ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
ETHYLAMINE
(CAS Reg. No. 75-04-7)

INTERIM

PREFACE

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

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

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

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

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

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

TABLE OF CONTENTS

LIST OF TABLES

EXECUTIVE SUMMARY

Ethylamine (EA) is a very basic (pK_a = 10.71), colorless, flammable primary aliphatic amine with a pungent ammonia-like odor. EA is used in oil refining and in the production of rubber latex, emulsifiers, detergents, cosmetic and medicinal preparations, fibers and resins, organic paints and dyes. Ethylamine is a potent eye and respiratory irritant, which in humans has caused vision disturbances ("halo vision" due to corneal edema). Animal studies consistently found eye and respiratory irritation, corneal erosions, edema, and opacity, labored breathing, rales, peribronchitis, pneumonitis, and lung lesions. No quantitative human data were available suitable for AEGL derivation.

The level of distinct odor awareness (LOA) for EA was calculated to be 0.74 ppm . The LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, and about 10% of the population will experience strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception.

In the absence of data that address AEGL-1 level effects, the data on other alkylamines were considered. Because EA and methylamine are both primary amines with similar toxicity values, the AEGL-1 for EA was based on methylamine. In the absence of empirical data, a modifying factor of 2 was applied to the methylamine AEGL-1 value of 15 ppm. The AEGL-1 of 15 ppm for methylamine was based on results of two studies: mild nasal irritation in a repeat-exposure study with rats (Kinney et al. 1990) and lung lesions in rats following an acute exposure (Sriramachari and Jeevaratnam 1994). A total uncertainty factor of 10 (3 for interspecies differences and 3 for human variation) was applied to both data sets because irritation from a direct-acting, alkaline chemical is not expected to vary greatly among species or between humans (NRC 2001). A modifying factor of ½ was applied to the acute study because it was not robust and the severity of the lesion was above the definition of an AEGL-1. The same value of 15 ppm was used across all AEGL-1 exposure durations for methylamine because there is adaptation to the mild irritation that defines the AEGL-1. Using the same reasoning as for methylamine, the 7.5 ppm value was applied across all exposure durations for EA. The AEGL-1 is supported by human data for the structurally related compounds diethylamine and dimethylethylamine, which caused eye and nasal irritation and/or vision disturbances in healthy adults at approximately 10 ppm.

In the absence of empirical data that fall within the scope of the AEGL-2, the values for EA were based on analogy with methylamine. Ethyl- and methylamines are both primary amines and have similar toxicity. The AEGL-3 and AEGL-2 values for methylamine were based on the threshold for lethality and severe irritation, respectively, suitable endpoints for the respective levels. The ratio between the AEGL-3 and AEGL-2 values for methylamine (at one hour) was used to modify the AEGL-3 values for EA in order to derive AEGL-2 values. The ratio between the 1-hour AEGL-3 and AEGL-2 values for methylamine is 5.5. The modifying factor of 5.5 was applied to the AEGL-3 values for EA to derive the AEGL-2 values.

The 6-, 20, and 60-minute lethality data sets of IRDC (1993) were used to derive the AEGL-3 values. The LC_{01} at each exposure duration was calculated using the probit-analysis based dose-response program of ten Berge (2006). The program incorporated all of the data at

the 6-, 20-, and 60-minute time points. The data indicated a time-scaling value of 1.6 ($C^{1.6} \times t = k$). A total uncertainty factor of 10 was applied, including 3 for interspecies uncertainty and 3 for human variability, because lethality from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and is not likely to vary greatly between species or among humans (NRC 2001).

AEGL values for EA are summarized in Table 1.

TABLE 1. Summary of AEGL Values for Ethylamine

Classification	10-min	30-min	1-h	4-h	8-h	Endpoints (References)
AEGL–1[1] (Non-disabling)	7.5 ppm (14 mg/m^3)	7.5 ppm (14 mg/m^3)	7.5 ppm (14 mg/m^3)	7.5 ppm (14 mg/m^3)	7.5 ppm (14 mg/m^3)	Analogy with methylamine - mild nasal and lung irritation (Kinney et al. 1990; Sriramachari and Jeevaratnam 1994)
AEGL–2 (Disabling)	150 ppm (280 mg/m^3)	76 ppm (140 mg/m^3)	49 ppm (90 mg/m^3)	22 ppm (40 mg/m^3)	14 ppm (26 mg/m^3)	Analogy with methylamine – ratio of 5.5 (AEGL-3/ AEGL-2) was applied to the EA AEGL-3 values
AEGL–3 (Lethal)	810 ppm (1500 mg/m^3)	420 ppm (770 mg/m^3)	270 ppm (500 mg/m^3)	120 ppm (220 mg/m^3)	76 ppm (140 mg/m^3)	LC_{01} in rats (IRDC 1993)

[1]A Level of Distinct Odor Awareness (LOA) of 0.74 ppm was calculated for EA based on an odor threshold of 0.46 ppm provided by Ruijten (2005). The LOA is defined as the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, and about 10% of the population will experience a strong odor intensity (van Doorn et al. 2002).

1. INTRODUCTION

Ethylamine is a very basic ($pK_a = 10.71$), flammable, water-soluble, colorless gas and an aliphatic amine. It is used in oil refining, as a stabilizer for rubber latex, and in the synthesis of emulsifiers, detergents, cosmetic and medicinal preparations, fibers and resins, organic paints and dyes (O'Neil et al. 2001). Ethylamine is found in many foods, including spinach, carrots, beets, radishes, cheese, maize, and barley, and is a normal constituent of human urine (Neurath et al. 1977; Mitchell et al. 2000). Ethylamine is produced as a pure substance or as a 40-50% aqueous solution, and can be synthesized by the hydrogenation of nitroethane, by reacting ethyl chloride and alcohol ammonia under heat and pressure, or by the catalytic hydrogenation of aziridines (Cavender 2001). Ethylamine is currently a high production volume chemical in the U.S., i.e., $>10^6$ lbs are produced annually, although specific production data were not available.

Ethylamine is a potent eye and upper airway irritant for animals and humans. Reported effects include dyspnea, laryngeal edema, bronchial and pulmonary edema, nausea, vomiting, chemical pneumonia, and corneal ulceration.

Selected physical and chemical properties of EA are shown in Table 2.

TABLE 2. Physical and Chemical Properties Of Ethylamine		
Parameters	**Value**	**Reference**
Synonyms	Aminoethane, ethanamine, MEA, EA, monoethylamine,	Cavender 2001
Chemical Formula	$CH_3CH_2NH_2$	NIOSH 2006a
Molecular Weight	45.08	O'Neil et al. 2001
CAS Reg. No.	75-04-7	NIOSH 2006a
Physical State	Colorless gas or water-white liquid	NIOSH 2006a
Solubility	Miscible with water, alcoho1, ether	O'Neil et al. 2001
Acid ionization constant, pK_a	10.71 at 25°C	Cavender 2001
Boiling Point	16.6°C	O'Neil et al. 2001
Melting Point	-81°C	Cavender 2001
Vapor Pressure	874 mm Hg	NIOSH 2006a
Relative Vapor Density (air=1)	1.55	Cavender 2001
Relative density (water =1)	0.6836 (liquid)	Cavender 2001
Flash Point	< -17°C, closed cup	ACGIH 1996
Explosive Limits	3.5-14% by volume in air	NIOSH 2006a
Conversion factors at 25°C	1 ppm =1.84 mg/m^3; 1 mg/m^3 = 0.542 ppm	Cavender 2001

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data were available on human lethality from EA exposure.

2.2. Non-lethal Toxicity

2.2.1. Odor Threshold/Odor Awareness

EA has a pungent ammonia-like odor. The EA odor awareness threshold in humans was reported as 0.027 ppm (Tkachev 1969), 0.046 (Ruijten 2005), 0.26 ppm (Ruth 1986), 0.27 ppm (Hellman and Small 1974), 0.95 ppm (Amoore and Hautala 1983), and 3.5 ppm (Laing et al. 1978).

Based on an odor threshold of 0.046 ppm, a level of distinct odor awareness (LOA) of 0.74 ppm was calculated for EA (Ruijten 2005) (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 a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception.

2.2.2. Incidental or Occupational Exposure

No quantitative human data were available in which both the EA concentration and exposure time were specified. A secondary source reported the EA irritation threshold as 98 ppm (Ruth 1986). EA of undefined concentration was stated to cause "blue haze – a thin blue film on the cornea" in occupationally exposed workers (Amor 1949). Other aliphatic amines (e.g. diethylamine, triethylamine, dimethylamine, dimethylethylamine) have also been reported to cause similar visual effects after exposure for several hours. These effects were due to edema of the corneal epithelium (see Section 4.3) (Amor 1949; Munn 1967; Jones and Kipling 1972; Ståhlbom et al. 1991; Grant and Schuman 1993).

2.2.3. Epidemiologic Studies

A two-year study of stationary ambient air samples collected in the vicinity of a Russian aliphatic amine production facility found EA concentrations up to 0.47 ppm at 1000 meters, and up to 0.02 ppm at 4000 meters from the pollution source (Tkachev et al. 1967; Tkachev 1969). The town had increased morbidity in children suffering from acute respiratory diseases, ear and mastoid process diseases, eye inflammation diseases, and other disorders. The children had increased blood cholinesterase activity, disruption in porphyrin balance, modification in erythrocyte acidity resistance, hypochromic anemia, and alterations in other hematological parameters.

2.3. Neurotoxicity

No data were found in available literature about neurotoxic properties of EA.

2.4. Developmental/Reproductive Toxicity

Data were absent on developmental and reproductive EA toxicity for humans.

2.5. Genotoxicity

No data were available on the genetic toxicity of EA to humans.

2.6. Carcinogenicity

No data were found on EA carcinogenicity in humans.

2.7. Summary

EA has a pungent ammonia-like odor with reported detection thresholds ranging from 0.027-3.5 ppm. An LOA of 0.74 ppm was calculated for EA (Ruijten 2005). No human data were available in which there was both an exposure concentration and duration. A secondary source reported the EA irritation threshold as 98 ppm (Ruth 1986). EA of undefined concentration was stated to cause corneal edema, resulting in workers seeing "blue haze" (Amor 1949). A two-year study of ambient air samples collected near a Russian aliphatic amine production facility found EA concentrations up to 0.47 ppm at 1,000 meters, and increased

morbidity in children, who had respiratory, ear, and eye diseases, and alterations in hematological parameters (Tkachev et al. 1967; Tkachev 1969).

No data were found regarding human exposures resulting in neurotoxicity, developmental or reproductive toxicity, genotoxicity, or carcinogenicity.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Data on acute lethal toxicity of EA in laboratory animals are presented in Table 3.

TABLE 3. Ethylamine Acute Lethality Animal Studies

Species	Exposure Time (min)	Concentration (ppm)	Mortality	Effects (Reference)
Rat	6 20 60	14,000-24,800 8220-12,900 4100-7050	LC_{50}=22,240 ppm[1] LC_{50}=9610 ppm[1] LC_{50}=6260 ppm[1]	Corneal opacity, reddened lungs, labored breathing, rales, gasping; lower body weight gain during first week for most groups. (IRDC 1993)
	2.5 28 240	Near-saturated 16,000 4000; 8000	6/6 6/6 1/6; 2/6	Mortality and nose and eye irritation observed; no other results provided (Smyth et al 1954; MIIR 1987)
	240	1) 625, 2962, 4462; 2) 3723, 4087, 6293	1) 0/20, 3/20, 17/20; 2) 0/20, 0/20, 6/20	Two tests conducted; LC_{50}= 3640 ppm in 1st test; LC_{50}= 6570 ppm in 2nd. No other results were reported. (BASF AG 1980)
	360 x 120 d	500	≥ 2/60	24-week study; eye and nasal toxicity; see Section 3.2.1. (RPA 1984; Lynch et al. 1988)

[1]LC_{50} values were calculated using EPA BenchMark Dose Software, version 1.3.2; study author obtained values of 22,200, 9136, and 5540 ppm using the method of C.I. Bliss (1938).

3.1.1. Rats

IRDC (1993) exposed Crl:CD rats (5/sex/dose; 48-76 days old) to anhydrous EA for 6 minutes (14,000-24,000 ppm), 20 minutes (8200-12,900 ppm), or 60 minutes (4100-7050 ppm), as shown in Table 4. The rats were exposed whole-body in chambers with pre-established EA air concentrations. Animals were observed for signs of toxicity and mortality for 14 days after exposure, and were weighed on days 0, 7, and 14. All animals were necropsied, but histopathology was not conducted. Most groups had decreased body weight gain only during the first post-exposure week. Observations during or immediately after exposure included gasping, labored breathing, rales, and corneal opacity in all groups. Necropsy revealed cloudy corneas with no clear dose-response, and lung congestion (red, discolored lungs) that was dose-related for the 20-minute and 60-minute exposures, but not for the 6-minute exposure. Mortality occurred primarily during the first week after exposure, and was dose-related for the 20-minute and 60-minute exposure groups, but a more variable response was seen in the 6-minute exposure group. To determine if the variable mortality was due to condensation of EA on the walls of the exposure equipment, the equipment was slightly heated to prevent condensation. Treatment of rats with 14,000 and 24,800 ppm for 6 minutes using the heated equipment produced results

similar to those obtained without heating. LC_{50} values were calculated by the method of Bliss (1938) as 22,200 ppm for 6 minutes, 9136 ppm for 20 minutes, and 5540 ppm for 60 minutes. The mortality data were subsequently re-evaluated using EPA BenchMark dose software (Version 1.3.2.), which yielded LC_{50} values for 6, 20, and 60 minutes of 22,240 ppm, 9610 ppm, and 6270 ppm, respectively; $BMCL_{05}$ values of 10,460 ppm, 7720 ppm, and 2450 ppm, respectively; and BMC_{01} values of 11,010 ppm, 8440 ppm, and 4910 ppm, respectively. Confidence in the values was good for the 20- and 60-minute mortality data (p=0.73; p=0.64), but poor for the 6-minute data (p= 0.0047), reflecting the lack of a dose-response in this data set.

TABLE 4. IRDC (1993) Rat Acute Inhalation Study With Ethylamine

Exposure time (min)	Concentration (ppm)	Lethality	Lc_{50} (ppm)	Necropsy findings		Observations
				Cloudy cornea	Congested or red lungs	
6	14,000	1/10	22,200 (22,240)[1]	10/10	0/10	Inconsistent mortality response; corneal opacity in all rats; labored breathing, rales, and gasping in most rats; lower body weight gain during first week only.
	14,700	0/10		10/10	0/10	
	15,700	1/10		8/10	1/10	
	16,500	0/10		10/10	0/10	
	17,800	7/10		10/10	7/10	
	19,900	1/10		10/10	1/10	
	22,800	6/10		10/10	0/10	
	24,800	6/10		10/10	6/10	
20	8220	3/10	9136 (9610)[1]	9/10	2/10	Death; corneal opacity in all rats; labored breathing, rales, and gasping in most rats; lower body weight gain during first week only for most groups.
	9060	2/10		10/10	2/10	
	9080	5/10		9/10	2/10	
	9910	8/10		10/10	8/10	
	11,000	10/10		8/10	4/10	
	12,900	10/10		7/10	7/10	
60	4100	2/10	5540 (6260)[1]	7/10	2/10	Observations as for 20-min exposure but not all 4100 and 6150 ppm rats had corneal opacity.
	6150	6/10		7/10	6/10	
	6160	5/10		6/10	4/10	
	7050	9/10		9/10	9/10	

[1]The LC_{50} values in parentheses were calculated using EPA BenchMark Dose Software, version 1.3.2.

In a range-finding study conducted by Smyth et al. (1954; also reported in MIIR 1987), EA toxicity was determined for Carworth-Wistar rats, 5-6 weeks old. EA vapor was created by blowing air (2.5 L/min) through a porous glass disk submerged in 72% pure liquid EA. Air concentrations of EA were not verified analytically. All rats exposed to "substantially saturated" vapor at room temperature (6/6) died in 2.5 minutes, as did all rats (6/6) that inhaled 16,000 ppm for 28 minutes. Fractional mortality occurred in rats exposed for 4 hours to 8000 ppm (2/6 died) or to 4000 ppm (1/6 died). It was noted that at 8000 ppm very strong irritation was observed in the rats, whereas 4000 ppm caused mild irritation of the nose and eyes. No further study results were provided.

Sprague-Dawley rats (10/sex) were exposed to 625-6293 ppm EA for 4 hours in two unpublished experiments conducted by BASF AG (1980), which were incompletely described in a secondary source (IUCLID 2002). The only provided methods information was that the animals were observed for two weeks, their body weights were measured prior to treatment and after 7 and 14 days, and that the EA concentration was measured analytically. The only reported

results were mortality rates. In the first test, rats exposed to 625, 2962, or 4462 ppm had mortalities of 0/20, 3/20, and 17/20, respectively. In the second test, inhalation of 3723, 4087, and 6293 ppm caused mortalities of 0/20, 0/20, and 6/20, respectively. The discrepancies between these two sets of values were not addressed. Analysis of the mortality data using EPA BenchMark dose software (Version 1.3.2.) yielded LC_{50}= 3640 ppm, $BMCL_{05}$= 2120 ppm, and BMC_{01}= 2300 ppm for the first experiment, and LC_{50}= 6570 ppm, $BMCL_{05}$= 4200 ppm, and BMC_{01}= 5430 ppm for the second experiment.

3.2. Non-lethal Toxicity

Information on EA non-lethal acute inhalation toxicity for different laboratory animal species is presented in Table 5.

TABLE 5. Non-Lethal Toxicity And Multiple Exposure Animal Studies

Species	Exposure Time	Concentration (ppm)	Effect (Reference)
Rat	240 min	2580	Red nasal discharge, salivation, labored breathing, gasping, rales, closed eyes, matted coats, reduced activity, ano-genital staining, pallor, corneal irregularities, body weight loss; many signs persisted through first week. (Bio/Dynamics, Inc. 1986)
	6 hr/d × 10 6 hr/d × 10	250 1000	- Slight nasal necrotic inflammation - Moderate nasal necrotic inflammation and thymic atrophy; decreased body weight (RPA 1984; Lynch et al. 1999)
	6 hr/d, 5 d/wk, for 24 wk	10, 100 500	- No nasal lesions or impact on animal condition - 2/60 died; closed eyes and buried noses during exposure; had nasal lesions; decreased weight gain; males had longer QT-interval (RPA 1984; Lynch et al. 1988)
Mouse	15 min	88-190	RD_{50} = 151 ppm (calculated 50% decrease in breathing rate) (Gagnaire et al. 1989)
	93-d continuous	0.008 0.10; 0.61 2.0	-No effects -Decreased muscular excitability, cholinesteraseacativity, etc. -As above, and neuronal and lung pathology (Tkachev 1969)
Rabbit	7 hr/d, 5 d/wk, for 6 wk	50 100	- Lung vessel thickening, peribronchitis, pneumonitis; heart focal muscular degeneration; corneal epithelial erosions and edema, nictitating membrane edema; seen after two weeks. - Lung hemorrhage, peribronchitis, vascular wall thickening; slight to moderate parenchymatous kidney degeneration. (Brieger and Hodes 1951)

3.2.1. Rats

Sprague-Dawley CD rats (5/sex) were exposed for 4 hours to 2580 ppm (3000 ppm nominal) EA vapor and observed for 14 days in a study conducted by Bio/dynamics Inc. (1986). Exposure was dynamic in a 100-L chamber, and EA air concentration was measured every 30 minutes with a Miran® 1A Ambient Air analyzer. Rats were observed twice daily. On the day of exposure, they were observed individually before exposure and 30 and 240 minutes after exposure, but during exposure were observed as a group at 15, 30, 45, 60, 120, 180, and 240

minutes. The rats were weighed on days 1 (preceding exposure), 2, 3, 4, 8, 11, and 15 (prior to sacrifice). Necropsies were performed on all animals, but no histopathology was conducted. No animals died on study. Signs during and after exposure are summarized in Table 6. During exposure and up to 4 hours afterwards, rats had increased secretion (red or dried red nasal discharge, salivation, dried red or brown material on fur), respiratory distress (labored breathing, gasping, moist or dry rales), hunched appearance, closed eyes, matted coats, and reduced general activity. Shortly after exposure (30 or 240 minutes), rats also had wet coats, yellow or brown ano-genital staining, pallor, and corneal irregularities. Many of these signs persisted throughout the first week of observation, and some persisted into the second observation week. Both sexes had a 6-8% body weight loss during the first week only. Necropsy revealed no significant findings.

TABLE 6. Observations in Rats Inhaling Ethylamine Vapor for 4 Hours

Observation (n = 10)	Time during exposure (min.): Number of affected animals[1]					Time after exposure (min. or days): Number of affected animals[2]						
	15	30	60	120	240	30'	240'	2-3d	4-6d	7-9d	0-12d	13-15d
Secretory changes												
Red or dried red nasal discharge	-	-	-	-	-	1	1	10	10	2	4	1
Salivation	-	all	all	all	All	3	-	-	-	-	-	-
Dried red/brown material on fur	-	-	-	-	-	10	10	6	5	-	4	-
Respiratory changes												
Labored breathing	few	-	-	-	-	6	10	2	5	2	-	-
Gasping	most	all	all	all	all	4	-	3	-	-	1	-
Rales, moist or dry	-	-	-	-	-	1	4	5	10	10	10	1
Other changes												
Reduced activity	all	all	all	all	all	9	-	4	-	-	-	-
Hunched appearance	-	-	some	some	-	-	-	-	10	-	-	-
Wet and/or matted fur	-	-	-	few	few	-	-	10	-	-	-	-
Yellow ano-genital staining		-	-	-	-	10	7	5	1	1	1	-
Eyes closed	all	all	all	all	all	-	-	1	-	1	-	-
Corneal irregularity or opacity	-	-	-	-	-	2	2	2	-	-	-	-
Pallor	-	-	-	-	-	10	10	-	-	-	-	-

[1]The animals (5/sex) were observed as a group, and the number of affected animals was presented as: "—" = none "few" = 10-30%, "some" = 40-60%, "most" = 70-90%, "all" = 100%.
[2]Observations were made 30 minutes and 4 hours after exposure and thereafter daily until sacrifice. The highest daily incidence at the stated time interval is presented.
Source: Bio/dynamics, Inc. (1986).

F344 rats exposed whole-body for 10 days (6 hours/day over a 14-16 day period) to 250 ppm or 1000 ppm had, respectively, mild (3/5 rats) and moderate (5/5 rats) necrotic inflammation of the nasal cavity (RPA 1984; Lynch et al. 1999). The method of generating and maintaining the EA air concentrations was not presented. Animal body weights were relatively unaffected at 250 ppm but were significantly decreased (50% in males; 36% in females) in both sexes at 1000 ppm. Histopathology of the major organs and tissues (nares, trachea, lungs, tracheobronchial lymph nodes, liver, kidneys, heart, aorta, spleen, pancreas, adrenals, testes, epididymides, and ovaries) showed no effects other than the nasal lesions.

In a related study, male and female F-344 rats (30/sex/dose) were exposed 6 hours/day, 5 days/week for up to 24 weeks to 0, 10, 100, or 500 ppm EA (RPA 1984; Lynch et al. 1988). EA concentrations were measured analytically 2-4 times/hour with an infrared analyzer. Animal subgroups were sacrificed after 30, 60, and 120 days, and after 24 weeks of exposure. Hematology parameters (hemoglobin, hematocrit, differential blood count) were evaluated only at terminal sacrifice, biochemistry parameters (alanine and aspartate aminotransferase, creatine phosphokinase, lactate dehydrogenase, blood urea nitrogen, creatine, and sorbitol dehydrogenase) at the 30-day prior to terminal sacrifice. Electrocardiograms were obtained for 10 anesthetized rats at terminal sacrifice. Organs examined microscopically included those listed in the previous paragraph as well as eye, mesenteric lymph nodes, uterus, bone marrow, and thymus. Rats exposed to 500 ppm kept their eyes closed and their noses buried in their fur during exposure. Two rats exposed to 500 ppm died (one male and one female), although the day of death was not specified. Gross and microscopic pathology evaluated at the 120-day sacrifice (other pathology data not provided) showed no nasal lesions or visible impact on the health status of rats exposed to 0, 10, or 100 ppm, but rats exposed to 500 ppm had moderate to marked atrophic rhinitis in the anterior nasal cavity, and moderate thymic atrophy. The rhinitis was characterized by occurrence of suppurative exudate in the nasal passageways, chronic inflammation often with development of ulcers, necrosis, and loss of cartilage in the nasal septum, squamous epithelial metaplasia, and in some cases resorption of the conchal bone. There were no effects on hematology or biochemistry parameters, but males exposed to 500 ppm had a significantly longer QT-interval in their electrocardiographs.

3.2.2. Mice

Gagnaire et al. (1989) examined the effects of EA on the respiratory rate of male Swiss-OF_1 mice using a plethysmographic technique. The oronasal exposure was conducted in 200-liter steel inhalation chambers chamber by bubbling air through the liquid amine. The air EA concentrations were analyzed by high resolution liquid chromatography. Exposure was for a total of 15 minutes to 88-190 ppm EA. The breathing rate change was seen within 30-60 seconds, and recovery after the 15-minute exposure occurred within one minute. The RD_{50} i.e., concentration of EA causing a 50% decrease in the breathing rate, was calculated to be 151 ppm.

Continuous exposure of white mice for 93 days to 0.10, 0.61, or 2.0 ppm, but not 0.008 ppm EA decreased muscular excitability, blood cholinesterase activity, acidic resistance of erythrocytes, and other effects (Tkachev 1969). The degree of effect depended on the exposure concentration. Pathomorphological changes were observed only at 2.0 ppm, consisting of irregularities in Nissl bodies and in reticulate protoplasm of major neurons in the brain, and

perivascular cellular infiltrates in the lungs. The authors recommended the no-effect concentration of 0.008 ppm as the maximal single- and mean daily maximal permissible EA concentration in ambient air.

3.2.3. Rabbits

In an incompletely reported study, groups of 6 rabbits (strain, sex, and age not specified) were exposed to 50 or 100 ppm EA 7 hours/day, 5 days/week, for 6 weeks (Brieger and Hodes 1951). The 50 ppm experiment was conducted twice but separate results were not reported. The atmosphere was generated dynamically by passing dry air through liquid EA, and the chamber concentration was measured analytically by sodium hydroxide titration. The study report did not state how, when, or which animals were examined. However, based on the provided results for EA and two related chemicals which were also evaluated (diethylamine and triethylamine), it appeared that the eyes of the animals were examined weekly *in vivo* by corneal microscopy at 50 ppm, and that histological examination was performed on the lungs, kidneys, heart, and liver. No animals died on study. The 50 ppm animals had lesions in the lungs (peribronchitis and pneumonitis, thickening of small blood vessels), heart (focal muscular degeneration), and eyes (corneal epithelial erosions and edema, nictitating membrane edema). The eye lesions were seen only after two weeks of exposure. The 100 ppm group animals had lung hemorrhage in addition to peribronchitis and vascular wall thickening and slight to moderate parenchymatous degeneration of the kidneys. It is peculiar that eye lesions were not reported at 100 ppm (it was not stated that they were absent); several study statements suggest that this was not due to the lack of effect at 100 ppm, but a lack of reporting. Thus, (1) the methods description does not specify that eyes of both the 50 and 100 ppm groups were examined; (2) all three of the chemicals tested caused corneal erosions and edema at 50 ppm but no results were presented at 100 ppm; and (3) in the study summary, the authors state that "the vapors of monoethylamine, diethylamine and trimethylamine, in concentrations as low as 50 ppm., showed marked irritation of the cornea and of the lung tissue."

3.3. Neurotoxicity

No data were found in available literature on EA neurotoxic properties.

3.4. Developmental/Reproductive Toxicity

No data on developmental or reproductive toxicity in animal models were available.

3.5. Genotoxicity

EA concentrations of 0.033; 0.10; 0.33; 1.0; 3.3 and 10 mg/plate were not mutagenic in the Ames test using *Salmonella typhimurium* strains TA1535, TA1537, TA97, TA98, and TA100 with or without metabolic activation with S9 (rat or hamster liver) (Mortelmans et al. 1986). No mutagenic activity was also observed in *S. typhimurium* TA100 by Air Products and Chemicals (1977) when testing up to 1000 μg/plate EA in the presence of rat liver S9 activation. Ethylamine (100 μL) was very weakly mutagenic in the Ames test using *Salmonella* strains TA1530, TA100, G46, TA1537, and TA97, although the individual strain results were not

provided (Owais et al. 1983). EA (≤ 25 µL) was not mutagenic in *Escherichia coli* Sd-5-73 in the paper disk streptomycin-independence assay (Szybalski 1958).

A slight increase in sister chromatid exchanges was found in V79 Chinese hamster cells incubated with 5 mM EA-HCl (12.2 vs. 6.5 in control) (Speit et al. 1980).

Negative results were obtained with EA in the mouse testicular DNA synthesis inhibition (DSI) test (Seiler 1981). The mice were injected intraperitoneally with up to 50 mg/kg EA. This short-term test was designed as an indicator of carcinogenic potential, and is based on the ability of a compound to bind DNA, thereby inhibiting (radioactive) thymidine incorporation and DNA replication.

3.6. Carcinogenicity

No EA carcinogenicity studies were located. A short-term test designed to predict the carcinogenic potential of compounds by their ability to inhibit DNA replication in mouse testes yielded negative results (Seiler 1981).

3.7. Summary

Acute lethality studies were available from three laboratories. In the most comprehensively reported study (IRDC 1993), Crl:CD rats exposed for 6 minutes, 20 minutes, or 60 minutes had calculated LC_{50} values of 22,240 ppm, 9610 ppm, and 6270 ppm, respectively. The rats had decreased body weight gain, gasping, labored breathing, rales, and corneal opacity; necropsy revealed cloudy corneas and lung lesions. In a range-finding study (Smyth et al. 1954; also reported in MIIR 1987), Carworth-Wistar rats exposed to "substantially saturated" vapor for 2.5 minutes or to 16,000 ppm for 28 minutes all died, whereas exposure for 4 hours to 4000 ppm or 8000 ppm killed 1/6 and 2/6, respectively. The only other provided results were that 8000 ppm very irritating and 4,000 ppm was mildly irritating to the nose and eyes. A secondary source (IUCLID 2002) provided only mortality data for Sprague-Dawley rats exposed to 625-4462 ppm in one trial and to 3723-6293 ppm in another trial (BASF AG 1980), for which EPA BenchMark dose software (Version 1.3.2.) yielded LC_{50} values of 3640 ppm and 6570 ppm, respectively.

No lethality occurred in Sprague-Dawley CD rats exposed for 4 hours to 2580 ppm (Bio/dynamics Inc. 1986), but the animals had severe respiratory and ocular irritation (red nasal discharge, salivation, labored breathing, gasping, rales, closed eyes, pallor, and corneal irregularities) that persisted throughout the first and sometimes second post-exposure week. In the only other available single-exposure study, male Swiss-OF_1 mice exposed for 15 minutes to 88-190 ppm EA had a decreased respiratory rate, which was calculated to be 50% (i.e., RD_{50}) at 151 ppm (Gagnaire et al. 1989).

Multiple-exposure studies were conducted with rats, mice, and rabbits. F344 rats exposed to 250 ppm or 1000 ppm 6 hours/day for 10 days had necrotic inflammation of the nasal passages, and the rats exposed to 1000 ppm had decreased weight gain (RPA 1984; Lynch et al. 1999). F-344 rats similarly exposed to 10 or 100 ppm EA for up to 24 weeks had no toxic effects, whereas rats exposed to 500 ppm kept their eyes closed and buried their noses during exposure, two died (day not stated), and histopathology revealed nasal atrophic rhinitis and

thymic atrophy. White mice exposed continuously for 93 days to 0.10, 0.61, or 2.0 ppm, but not 0.008 ppm EA, had neurotoxic effects, and the 2.0 ppm mice had histopathological changes in brain neurons and in the lungs (Tkachev 1969). Rabbits exposed to 50 ppm EA for 7 hours/day, 5 days/week, for 6 weeks had lesions in the lungs, heart, and eyes, and those exposed to 100 ppm had lung and kidney lesions; ocular effects were not addressed at 100 ppm (Brieger and Hodes 1951).

No data were found on EA neurotoxicity, developmental or reproductive toxicity, or carcinogenicity. Genotoxicity studies were largely negative.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No information was located regarding the metabolism of EA in mammals following inhalation exposure, and little information was found after administration by other routes.

EA is present in many foods and is a normal constituent of human urine, although its urinary etiology has not been determined. EA, like the related compound methylamine (MMA), is not a substrate of monoamine oxidase but is metabolized by semicarbazide-sensitive amine oxidase (SSAO; EC 1.4.3.6), to form an aldehyde (acetaldehyde for EA; formaldehyde for MMA), hydrogen peroxide, and ammonia (Yu 1989; 1990). The aldehyde is further metabolized to CO_2, as shown in Sprague-Dawley rats administered ^{14}C-labeled EA orally (Sourkes et al. 1977), although the degree of metabolism by this route was not evaluated.

It is unknown if enzymes other than SSAO are involved in mammalian EA metabolism. An *in vitro* study found that EA was a poorer substrate (lower V_{max}; higher K_m) for rat aorta SSAO than MMA, with a 3-fold lower turnover number (V_{max}/K_m) (Yu 1990), indicating that there are differences in the pharmacokinetics between these compounds. This was also suggested by the urinary excretion study of Rechenberger (1940), which found that the urine of a human who ingested 2 g of EA or MMA contained 31.1% and 1.8%, respectively, of the administered (unmetabolized) amine within 24 hours of intake. Conversely, Greim et al. (1998) stated that EA is excreted in the urine for the most part unmetabolized, but no other details were provided.

4.2. Mechanism of Toxicity

The mechanism of EA toxicity has not been elucidated, although its irritant properties are likely related to its high alkalinity (pK_a of 10.71 at 25°C) and corrosiveness to exposed tissues such as skin, eyes, and the respiratory mucosa. Single-exposure rat studies found irritation-related effects including gasping, labored breathing, rales, closed eyes, and lesions in the cornea and lungs, which led to death at sufficiently high concentrations. Multiple-exposure studies also found irritant effects, but additionally reported systemic effects of unknown etiology. For example, in addition to eye, lung, and/or nasal lesions, F344 rats exposed to 500 ppm 6 hours/day for 120 days had thymic atrophy (RPA 1984; Lynch et al. 1988); white mice exposed continuously for 93 days to 2.0 ppm had neurotoxic effects (Tkachev 1969); and rabbits exposed to 50 or 100 ppm EA for 7 hours/day, 5 days/week for 6 weeks had lesions in the heart and kidneys, respectively (Brieger and Hodes 1951). Because the effects on the thymus in rats, CNS in mice, and heart and kidneys in rabbits were not

seen consistently among the species and occurred after at least 3 months of exposure, their significance as endpoints for a single exposure appears to be minimal.

4.3. Structure-Activity Relationships

IRDC (1992a,b; 1993) determined LC_{50} values for Sprague-Dawley rats exposed for 6, 20, or 60 minutes to EA, MMA, and DMA, which caused gasping, labored breathing, rales, corneal opacity, reddened lungs, and decreased body weight. For EA, MMA, and DMA, respectively, the calculated LC_{50} values were 22,200, 24,400, and 17,600 ppm for 6 minutes; 9136, 9600, and 7340 ppm for 20 minutes; and 5540, 7110, and 5290 ppm for 60 minutes. Thus the relative acute toxicities to rats were DMA>EA>MMA, although the differences in the LC_{50} values between the three compounds were relatively small.

The concentration that caused a 50% decrease in the breathing rate of male Swiss-OF_1 mice (i.e., RD_{50}), an indicator of upper airway irritation, was similar for a number of amines structurally related to EA (Gagnaire et al. 1989). The mice were exposed oronasally for 15 minutes while their respiratory rates were measured with a plethysmograph. The RD_{50} was 151 ppm for EA, 202 ppm for diethylamine, 156 ppm for triethylamine, 141 ppm for MMA, and 115 ppm for n-propylamine.

No quantitative EA human exposure data were found, but an occupational survey reported that EA and triethylamine caused visual “blue haze,” and diethylamine caused intense eye irritation and edema (Amor 1949). Because the ocular response to EA was similar to that of other ethylamines, quantitative studies with closely related ethylamines are considered relevant to estimating EA concentrations that would cause eye toxicity in humans. Thus, Table 7 summarizes the results of experimental studies with volunteers exposed to diethylamine, dimethylethylamine, and triethylamine. Irritation of the eyes and/or nasal passages occurred at concentrations as low as 4.3 ppm after an 8-hour exposure, and at approximately 10 ppm, all three compounds caused eye irritation and in some cases marked visual disturbances (hazy and blurry vision, corneal edema, etc.) starting as soon as one hour into the exposure. The results of several occupational studies are also shown in Table 7, which found that dimethylethylamine and triethylamine caused visual disturbances and eye and nose irritation at time-weighed concentrations lower than those determined in experimental studies. Ståhlbom et al. (1991) considered the effects in the occupational studies due to short-term exposure peaks.

TABLE 7. Human exposure studies with structurally related amines			
Compound (Reference)	**Exposure Time**	**Concentration (ppm)**	**Effect and subject description**
Clinical studies			
Diethylamine (Lundqvist et al. 1992)	60 min 15 min	10 (0-12) 25	-Distinct eye and nasal irritation and a moderate to strong olfactory response (healthy adults) -Nasal volume and airway resistance unchanged, as determined by acoustic rhinometry and rhinomanometry
Dimethylethylamine (Ståhlbom et al. 1991)	8 hr 8 hr 15 min	3.3, 6.7 13 27 or 53	-No effects (4 non-smoker males age 33-53) -Eye irritation (3/4); reversible visual disturbance corneal edema) (1/4) -Eye irritation (3/4) but no visual disturbances
Triethylamine (Åkesson et al. 1985)	8 hr 4 hr 8 hr 4 hr 4 hr	2.4 4.3 4.3 11.6 8.2	-No effects (2 men, ages 44 and 46) -No effects -Slight epithelial corneal edema and increased corneal thickness, starting after 4-6 hours of exposure; no subjective eye discomfort. -Hazy vision, blurred objects, blue halos starting after 1 hour; slight eye discomfort without definite irritation; eyes had corneal edema, conjunctivitis, increased corneal thickness; cleared in approximately 4 hours. -Visual disturbance and eye changes as at 11.6 ppm but less severe; began after 2 hours and cleared in approximately 2 hours; no eye irritation.
Triethylamine (Jarvinen et al. 1999)	4 hr	0.72 1.6 9.8	-No effects (4 subjects) -Blurred vision; decreased contrast sensitivity -Blurred vision; decreased contrast sensitivity and visual acuity; marked corneal edema, subepithelial microcysts, slightly inc. corneal thickness
Occupational studies			
Dimethylethylamine (Warren and Selchan 1988)	8 hr	>3*	Hazy, blurry vision, eye watering and itching, halo vision, irritation of the eyes, nose, and throat in 85 workers in 42 foundries. Personal breathing zone samples were collected. Effects ceased with exposure.
Dimethylethylamine (Stephenson and Albrecht 1986)	8 hr 15 min	2 – 3.3* 10*	-Transient visual disturbances among workers -Transient visual disturbances among workers
Triethylamine (Åkesson et al. 1986)	8 hr	<2.4* 2.4 -3.6*	-No effects in polyurethane workers -Visual disturbances after 1-6 hours; resolved after one hour
Triethylamine (Warren and Selchan 1988)	8 hr	>3*	Hazy, blurry vision, eye watering and itching, halo vision, irritation of eyes, nose, and throat in 85 workers in 42 foundries. Personal breathing zone samples collected. Effects ceased with exposure.

*Concentrations are time-weighted averages

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4.4. Other Relevant Information

4.4.1. Species Variability

EA acute lethality studies were only available for rats. Species variability therefore cannot be assessed directly, but variability can be estimated from studies with structurally related amines. Rats and mice exposed to EA or the related amines MMA, DMA, and TMA had similar LC_{50} values, toxic effects (primarily of eye and respiratory lesions, and neurotoxicity for TMA; see Section 4.3.), and death apparently due to lung lesions. Thus variability between rats and mice for EA acute lethality is also likely small.

Non-lethal EA toxicity studies were conducted with rats, mice, and rabbits. The mouse studies consisted of a 15-minute respiratory inhibition study (Gagnaire et al. 1989) and a 93-day continuous exposure study at ≤ 2 ppm (Tkachev 1969). These studies could not be compared to other species because the experimental protocols were too dissimilar. The studies with rats and rabbits, however, provide some insight regarding species variability at non-lethal concentrations, and consistently point to the rat being less sensitive than other species for detecting ocular and respiratory toxicity.

F-344 rats exposed to 500 ppm EA 6 hours/day, 5 days/week for 24 weeks kept their eyes closed and noses buried during exposure, had nasal atrophic rhinitis and thymic atrophy, and two died (day not stated), whereas rats similarly exposed to 10 or 100 ppm had no effects (RPA 1984; Lynch et al. 1988). However, rabbits exposed to 50 ppm EA for 7 hours/day, 5 days/week for 6 weeks had lesions in the lungs, heart, and eyes, and those exposed to 100 ppm had lung and kidney lesions; ocular effects were not addressed at 100 ppm (Brieger and Hodes 1951). Both the rat and rabbit studies showed the presence of eye and respiratory irritation, although the effects were more severe and occurred at a much lower concentration in rabbits. Although rabbit eyes were examined *in vivo* with a corneal microscope, whereas rat eyes were examined only post-mortem, the data indicate that rabbits are a more sensitive indicator of EA-induced respiratory and eye lesions at non-lethal concentrations. A similar response was found for the related amine DMA, as rabbits and guinea pigs treated with 9 exposures to 97 or 183 ppm DMA (7 hours/day, 5 days/week) had slight corneal "injury" whereas none was seen in rats (Hollingsworth et al. 1959).

Human eyes were more sensitive than those of rats when exposed to the structurally related compound diethylamine. Healthy adult humans exposed to approximately 10 ppm diethylamine experienced distinct eye and nasal irritation (Lundqvist et al. 1992), whereas F-344 rats exposed to 25 ppm DEA 6.5 hours/day, 5 days/week, for 24 weeks had no treatment-related effects (Lynch et al. 1986). Rats similarly exposed to 250 ppm, however, had sneezing, tearing, reddened noses, and nasal lesions (suppurative rhinitis, lymphoid hyperplasia).

4.4.2. Susceptible Populations

No sensitive populations were identified.

4.4.3. Concentration-Exposure Duration Relationship

A computer program, developed by ten Berge (2006) and based on probit analysis according to Finney (1971), integrates all concentration and time information for a range of

lethality data. Concentration, time, and response (including number of animals responding) are considered simultaneously in a linear regression equation, with the Maximum Likelihood statistical method used to find the closest estimates of the regression coefficients for each parameter. The probit-analysis dose-response program of ten Berge was applied to the IRDC (1993) data to estimate the LC_{01}, considered the threshold for lethality, at each AEGL exposure duration (with confidence limits of 95%). The full data set on lethality was used. The calculated n value was 1.63, rounded to 1.6.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No relevant quantitative EA studies were available. Amor (1949) reported that EA caused workers to see "blue haze" but the test concentration was undefined; this effect is due to corneal edema. Amor (1949) and others have reported that structurally related ethylamines also cause visual disturbances and/or eye irritation, including diethylamine, triethylamine, and dimethylethylamine. Experimental and occupational studies with the latter compounds are summarized in Section 4.3. and Table 7. Eye irritation and in some cases marked visual disturbances (hazy and blurry vision, corneal edema, etc.) was caused by all three compounds at approximately 10 ppm, starting as soon as after an hour of exposure. Occupational studies found ocular effects at somewhat lower (time-weighed) concentrations, likely caused by short-term exposure peaks (Ståhlbom et al. 1991).

5.2. Summary of Animal Data Relevant to AEGL-1

The only single-exposure animal study was the respiratory inhibition study of Gagnaire et al. (1989), in which male OF_1 Swiss mice exposed to 88-190 ppm for 15 minutes had a calculated 50% decrease in the breathing rate (RD_{50}) at 151 ppm. According to Alarie (1981), exposure to the RD_{50} is intolerable to humans, exposure to 0.1 of the RD_{50} (i.e., 15 ppm) for several hours-days causes sensory irritation in humans, 0.01 x RD_{50} (1.5 ppm) should cause no sensory irritation.

5.3. Derivation of AEGL-1

In the absence of data that address AEGL-1 level effects, the data on other alkylamines were considered. Because EA and methylamine are both primary amines with similar toxicity values, the AEGL-1 for EA was based on methylamine. The AEGL-1 for methylamine was based on two studies (Kinney et al. 1990; Sriramachari and Jeevaratnam 1994). The point of departure in the Kinney et al. (1990) study was a single 6-hour exposure of male CD rats to 75 ppm. Exposures were actually repeated for two-weeks (10 exposures) and resulted in mild irritation of the nasal turbinates. Repeat exposure to higher concentrations (250 and/or 750 ppm) caused more severe nasal lesions and /or systemic toxicity and mortality. A single 6-hour exposure to 75 ppm is expected to cause no more than mild sensory irritation. In the second study (Sriramachari and Jeevaratnam 1994), exposure of male Wistar rats to 465 ppm for 30 minutes was a NOAEL for notable signs of discomfort, but caused interstitial pneumonitis progressing to fibrosis. A total UF of 10 was applied, including 3 for interspecies uncertainty and 3 for human variability, because mild nasal irritation from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and is not likely to vary greatly between species

or among humans (NRC 2001). Because the well-conducted study of Kinney et al. (1990) was a repeat exposure study and the effect was essentially a NOAEL, a modifying factor of 0.5 was applied. The study of Sriramachari and Jeevaratnam (1994) used only one exposure, the description of the study results lacked details, and the endpoint was more serious than that defined by an AEGL-1. In the absence of robustness and due to lung histopathology, a modifying factor of 3 was applied.

In the absence of empirical data, a modifying factor of 2 was applied to the methylamine AEGL-1 value of 15 ppm. For methylamine, the same value was used across all AEGL-1 exposure durations because there is adaptation to the mild irritation that defines the AEGL-1. Using the same reasoning as for methylamine, the 7.5 ppm value was applied across all exposure durations for EA. The AEGL-1 is supported by human data for the structurally related compounds diethylamine and dimethylethylamine, which caused eye and nasal irritation and/or vision disturbances in healthy adults at approximately 10 ppm (Table 7). The AEGL-1 values are listed in Table 8, and the calculations are detailed in Appendix B. A category graph of the toxicity data in relation to the AEGL values is in Appendix C.

TABLE 8. AEGL-1 Values for Ethylamine

10-min	30-min	1-h	4-h	8-h
7.5 ppm (14 mg/m^3)	7.5 ppm (14 mg/m^3)	7.5 ppm (14 mg/m^3)	7.5 ppm (14 mg/m^3)	7.5 ppm (14 mg/m^3)

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

The available literature contained no human data that could be used for development of AEGL-2 values.

6.2. Summary of Animal Data Relevant to AEGL-2

Studies with endpoints that meet the definition of an AEGL-2 were unavailable. Available acute studies generally addressed lethality (BASF AG 1980; Bio/Dynamics, Inc. 1986; (RPA 1984; IRDC 1993) and were suitable for AEGL-3 derivation.

6.3. Derivation of AEGL-2

In the absence of empirical data that address the definition of an AEGL-2, the AEGL-2 values for EA were based on analogy with methylamine. Ethyl- and methylamines are both primary amines and have similar toxicity. The ratio between the AEGL-3 and AEGL-2 values for methylamine was considered. The AEGL-2 values for methylamine were derived from the repeat-exposure study with the rat (Kinney et al. 1990). Ten exposures of male CD rats to 250 ppm, 6 hours/day, caused reversible lesions of the anterior nasal region. The severity of the lesions (focal erosion and ulceration of the nasal turbinate mucosa) was attributed to the repeat exposure scenario, i.e., repeated local irritation. Lesions did not extend into the trachea or lungs. Lesions following a single exposure would be less severe and also reversible. The AEGL-3 for

methylamine was based on the on a lethality study with rats (IRDC 1992a). The probit-analysis based dose-response program of ten Berge (2006) was used to calculate the threshold for lethality at each AEGL-3 exposure duration. The program incorporated all of the lethality data at three time points: 6-, 20-, and 60-minutes. A total uncertainty factor of 10 was applied to both the methylamine AEGL-2 and AEGL-3, including 3 for interspecies uncertainty and 3 for human variability, because nasal irritation from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and is not likely to vary greatly between species or among humans (NRC 2001).

The ratio between the AEGL-3 and AEGL-2 values for methylamine (at one hour) was used to modify the AEGL-3 values for EA in order to derive AEGL-2 values. The 1-hour AEGL-3 and AEGL-2 values for methylamine are 350 and 64 ppm, respectively; the ratio is 5.5. The modifying factor of 5.5 was applied to the respective AEGL-3 values for EA (see Section 7.3), in order to derive AEGL-2 values. The derived AEGL-2 values are presented in Table 9, and the calculations are shown in Appendix B.

TABLE 9. AEGL-2 Values for Ethylamine

10-min	30-min	1-h	4-h	8-h
150 ppm (280 mg/m^3)	76 ppm (140 mg/m^3)	49 ppm (90 mg/m^3)	22 ppm (40 mg/m^3)	14 ppm (26 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No data were found on ethylamine exposure for humans relevant to derivation and calculation of AEGL-3 values.

7.2. Summary of Animal Data Relevant to AEGL-3

Three relevant studies were identified. In the first study, Crl:CD rats (5/sex/dose) were exposed for 6 minutes (14,000-24,000 ppm), 20 minutes (8200-12,900 ppm), or 60 minutes (4100-7050 ppm) and observed for 14 days (IRDC 1993). All groups exhibited gasping, labored breathing, rales, and corneal opacity during or shortly after exposure and necropsy revealed cloudy corneas and red, discolored lungs; the incidence of lung lesions was correlated with that of mortality.

In a range-finding study, Carworth-Wistar rats that inhaled 16,000 ppm for 28 minutes all died (6/6), whereas fractional mortality occurred from exposure for 4 hours to 8000 ppm (2/6 died) or to 4000 ppm (1/6 died) (Smyth et al. 1954; MIIR 1987). Results were limited to observations that exposure to 8000 ppm caused very strong irritation, whereas 4000 ppm caused mild irritation of the nose and eyes.

Only the mortality data were provided for two unpublished experiments in which Sprague-Dawley rats (10/sex) were exposed for 4 hours (BASF AG 1980). Rats exposed to 625, 2962, or 4462 ppm had mortality of 0/20, 3/20, and 17/20, respectively, in one trial. In a second

trial, inhalation of 3723, 4087, and 6293 ppm caused mortality of 0/20, 0/20, and 6/20, respectively. Analysis of the mortality data with EPA BenchMark dose software (Version 1.3.2.) yielded a $BMCL_{05}$= 2120 ppm for the first data set and a $BMCL_{05}$ = 4200 ppm for the second data set.

7.3. Derivation of AEGL-3

Using the data of IRDC (1993), the probit-analysis based dose-response program of ten Berge (2006) was used to calculate the LC_{01} (the threshold for lethality) at each AEGL-3 exposure duration. The program incorporated all of the data at the 6-, 20-, and 60-minute time points in Table 4. The data indicated a time-scaling value of 1.6 ($C^{1.6} \times t = k$). A total uncertainty factor of 10 was applied, including 3 for interspecies uncertainty and 3 for human variability, because lethality from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and is not likely to vary greatly between species or among humans (NRC 2001). The derived AEGL-3 values are presented in Table 10, and the calculations are shown in Appendix B.

TABLE 10. AEGL-3 Values for Ethylamine

10-min	30-min	1-h	4-h	8-h
810 ppm (1500 mg/m^3)	420 ppm (770 mg/m^3)	270 ppm (500 mg/m^3)	120 ppm (220 mg/m^3)	76 ppm (140 mg/m^3)

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

In the absence of data that address AEGL-1 level effects, the data on other alkylamines were considered. Because EA and methylamine are both primary amines with similar toxicity values, the AEGL-1 for EA was based on methylamine. In the absence of empirical data, a modifying factor of 2 was applied to the methylamine AEGL-1 value of 15 ppm. The AEGL-1 of 15 ppm for methylamine was based on mild nasal irritation in a repeat-exposure study with rats (Kinney et al. 1990); the same value was used across all AEGL-1 exposure durations because there is adaptation to the mild irritation that defines the AEGL-1. Using the same reasoning as for methylamine, the 7.5 ppm value was applied across all exposure durations for EA.

In the absence of empirical data that address the definition of an AEGL-2, the AEGL-2 values for EA were based on analogy with methylamine. The AEGL-3 and AEGL-2 values for methylamine were based on the threshold for lethality and severe irritation in rats, respectively. The ratio between the AEGL-3 and AEGL-2 values for methylamine (at one hour) was used to modify the AEGL-3 values for EA in order to derive AEGL-2 values. The ratio between the 1-hour AEGL-3 and AEGL-2 values for methylamine is 5.5. The modifying factor of 5.5 was applied to the respective AEGL-3 values for EA.

The 6-, 20, and 60-minute rat lethality data sets of IRDC (1993) were used to derive the AEGL-3 values. The threshold for lethality at each AEGL-3 exposure duration was calculated

using the probit-analysis based dose-response program of ten Berge (2006). The program incorporated all of the data at the 6-, 20-, and 60-minute time points. The data indicated a time-scaling value of 1.6 ($C^{1.6} \times t = k$). A total uncertainty factor of 10 was applied, including 3 for interspecies uncertainty and 3 for human variability.

Summary data on AEGL values for EA are presented in Table 11. A derivation summary is in Appendix D.

TABLE 11. Summary of AEGL Values for Ethylamine

Classification	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
AEGL–1 (Non-disabling)	7.5 ppm (14 mg/m^3)	7.5 ppm (14 mg/m^3)	7.5 ppm (14 mg/m^3)	7.5 ppm (14 mg/m^3)	7.5 ppm (14 mg/m^3)
AEGL–2 (Disabling)	150 ppm (280 mg/m^3)	76 ppm (140 mg/m^3)	49 ppm (90 mg/m^3)	22 ppm (40 mg/m^3)	14 ppm (26 mg/m^3)
AEGL–3 (Lethal)	810 ppm (1500 mg/m^3)	420 ppm (770 mg/m^3)	270 ppm (500 mg/m^3)	120 ppm (220 mg/m^3)	76 ppm (140 mg/m^3)

8.2. Comparison with Other Standards and Guidelines

The existing standards and guidelines for EA are shown in Table 12. The ACGIH (1996) TLV-TWA of 5 ppm and STEL of 15 ppm are intended to protect workers from eye and respiratory irritation. The AEGL-1 value of 7.5 ppm falls between the two ACGIH guidelines. The NIOSH IDLH of 600 ppm was based on rat acute inhalation studies in which the lowest 4-hour lethal concentrations were 3000 and 6000 ppm (NIOSH 2006b). The AEGL-3 was based on a more recent lethality study (IRDC 1993).

TABLE 12. Extant Standards and Guidelines for Ethylamine

Guidelines	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	7.5 ppm	7.5 ppm	7.5 ppm	7.5 ppm	7.5 ppm
AEGL-2	150 ppm	76 ppm	49 ppm	22 ppm	14 ppm
AEGL-3	810 ppm	420 ppm	270 ppm	120 ppm	76 ppm
PEL-TWA (OSHA) [a]					10 ppm
IDLH (NIOSH)[b]		600 ppm			
REL-TWA (NIOSH)[c]					10 ppm
TLV-TWA (ACGIH)[d]					5 ppm
TLV-STEL (ACGIH)[e]	15 ppm				
MAK (Germany)[f]					5
MAK Peak Limit (Germany) [g]	10 ppm (momentary)				
MAC (Netherlands) [h]					5 ppm
LLV (Swedish)[i]					10 ppm
STV (Swedish)[j]	15 ppm (15 min)				

[a]**OSHA PEL-TWA (Occupational Safety and Health Administration, Permissible Exposure Limits - Time Weighted Average)** (OSHA 2006) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

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

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

[d]**ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH 2006) 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.

[e]**ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit)** (ACGIH 2006) 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.

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

[g]**MAK Spitzenbegrenzung (Peak Limit [Category I, excursion factor 2])** (Deutsche Forschungsgemeinschaft [German Research Association] 2007) constitutes the maximum average concentration to which workers can be exposed for a period of 15 minutes, no more than 4 times per shift at 1-hour intervals; total exposure may not exceed the 8-hour MAK. A momentary value of 10 ppm should not be exceeded.

[h]**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.

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

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

8.3. Data Adequacy and Research Needs

Lack of EA quantitative human data hampered the development of AEGL-1 and AEGL-2 values. Therefore, they were derived by structure-activity comparisons with other amines. There were no human data relevant to developing AEGL-3 values, which instead relied on animal studies. The overall database of animal studies was relatively small, and consisted mainly of rat studies with a relevant rabbit and mouse study. The similarity in the toxic response between rabbits and rats (eye and respiratory toxicity), and between EA and the structurally related amines MMA and DMA (eye and respiratory toxicity), however, permitted the development of AEGL-3 values for EA with a reasonable degree of confidence.

It would have been helpful if a study were available that examined EA toxicity following both long-term (>4 hour) and short-term (<4 hour) exposures, as there was some overlap in LC_{50} values for one and 4-hour exposure durations [e.g. 60-minute rat LC_{50} of 6260 ppm (IRDC 1993) vs. 4-hour rat LC_{50} of 6570 ppm (BASF AG 1980)]. If one study had been conducted over a period of ≥4 hours, it would have added confidence to the choice of studies used for AEGL derivation, and for the calculation of n in $C^n \times t = k$.

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

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

The odor detection threshold (OT_{50}) for ethylamine was reported to be 0.046 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
$C = (10^{1.07}) \times 0.046 = 0.54$ 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, increase the odor detection threshold by a factor of 4. In addition, it takes into account that odor perception is very fast (about 5 seconds) which leads to the perception of concentration peaks. Based on the current knowledge, a factor of 1/3 is applied to adjust for peak exposure. Adjustment for distraction and peak exposure lead to a correction factor of 4/3 = 1.33

$LOA = C \times 1.33 = 0.54 \text{ ppm} \times 1.33 = 0.74$ ppm

The LOA for ethylamine is 0.74 ppm.

APPENDIX B: Derivation of AEGL Values

Derivation of AEGL-1

Key study: Kinney et al. 1990; Jeevaratnam and Sriramachari 1994. The EA AEGL-1 values were derived by analogy to methylamine. The EA AEGL-1 was taken as ½ of the methylamine AEGL-1 value of 15 ppm

Toxicity endpoint: Mild nasal irritation in rats exposed to 75 ppm methylamine for 6 hours/day for two weeks (Kinney et al. 1990); NOAEL for notable signs of discomfort following a 30-minute exposure to 465 ppm , but lung lesions were reported (Jeevaratnam and Sriramachari 1990).

Scaling: None: The same AEGL-1 value was used for 10 minutes to 8 hours because mild nasal irritation does not vary greatly over time and the exposure duration of one of the key studies was 6 hours

Uncertainty Factors:

Kinney et al. 1990:

Total uncertainty factor: 10

- Interspecies: 3: Irritation from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and is not likely to vary greatly between species. or among humans (NRC 2001).
- Intraspecies: 3: Mild nasal irritation from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and not likely to vary greatly among humans.
- Modifying Factor: 0.5. The value was basically a NOAEL and the exposures were repeated

Sriramachari and Jeevaratnam 1994:

Total uncertainty factor: 10

- Interspecies: 3. Irritation from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and is not likely to vary greatly between species. or among humans (NRC 2001).
- Intraspecies: 3: Mild nasal irritation from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and not likely to vary greatly among humans.
- Modifying Factor: 3. Only one exposure duration was used, details of the study were lacking, and the endpoint was severe for the definition of an AEGL-1.

Calculations:

Methylamine:

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

Ethylamine:

10-minute through 8-hour AEGL-1 for EA =
methylamine AEGL-1 of 15 ppm/2 = 7.5 ppm

Derivation of AEGL-2

Key study: The ratio between the AEGL-3 and AEGL-2 values derived from the key studies for methylamine was used. The key studies for the AEGL-3 and AEGL-2 for methylamine were IRDC (1992a) and Kinney et al. (1990), respectively.

Toxicity endpoint: The AEGL-3 and AEGL-2 values for methylamine were based on the threshold for lethality and severe irritation, respectively.

Scaling: Time scaling ($C^n \times t = k$) was based on empirical lethality data for EA. The probit-analysis dose-response program of ten Berge (2006) was used to calculate AEGL-3 values from the IRDC (1993) data set.

Uncertainty Factors: Not applicable; the ratio between the AEGL-3 and AEGL-2 for methylamine was used to modify the EA AEGL-3 values.

Modifying Factor: None

Calculations: The ratio between the 1-hour AEGL-3 and AEGL-2 values for methylamine (350 ppm/64 ppm,) is 5.5. The AEGL-3 values for EA were each divided by 5.5

10-min AEGL-2: 810 ppm/5.5 = 150 ppm

30-min AEGL-2: 420 ppm/5.5 = 76 ppm

1-hour AEGL-2: 270 ppm/5.5 = 49 ppm

4-hour AEGL-2: 120 ppm/5.5 = 22 ppm

8-hour AEGL-2: 76 ppm/5.5 = 14 ppm

Derivation of AEGL-3

Key study: IRDC (1993). Crl:CD rats (5/sex/dose) were exposed whole-body to 14,000-24,800 ppm for 6 minutes, 8220-12,900 ppm for 20 minutes and 4100-7050 ppm for 60 minutes. Effects included gasping, labored breathing, rales, corneal opacity during or shortly after exposure, and death. Necropsy revealed cloudy corneas and red, discolored lungs; the incidence of lung lesions was correlated with mortality.

Toxicity endpoint: LC_{01} (lethality threshold) in rats calculated at each AEGL exposure duration by the method of ten Berge (2006).

Scaling: The probit-analysis dose-response program of ten Berge was used to estimate the threshold for lethality at each AEGL exposure duration. The full data set on lethality was used (see table below). The calculated n value was 1.63 (rounded to 1.6).

Uncertainty Factors: Total uncertainty factor: 10

Interspecies: 3: Sensory irritation and death from a direct-acting, alkaline irritant is not expected to vary greatly between species.

Intraspecies: 3: Sensory irritation and death from a direct-acting, alkaline irritant is not expected to vary greatly among humans.

Modifying Factor: None

Data for calculations:

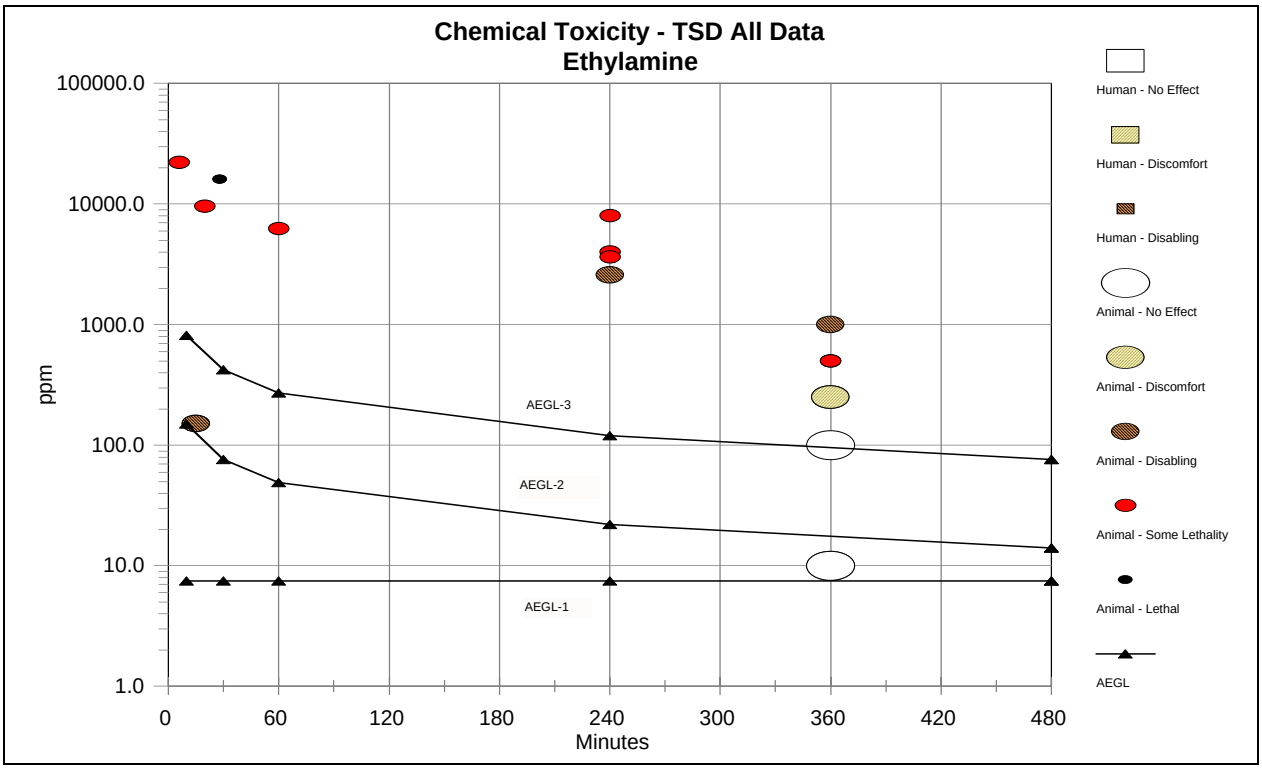
Exposure time (minutes)	Concentration (ppm)	Lethality
6	14,000	1/10
	14,700	0/10
	15,700	1/10
	16,500	0/10
	17,800	7/10
	19,900	1/10
	22,800	6/10
	24,800	6/10
20	8220	3/10
	9060	2/10
	9080	5/10
	9910	8/10
	11,000	10/10
	12,900	10/10
60	4100	2/10
	6150	6/10
	6160	5/10
	7050	9/10

Program output:

Exposure Duration	AEGL-3 Value
10 minutes	810 ppm
30 minutes	420 ppm
60 minutes	270 ppm
4 hours	120 ppm
8 hours	76 ppm

n = 1.63

APPENDIX C: Category Plot for Ethylamine



This plot included all single-exposure data and the multiple-exposure studies of RPA 1984, as shown below.

Category 0 = No effect, 1 = Discomfort, 2 = Disabling, PL = Partially Lethal, 3 = Lethal							
Source	**Species**	**Sex**	**No. of Exposures**	**Concentration (ppm)**	**Time (min)**	**Category**	**Comments/Noted Effects**
NAC/AEGL-1				7.5	10		Analogy with methylamine
NAC/AEGL-1				7.5	30		
NAC/AEGL-1				7.5	60		
NAC/AEGL-1				7.5	240		
NAC/AEGL-1				7.5	480		
NAC/AEGL-2				150	10		Analogy with methylamine
NAC/AEGL-2				76	30		
NAC/AEGL-2				49	60		
NAC/AEGL-2				22	240		
NAC/AEGL-2				14	480		
NAC/AEGL-3				810	10		LC_{01} (threshold for lethality) (IRDC 1993)
NAC/AEGL-3				420	30		
NAC/AEGL-3				270	60		

Category 0 = No effect, 1 = Discomfort, 2 = Disabling, PL = Partially Lethal, 3 = Lethal							
Source	**Species**	**Sex**	**No. of Exposures**	**Concentration (ppm)**	**Time (min)**	**Category**	**Comments/Noted Effects**
NAC/AEGL-3				120	240		
NAC/AEGL-3				76	480		
IRDC 1993	Rat	m,f	1	22240	6	sl	LC_{50} in rats; tested concentrations of 14,000-24,800 ppm
			1	9610	20	sl	LC_{50} in rats; tested concentrations of 8220-12,900 ppm
			1	6260	60	sl	LC_{50} in rats; tested concentrations of 4100- 7050 ppm
Smyth et al. 1954	Rat	m,f	1	16000	28	3	6/6 died
			1	8000	240.0	sl	2/6 died; very irritating to nose and eyes
			1	4000	240.0	sl	1/6 died; mildly irritating to nose, eyes
BASF AG 1980	Rat	m,f	1	3640	240	sl	LC_{50}; no other results provided
RPA 1984; Lynch et al. 1988	Rat	m,f	120	500	360	sl	Mortality; eye and nasal toxicity
			120	100	360	0	No effect
			120	10	360	0	No efect
RPA 1984; Lynch et al. 1999	Rat	m,f	10	250	360	1	Slight nasal necrotic inflammation
				1000	360	2	Moderate nasal necrotic inflammation, thymic atrophy, decreased body weight
Bio/dynamics Inc. 1986	Rat	m,f	1	2580	240	2	Severe lung and eye toxicity, body weight loss
Gagnaire et al. 1989	Mouse	m	1	151	15	2	RD_{50} in mice; tested 88-190 ppm

1

APPENDIX D: Derivation Summary for Ethylamine AEGLs

AEGL-1 Values				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
7.5 ppm (14 mg/m^3)	**7.5 ppm (14 mg/m^3)**	**7.5 ppm (14 mg/m^3)**	**7.5 ppm (14 mg/m^3)**	**7.5 ppm (14 mg/m^3)**

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

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

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

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

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

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

Modifying Factor: (1) 0.5 based on the mild endpoint; (2) 3 based on the lack of robustness of the study and the lung histopathology
A modifying factor of 2 was applied to the AEGL-1 value for methylamine of 15 ppm: 15 ppm/2 = 7.5 ppm

Animal to Human Dosimetric Adjustment: Not applied

Time Scaling: None; the same AEGL-1 value was used for 10 minutes to 8 hours because mild nasal irritation does not vary greatly over time, and one of the key study exposure durations was 6 hours

Data Adequacy: The AEGL-1 is supported by human data for the structurally related compounds diethylamine and dimethylethylamine, which caused eye and nasal irritation and/or vision disturbances ("halo vision" due to corneal edema) in healthy adults at approximately 10 ppm. The AEGL-1 is also consistent with the mouse respiratory inhibition study of Gagnaire et al. (1989), which predicts that 15 ppm will cause some sensory irritation in humans, whereas 1.5 ppm will cause no sensory irritation, per methodology of Alarie (1981).

1

AEGL-2 Values				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
150 ppm (280 mg/m^3)	**76 ppm (140 mg/m^3)**	**49 ppm (90 mg/m^3)**	**22 ppm (40 mg/m^3)**	**14 ppm (26 mg/m^3)**

Key references: The AEGL-2 values for ethylamine were based on analogy with methylamine. The methylamine references are:
AEGL-2: Kinney, L.A., R. Valentine, H.C. Chen et al. 1990. Inhalation Toxicology of Methylamine. Inhal. Toxicol. 2: 29-39;
AEGL-3: IRDC (International Research and Development Corporation). 1992a. Acute inhalation toxicity evaluation on monomethylamine in rats. Study sponsored by Air Products and Chemicals, Inc., Allentown, PA.

Tested species/Strains/Number: Not applicable

Exposure Route/Concentrations/Duration: Not applicable

Effects: Not applicable

Endpoint/Concentration/Rationale:
Based on structural similarity and similar toxicity, the AEGL-2 values for ethylamine were based on methylamine. The ratio of the methylamine AEGL-3/AEGL-2 of 5.5 (taken at the 1-hour exposure duration) was applied to the empirically-derived ethylamine AEGL-3 values.

Uncertainty Factors/Rationale: Not applicable
Interspecies:
Intraspecies:

Modifying Factor: None

Animal to Human Dosimetric Adjustment: Not applied

Time Scaling: In effect, the same time-scaling as used for the ethylamine AEGL-3 (see AEGL-3 derivation) was used for the AEGL-2 values.

Data Adequacy: The overall database of studies that address AEGL-2 level effects studies was relatively small, but the chemical structure similarity and the similarity in toxicity to methylamine allowed derivation of AEGL-2 values with a reasonable degree of confidence.

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AEGL-3 Values				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
810 ppm (1500 mg/m^3)	**420 ppm (770 mg/m^3)**	**270 ppm (500 mg/m^3)**	**120 ppm (220 mg/m^3)**	**76 ppm (140 mg/m^3)**
Key reference: IRDC (International Research and Development Corporation). 1993. Acute inhalation toxicity evaluation on monoethylamine in rats with cover letter dated 041293. Study sponsored by Air Products and Chemicals, Inc., Allentown, PA. Study completed March 26, 1993. EPA Doc. ID 86-930000193.				
Tested species/Strains/Number: Crl:CD rats, 5/group/sex				
Exposure Route/Concentrations/Duration: Inhalation of 14,000-24,800 ppm for 6 minutes; 8220-12,900 ppm for 20 minutes. 4100-7050 ppm for 60 minutes				
Effects: Gasping, labored breathing, rales, corneal opacity during or shortly after exposure and necropsy revealed cloudy corneas and red, discolored lungs; the incidence of lung lesions was correlated with mortality.				
Endpoint/Concentration/Rationale: The probit-analysis based dose-response program of ten Berge (2006) was used to calculate the LC_{01} (threshold for lethality) at each AEGL-3 exposure duration. The program incorporated all of the data at the 6-, 20-, and 60-minute time points.				
Uncertainty Factors: Total uncertainty factor: 10 Interspecies: 3: Severe irritation (resulting in lung edema) from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and not likely to vary greatly between species. Intraspecies: 3: Severe irritation (resulting in lung edema) from an alkaline irritant gas is a direct surface-contact effect not involving metabolism, and not likely to vary greatly among humans.				
Modifying factor: None				
Animal to Human Dosimetric Adjustment: None applied.				
Time Scaling: The ten Berge (2006) probit-analysis based dose-response program calculated a time scaling value of 1.6 ($C^{1.6} \times t = k$).				
Data Adequacy: The overall database of AEGL-3 studies was small, but the similarity in the toxic response, including death due to lung lesions, between EA and structurally related amines permitted the development of AEGL-3 values for EA with a reasonable degree of confidence.				

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3