived from the IRDC (1992a) study in which CD Sprague-Dawley rats were exposed to 11,200-18,200 ppm for 20 minutes or 6150-8170 ppm TMA for 60 minutes. The rats exhibited gasping, labored breathing, salivation, corneal opacity, congested or reddened lungs, and mortality. Similar effects were seen in the rat and mouse acute lethality studies. The data allowed calculation of LC_{50}, $BMCL_{05}$ and BMC_{01} values for both time points. The 20- and 60-minute $BMCL_{05}$ values of 5719 and 3841 ppm, respectively were used as points of departure for deriving AEGL-3 values. Interspecies and intraspecies uncertainty factors of 3 each for a total of 10 were applied because lethality data from mice and rats suggested little interspecies variability, and the effects of an alkaline, direct-acting irritant are unlikely to vary greatly between species or among humans (NRC 2001). Time-concentration scaling for 10 minutes to 8 hours was performed using the ten Berge et al. (1986) relationship $C^n \times t = k$, where $n = 2.5$ was calculated from a linear regression of three LC_{50} values with exposure durations of 20 minutes to 4 hours. The 20-minute $BMCL_{05}$ was time-scaled to the 10- and 30-minute AEGL-3 exposure durations, and the 60-minute $BMCL_{05}$ was time-scaled to the 4- and 8-hour exposure durations. The derived AEGL-3 values are presented in Table 9, and the calculations are detailed in Appendix C. A category graph of the AEGL values in relation to the toxicity data is in Appendix D.

TABLE 9. AEGL-3 Values for Trimethylamine

10-min	30-min	1-h	4-h	8-h
750 ppm (1800 mg/m³)	490 ppm (1200 mg/m³)	380 ppm (920 mg/m³)	220 ppm (530 mg/m³)	170 ppm (410 mg/m³)

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

The AEGL-1 was based on a report that no toxic effects were found during "routine medical and biological monitoring" of workers exposed to 0.1-8 ppm TMA for 8 hours, whereas >20 ppm produced "moderate" upper respiratory irritation (undefined exposure period) (AIHA 2005). An intraspecies uncertainty factor of 1 was applied as the value was a NOAEL for the mild irritation that defines an AEGL-1, and the healthy worker population is

thought to encompass a range of variability. The same concentration 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 an acute inhalation study in which 0/6 male CD rats died after a 4-hour exposure to 2000 ppm, whereas 3/6 died at 3500 ppm (Kinney et al. 1990). During exposure, rats at both concentrations had difficulty breathing, nasal and oral discharge, were immobile, and did not react to sound. Because the severity of these effects exceeds the scope of AEGL-2, the non-lethal concentration of 2000 ppm was divided by 3 to obtain 670 ppm as an estimate of the threshold for lung lesions and neurotoxicity. The 4-hour 670 ppm concentration was used as the point of departure for the AEGL-2. Inter-and intraspecies uncertainty factors of 3 each for a total of 10 were applied because TMA is an alkaline, direct-contact irritant; effects are not expected to vary greatly between species or among humans (NRC 2001). Time-concentration scaling for 10 minutes to 8 hours was performed using the ten Berge et al. (1986) relationship $C^n \times t = k$, where $n = 2.5$ was calculated from a linear regression of three LC_{50} studies in which the exposure duration was 20 minutes to 4 hours.

AEGL-3 values were derived from the IRDC (1992a) study in which CD Sprague-Dawley rats were exposed to 11,200-18,200 ppm for 20 minutes or 6150-8170 ppm TMA for 60 minutes. The rats exhibited gasping, labored breathing, salivation, corneal opacity, congested or reddened lungs, and mortality. Similar effects were seen in the rat and mouse acute lethality studies. The data allowed calculation of LC_{50}, $BMCL_{05}$ and BMC_{01} values for both time points. The 20- and 60-minute $BMCL_{05}$ values of 5719 and 3841 ppm, respectively were used as points of departure for deriving AEGL-3 values. Interspecies and intraspecies uncertainty factors of 3 each for a total of 10 were applied because lethality data from mice and rats suggested little interspecies variability, and the effects of an alkaline, direct-acting irritant are unlikely to vary greatly between species or among humans (NRC 2001). Time-concentration scaling for 10 minutes to 8 hours was performed using the ten Berge et al. (1986) relationship $C^n \times t = k$, where $n = 2.5$ was calculated from a linear regression of three LC_{50} values with exposure durations of 20 minutes to 4 hours. The 20-minute $BMCL_{05}$ was time-scaled to the 10- and 30-minute AEGL-3 exposure durations, and the 60-minute $BMCL_{05}$ was time-scaled to the 4- and 8-hour exposure durations.

A summary of the AEGL values for TMA is depicted in Table 10.

TABLE 10. Summary of AEGL Values.

Classification	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	8.0 ppm (19 mg/m³)	8.0 ppm (19 mg/m³)	8.0 ppm (19 mg/m³)	8.0 ppm (19 mg/m³)	8.0 ppm (19 mg/m³)
AEGL-2 (Disabling)	240 ppm (580 mg/m³)	150 ppm (360 mg/m³)	120 ppm (290 mg/m³)	67 ppm (160 mg/m³)	51 ppm (120 mg/m³)
AEGL-3 (Lethality)	750 ppm (1800 mg/m³)	490 ppm (1200 mg/m³)	380 ppm (920 mg/m³)	220 ppm (530 mg/m³)	170 ppm (410 mg/m³)

8.2. Comparison with Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures are listed in Table 11. The 1-hour ERPG-1 of 0.1 ppm was based on objectionable odor, whereas, the AEGL-1 was based on irritation. The 1-hour ERPG-2 of 100 ppm is similar to the 1-hour AEGL-2 of 120 ppm; both guidelines were based on the same study (Kinney et al. 1990), but used different points of departure. The ERPG committee also stated that the "blue haze" reported to occur at exposure concentrations exceeding 100 ppm does not impair ability to escape. The 1-hour ERPG-3 (500 ppm) and AEGL-3 (380 ppm) are based on the same IRDC (1992a) lethality data, but applied uncertainty factors in a slightly different manner.

There is currently no OSHA PEL for TMA. A footnote to the German MAK states that reaction of TMA with nitrosating agents can result in formation of the known carcinogen N-nitrosodimethylamine. The German guidance further states that although it is presently not possible to predict the amount of N-nitrosodimethylamine formation under workplace conditions, co-exposure to TMA and nitrosating agents should be minimized. The ACGIH TLV was based on rat subchronic studies in which 10 ppm was a NOAEL (Rotenberg and Mashbits 1967) and 75 ppm causes reversible nasal lesions (Kinney et al. 1990), and the STEL was based on analogy to methylamine, which was irritating to humans at ≥20 ppm (ACGIH 2005).

TABLE 11. Extant Standards and Guidelines for Trimethylamine

Guideline	Exposure Duration (ppm)				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	8.0	8.0	8.0	8.0	8.0
AEGL-2	240	150	120	67	51
AEGL-3	750	490	380	220	170
ERPG-1 (AIHA)[a]			0.1		
ERPG-2 (AIHA)[a]			100		
ERPG-3 (AIHA)[a]			500		
WEEL-TWA (AIHA)[b]					1
REL-TWA (NIOSH)[c]					10
REL-STEL (NIOSH)[d]	15 (15 min)				
TLV-TWA (ACGIH)[e]					5
TLV-STEL (ACGIH)[f]	15 (15 min)				
MAK (German)[g]					2
MAK Peak Limit (German)[h]	4 (15 min)				
MAC (Dutch)[i]					0.4
MPC industrial zone air (Russian)[j]					2.0
MPC ambient air (Russian)[k]					0.062

[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]**AIHA WEEL (Workplace Environmental Exposure Level) (AIHA 2005)** is defined as a recommended workplace 8-hour time-weighted average exposure level.

[c]**NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** (NIOSH 2005) is defined analogous to the ACGIH-TLV-TWA.

[d]**NIOSH REL-STEL (Recommended Exposure Limits - Short Term Exposure Limit)** (NIOSH 2005) is defined analogous to the ACGIH TLV-STEL.

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

[f]**ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit)** (ACGIH 2005) is defined as a 15-minute TWA exposure which should not be exceeded at any time during the workday even if the 8-hour TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 minutes and should not occur more than 4 times per day. There should be at least 60 minutes between successive exposures in this range.

[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 of 2])** (Deutsche Forschungsgemeinschaft [German Research Association] 2005) constitutes the maximum average concentration to which workers can be exposed for a period up to 15 minutes with no more than 4 exposure periods per work shift, with at least 1 hour between exposures; total exposure may not exceed 8-hour MAK.

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

[j]**MPC Industrial zone air (Maximum Permissible Concentration on workplace)** (Russia)

[k]**MPC Ambient air (Maximum Permissible Concentration in ambient air)** (Russia)

8.3. Data Adequacy and Research Needs

Although the data set for deriving AEGL values was modest, the studies painted a consistent picture of toxic effects for rats and mice, and similar AEGL values would have been obtained by using alternate studies. The confidence in the animal data would have been greater, however, if studies were available with non-rodents.

The biggest research need is human data associated with exposure concentrations and durations and with a specific effect, and to determine the response of individuals sensitive to TMA inhalation (i.e., deficient in the enzyme that metabolizes TMA to the less toxic TMAO). These data would have been helpful to establishing all of the AEGL levels. The

human study with structurally related tertiary amine DMEA did, however, provide a credible reference point for concentrations that were likely irritating to healthy humans.

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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 trimethylamine was reported to be 0.000032 ppm (Ruijten 2005).

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

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

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

$3 = 2.33 \times \log (C / 0.000032) + 0.5$ which can be rearranged to
$\log (C / 0.000032) = (3 - 0.5) / 2.33 = 1.07$ and results in
$C = (10^{1.07}) \times 0.000032 = 0.00038$ 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 up to 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

$LOA = C \times 1.33 = 0.000038 \text{ ppm} \times 1.33 = 0.00051$ ppm

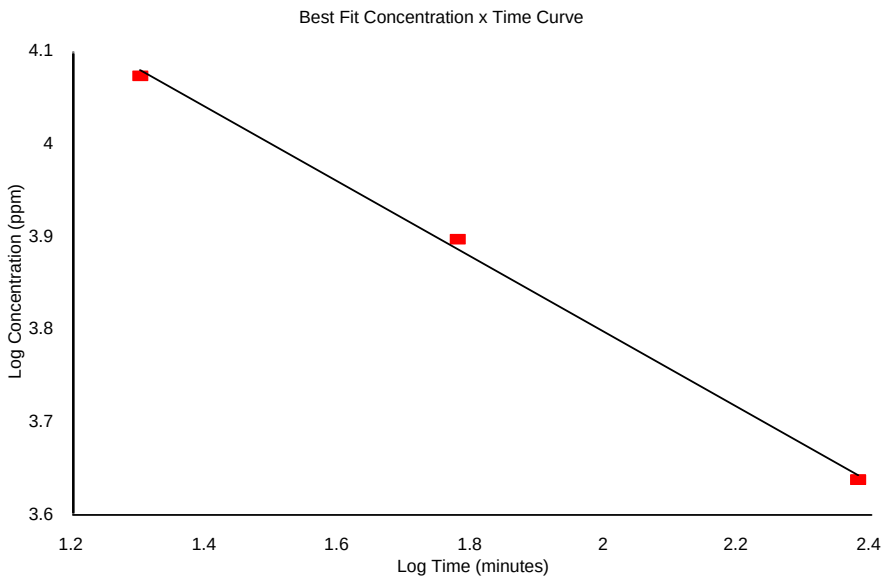
The LOA for trimethylamine is 0.00051 ppm.

APPENDIX B: Time-Scaling Calculations

The AEGL-1 values were not scaled because the minor effects associated with exposure to low concentrations of irritant gases are concentration related and do not increase over time.

The concentration-time relationship used to develop AEGL-2 and AEGL-3 values for TMA was described using the ten Berge et al. (1986) relationship $C^n \times t = k$. A value of n = 2.5 was calculated for the exponent n from a linear regression of the IRDC (1992a) 20 and 60-minute rat LC_{50} values and the 4-hour rat LC_{50} from Koch et al. (1980) (See Section 4.4.3).

Time	Concentration	Log Time	Log Concentration	Regression Output:	
20	11866	1.3010	4.0743	Intercept	4.6074
60	7913	1.7782	3.8983	Slope	-0.4050
240	4350	2.3802	3.6385	R Squared	0.9981
				Correlation	-0.9991
				Degrees of Freedom	1
n = 2.47				Observations	3



APPENDIX C: Derivation of AEGL Values

Derivation of AEGL-1

Key study: AIHA (2005). No toxic effects were found during "routine medical and biological monitoring" in workers exposed to 0.1-8 ppm TMA for 8 hours, whereas >20 ppm produced "moderate" upper respiratory irritation (undefined exposure duration).

Toxicity endpoint: NOAEL for mild sensory irritation in humans at 8.0 ppm

Scaling: None: The same AEGL-1 value of 8.0 ppm was used for 10 minutes to 8 hours because mild sensory irritation does not vary greatly over time

Uncertainty Factors: Total uncertainty factor: 1
Interspecies: Not applicable
Intraspecies: 1: Applied because point of departure was a NOAEL, below the mild irritation that defines the AEGL-1. Healthy workers encompass a sufficient range of variability in response to mild irritation.

AEGL-1 for 10 minutes to 8 hours: 8.0 ppm

Derivation of AEGL-2

Key study: Kinney et al. 1990. Male CD (SD)BR rats (6/group) were exposed to 2000 or 3500 ppm TMA for 4 hrs and observed for two weeks, but neither gross nor microscopic pathology were evaluated. No animals died at 2000 ppm, whereas 3/6 died at 3500 ppm. During exposure, rats at both concentrations had difficulty breathing, nasal and oral discharge, immobility, and lack of reaction to sound. After exposure, survivors had weight loss on days 1-2, and lung noise on days 1-9. Because the severity of these effects exceeds the scope of AEGL-2, the non-lethal concentration of 2000 ppm was divided by 3 to obtain 670 ppm, which is an estimate of the threshold for lung toxicity and neurotoxicity, and was the AEGL-2 point of departure.

Toxicity endpoint: Threshold for lung toxicity and neurotoxicity in rats

Scaling: $C^n \times t = k$ (ten Berge et al. 1986) where n = 2.5 was calculated from a linear regression of three LC_{50} studies with exposure durations of 20 minutes to 4 hours.

Uncertainty Factors: Total uncertainty factor: 10
Interspecies: 3: The response to TMA in acute lethality studies was similar in nature and severity in rats and mice, suggesting that interspecies variability is small. Furthermore, the effects of an alkaline, direct-contact irritant are not expected to vary greatly between species.
Intraspecies: 3: An intraspecies UF of 3 was used because the effects of an alkaline, direct-contact irritant are not expected to vary greatly among humans.
Modifying Factor: None

Calculations:

$$C^{2.5} \times t = k$$

$$(670 \text{ ppm})^{2.5} \times 240 \text{ minutes} = 2.79 \times 10^9 \text{ ppm}^{2.5}\text{-min}$$

10-min AEGL-2

$$C^{2.5} \times 10 \text{ min} = 2.79 \times 10^9 \text{ ppm}^{2.5}\text{-min};\ C = 2170 \text{ ppm}$$

2389/10 = 240 ppm (580 mg/m^3)

30-min AEGL-2

$$C^{2.5} \times 30 \text{ min} = 2.79 \times 10^9 \text{ ppm}^{2.5}\text{-min};\ C = 1540 \text{ ppm}$$

1540/10 = 150 ppm (360 mg/m^3)

1-hour AEGL-2

$$C^{2.5} \times 60 \text{ min} = 2.79 \times 10^9 \text{ ppm}^{2.5}\text{-min};\ C = 1166 \text{ ppm}$$

1166/10 = 120 ppm (290 mg/m^3)

4-hour AEGL-2

$$C = 670 \text{ ppm}$$

670/10 = 67 ppm (160 mg/m^3)

8-hour AEGL-2

$$C^{2.5} \times 480 \text{ min} = 2.79 \times 10^9 \text{ ppm}^{2.5}\text{-min};\ C = 507 \text{ ppm}$$

507/10 = 51 ppm (120 mg/m^3)

Derivation of AEGL-3

Key study: IRDC (1992a). CD Sprague-Dawley rats (5/sex/dose) were exposed to 11,200, 12,700, 12,700, 14,100, 16,200, or 18,200 for 20 minutes or 6150, 7100, 7680, 7720, or 8170 ppm for 60 minutes. Respective mortalities were 2/10, 6/10, 9/10, 9/10, 8/10, and 10/10 for the 20-minute exposure and 1/10, 3/10, 4/10, 3/10, and 7/10 for the 60-minute exposure. The rats exhibited gasping, labored breathing, rales, salivation, decreased body weight gain, corneal opacity, and congested or reddened lungs. The calculated 20-minute $BMCL_{05}$ was 5719 and the calculated 60-minute $BMCL_{05}$ was 3841 ppm. The $BMCL_{05}$ values were used as estimates of the lethality threshold for the respective time frames. The 20-minute $BMCL_{05}$ was time-scaled to the 10- and 30-minute AEGL-3 exposure durations, and the 60-minute $BMCL_{05}$ was time-scaled to the 4- and 8-hour exposure durations.

Toxicity endpoint: Lethality threshold in rats

Scaling: $C^n \times t = k$ (ten Berge et al. 1986) where n = 2.5 was calculated from a linear regression of three LC_{50} studies with exposure durations of 20 minutes to 4 hours.

Uncertainty Factors: Total uncertainty factor: 10
Interspecies: 3: The response to TMA in the acute lethality studies was similar in nature and severity in rats and mice, suggesting that interspecies variability is small. In addition, the interspecies variation in lethality for a direct-acting alkaline irritant is not expected to vary greatly.
Intraspecies: 3: The effects of an alkaline, direct-contact irritant are not expected to vary greatly among humans.
Modifying Factor: None

Calculations: $C^{2.5} \times t = k$

$(5719)^{2.5} \times 20 \text{ minutes} = 4.95 \times 10^{10} \text{ ppm}^{2.5}\text{-min}$

10-min AEGL-3 $C^{2.5} \times 10 \text{ min} = 4.95 \times 10^{10} \text{ ppm}^{2.5}\text{-min}$; C = 7546 ppm
7546/10 = 750 ppm (1800 mg/m^3)

30-min AEGL-3 $C^{2.5} \times 30 \text{ min} = 4.95 \times 10^{10} \text{ ppm}^{2.5}\text{-min}$; C = 4862 ppm
4862/10 = 490 ppm (1200 mg/m^3)

Calculations: $C^{2.5} \times t = k$

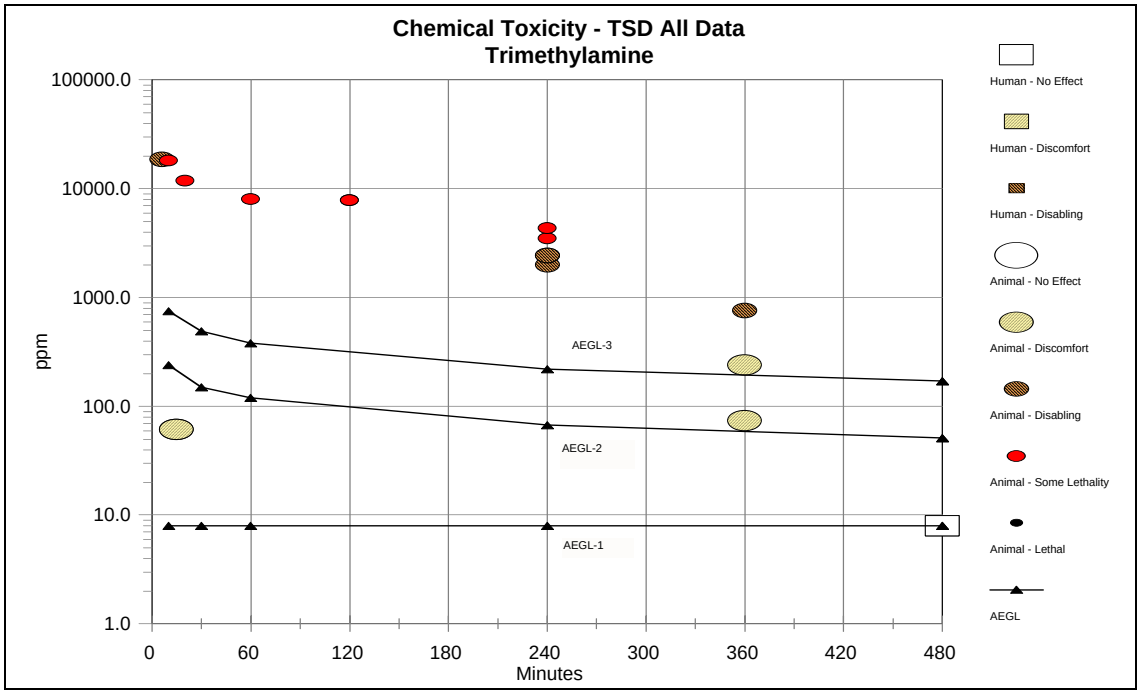
$(3841)^{2.5} \times 60 \text{ minutes} = 5.49 \times 10^{10} \text{ ppm}^{2.5}\text{-min}$

1-hour AEGL-3 3841/10 = 380 ppm (920 mg/m^3)

4-hour AEGL-3 $C^{2.5} \times 240 \text{ min} = 5.49 \times 10^{10} \text{ ppm}^{2.5}\text{-min}$; C = 2206 ppm
2206/10 = 220 ppm (530 mg/m^3)

8-hour AEGL-3 $C^{2.5} \times 480 \text{ min} = 5.49 \times 10^{10} \text{ ppm}^{2.5}\text{-min}$; C = 1671 ppm
1671/10 = 170 ppm (410 mg/m^3)

APPENDIX D: Category Plot for Trimethylamine



The data included in this plot are shown below, and consist of the single and multiple-exposure data for TMA where the number of exposures was 10 or fewer.

1

For Category 0 = No effect, 1 = Discomfort, 2 = Disabling, SL = Some Lethality, 3 = Lethal							
Source	**Species**	**Sex**	**# Exposures**	**ppm**	**Min**	**Category**	**Comments**
NAC/AEGL-1				8	10	AEGL	AIHA 2005; worker exposure
NAC/AEGL-1				8	30	AEGL	
NAC/AEGL-1				8	60	AEGL	
NAC/AEGL-1				8	240	AEGL	
NAC/AEGL-1				8	480	AEGL	
NAC/AEGL-2				240	10	AEGL	Kinney et al. 1990; threshold for lung toxicity and neurotoxicity
NAC/AEGL-2				150	30	AEGL	
NAC/AEGL-2				120	60	AEGL	
NAC/AEGL-2				67	240	AEGL	
NAC/AEGL-2				51	480	AEGL	
NAC/AEGL-3				750	10	AEGL	IRDC 1992a; $BMCL_{05}$ for rats
NAC/AEGL-3				490	30	AEGL	
NAC/AEGL-3				380	60	AEGL	
NAC/AEGL-3				220	240	AEGL	
NAC/AEGL-3				170	480	AEGL	
AIHA 2005	Human			8	480	0	Non-irritating
IRDC 1992a	Rat	m,f	1	18600	6	2	0/10 died; corneal lesions, lung toxicity, etc.
			1	18100	10	sl	2/10 died; corneal lesions, lung toxicity, etc.
			1	11870	20	sl	LC_{50} in rats; exposures to 11200-18200 ppm
			1	8010	60	sl	LC_{50} in rats; exposures to 6150-8170 ppm
Kinney et al. 1990	Rat	m	1	2000	240.0	2	Immobile, did not react to sound, difficulty breathing, lung noise, etc.
			1	3500	240.0	sl	3/6 died; Immobile, did not react to sound, difficulty breathing, lung noise, etc.
Koch et al. 1980	Rat	f	1	4350	240	sl	LC_{50} in rats; exposures to 3243-5750 ppm
Kinney et al. 1990	Rat	m	10	74	360	1	Mild nasal lesions
			10	240	360	1	Mild nasal lesions
			10	760	360	2	Nasal and lung lesions, neurotoxicity
Rotenberg & Mashbits 1967	Mouse	?	1	7850	120	sl	LC_{50}; Neurological effects
BASF AG 1979b	Rat	m,f	1	2440	240	2	Irregular respiration, nasal discharge; incomplete report
Gagnaire et al. 1989	Mouse	m	1	61	15	1	RD_{50} in Swiss-OF1 mice; 17-70 ppm tested

2

APPENDIX E: Derivation Summary of Acute Exposure Guideline Levels for Trimethylamine (CAS Reg. No. 75-50-3)

AEGL-1 Values				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
8.0 ppm (19 mg/m³)	**8.0 ppm (19 mg/m³)**	**8.0 ppm (19 mg/m³)**	**8.0 ppm (19 mg/m³)**	**8.0 ppm (19 mg/m³)**

Key Reference: AIHA (American Industrial Hygiene Association). 2005. Trimethylamine. Amer. Ind. Hyg. Assoc. J. 40: A35-A37.

Test species/Strain/Sex/Number: Humans; sex and number not specified

Exposure Route/Concentrations/Duration: Inhalation of 0.1 – 8 ppm for 8 hours, occupational exposure

Effects: No toxic effects were found during "routine medical and biological monitoring" in workers exposed to 0.1-8 ppm TMA for 8 hours, whereas >20 ppm produced "moderate" upper respiratory irritation (undefined exposure period).

Endpoint/Concentration/Rationale: NOAEL for mild sensory irritation from a single exposure to 8.0 ppm

Uncertainty Factors/Rationale: Total uncertainty factor: 1
Interspecies: Not applicable
Intraspecies: 1: The effect, NOAEL for mild sensory irritation, definition was below the definition of AEGL-1. The healthy worker population is thought to encompass a range of variability in response to an irritant.

Modifying Factor: None

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 sensory irritation is not expected to vary greatly over time.

Data Adequacy: The AEGL-1 of 8.0 ppm is consistent with the available animal studies, as well as with the human testing of the related tertiary amine dimethylethylamine. The value is close to the concentration of 6.1 ppm (0.1 x the RD_{50} of 61 ppm) proposed by Alarie (1981) to be tolerable for hours to days. The human study with the related tertiary amine DMEA (Ståhlbom et al. 1991) found that the lowest effect level for reversible eye irritation and visual disturbance in four healthy men was between 6.7 and 13 ppm, which is similar to the TMA AEGL-1.

1

AEGL-2 Values				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
240 ppm (580 mg/m³)	**150 ppm (360 mg/m³)**	**120 ppm (290 mg/m³)**	**67 ppm (160 mg/m³)**	**51 ppm (120 mg/m³)**
Key reference: Kinney, L.A., B.A. Burgess, H.C. Chen, and G.L. Kennedy. 1990. Inhalation toxicology of trimethylamine. Inhal. Toxicol. 2: 41-51.				
Tested species/Strains/Number: Male CD (SD)BR rats, 6/concentration				
Exposure Route/Concentrations/Duration: Inhalation for 240 minutes to 2000 or 3500 ppm TMA. Key scenario is exposure for 240 minutes to 2000 ppm, to which an adjustment factor of 3 is applied to yield 670 ppm as the AEGL-2 POD.				
Effects: No animals died at 2000 ppm, 3/6 died at 3500 ppm. During exposure, rats at both concentrations had difficulty breathing, nasal and oral discharge, immobility, and lack of reaction to sound. After exposure, survivors had weight loss on days 1-2, and lung noise on days 1-9. Neither gross nor microscopic pathology were evaluated.				
Endpoint/Concentration/Rationale: Because the severity of the toxic effects exceeded the scope of AEGL-2, the non-lethal concentration of 2000 ppm was divided by 3 to obtain 670 ppm, which was an estimate of the threshold for lung toxicity and neurotoxicity, and was the AEGL-2 point of departure.				
Uncertainty Factors/Rationale: Total uncertainty factor: 10 Interspecies: 3: The response to TMA in acute lethality studies was similar in nature and severity in rats and mice, suggesting that interspecies variability was small. Effects from a direct-contact, alkaline irritant are not expected to vary greatly between species. Intraspecies: 3: Effects from a direct-acting, alkaline irritant are not expected to vary greatly among humans.				
Modifying Factor: None				
Animal to Human Dosimetric Adjustment: Not applied				
Time Scaling: $C^n \times t = k$ (ten Berge et al. 1986) where n = 2.5 was calculated from a linear regression of three LC_{50} studies with exposure durations ranging from 20 minutes to 4 hours.				
Data Adequacy: The data were sufficient for determining AEGL-2 values. Similar toxicity (nature and severity) was seen in rats and mice in a number of studies.				

1

AEGL-3 Values				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
750 ppm (1800 mg/m³)	**490 ppm (1200 mg/m³)**	**380 ppm (920 mg/m³)**	**220 ppm (530 mg/m³)**	**170 ppm (410 mg/m³)**
Key reference: IRDC (International Research and Development Corporation). 1992a. Acute inhalation toxicity evaluation on trimethylamine 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 11,200, 12,700, 12,700, 14,100, 16,200, or 18,200 ppm for 20 minutes or 6150, 7100, 7680, 7720, or 8170 ppm for 60 minutes				
Effects: The rats exhibited gasping, labored breathing, rales, salivation, decreased body weight gain, corneal opacity, and congested or reddened lungs. Mortality rates at 11,200, 12,700, 12,700, 14,100, 16,200, and 18,200 were 2/10, 6/10, 9/10, 9/10, 8/10, and 10/10, respectively. Mortality rates at 6150, 7100, 7680, 7720, and 8170 ppm were 1/10, 3/10, 4/10, 3/10, and 7/10, respectively.				
Endpoint/Concentration/Rationale: The calculated 20-minute and 60-minute $BMCL_{05}$ values of 5719 ppm and 3841 ppm, respectively, were used as an estimate of the time-respective lethality thresholds.				
Uncertainty Factors: Total uncertainty factor: 10 Interspecies: 3: The response to TMA in acute lethality studies was similar in nature and severity in rats and mice, suggesting that interspecies variability is small. Effects from a direct-contact, alkaline irritant are not expected to vary greatly between species. Intraspecies: 3: Effects from a direct-acting, alkaline irritant are not expected to vary greatly among humans.				
Modifying factor: None				
Animal to Human Dosimetric Adjustment: Not applied				
Time Scaling: $C^n \times t = k$ (ten Berge et al. 1986) where n = 2.5 was calculated from a linear regression of three LC_{50} studies with exposure durations ranging from 20 minutes to 4 hours.				
Data Adequacy: The data was adequate for derivation of AEGL-3 values. The key study was consistent with the overall data set and was considered the best of the five available acute lethality studies.				

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