ETHYL ACRYLATE
(CAS Reg. No. 140-88-5)

INTERIM ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

For
NAS/COT Subcommittee for AEGLs

Oak Ridge National Laboratory, managed by UT-Battelle, LLC., for the U.S. Dept. of Energy under contract DE-AC05-00OR22725

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

SUMMARY

Ethyl acrylate (EA) is a highly flammable, clear liquid. The chemical is a monomer that polymerizes readily to a transparent, elastic substance in the presence of light, heat, or catalysts (Bisesi 2001; ECETOC 1994). EA is used in latex paints, binders, polishes, adhesives, coatings, and as an additive in foods and cosmetics (IARC 1986; ECETOC 1994). EA is the second largest-volume production commodity acrylate ester behind n-butyl acrylate (Lacson et al. 2001).

EA is a direct irritant to the mucus membranes. The target within the respiratory tract was shown to be the olfactory epithelium lining the dorsal meatus in both monkeys (Harkema et al. 1997) and rats (BASF 1989). Both the severity and extent of the lesions were concentration and time dependent. Metabolism and subsequent removal of the chemical by carboxylesterase in the upper respiratory tract reduces the toxicity (Silver and Murphy 1978, 1981).

Few data were available concerning human exposures to EA and none of the data were suitable for derivation of any AEGL values. Worker monitoring studies reported up to 30 ppm as a short-term exposure average concentration (Rohm and Haas, Co. 1987), but no health effects were included.

Limited data were available upon which to base AEGL-1 values. Male F344/N rats (n = 5/group) were exposed nose only to 0, 5, 25, or 75 ppm EA for 1, 3, or 6 hours (Frederick et al. 2002). No effects were seen following exposure to 5 ppm for up to 6 hours or following a 1-hour exposure to any of the concentrations tested. After a 3-hour exposure to 25 ppm, two rats had unilateral sustentacular cell necrosis and olfactory neuron degeneration and desquamation located on the lateral wall of the dorsal meatus observed in one section. After a 6-hour exposure to 25 ppm, the lesion was observed in three animals and distributed to two sections. The distribution and severity of the lesions in the olfactory epithelium increased with exposure to 75 ppm and were greatest after 6 hours. Nearly complete recovery of normal olfactory tissue was observed in affected animals in the 25- and 75-ppm groups following a 6-week recovery period. No deaths, clinical signs, or pathology occurred in monkeys exposed to 24.5 or 26.2 ppm , 7 hours/day for 130 exposures in 199 days (Treon et al. 1949). Dogs subchronically exposed to concentrations as low as 25 ppm had irritation of the eyes with slight conjunctivitis; however clinical signs from individual exposures were not reported (DuPont 1946). Therefore, 25 ppm was chosen as a probable threshold for AEGL-1 effects. Extrapolations were not performed. A total uncertainty factor of 3 was used including a 1 for interspecies extrapolation and 3 for intraspecies extrapolation. Use of greater uncertainty factors was not necessary because the mechanism of irritation is not expected to differ between individuals and similar lesions were found in monkeys and rats.

The best animal data for derivation of AEGL-2 values is the study in which monkeys were exposed head-only to 75 ppm EA for 3 or 6 hours (Harkema et al. 1997; Rohm and Haas 1994). Following exposure, the animals were sacrificed and the nasal cavity examined microscopically. After 3 hours, lesions consisted of focal degeneration, necrosis, and exfoliation with mild inflammation and were limited to approximately 15% of the olfactory epithelium lining the dorsal medial meatus. The effects after the 6-hour exposure were considered too severe for AEGL-2. Values were scaled using the equation $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed

using n = 3 for extrapolating to the 10- and 30-minute time points and n = 1 for the 4- and 8-hour time points. A total uncertainty factor of 3 was used including a 1 for interspecies extrapolation and 3 for intraspecies extrapolation. Use of greater uncertainty factors was not necessary because the lesion is reversible, the mechanism of irritation is not expected to differ between individuals, and similar lesions were found in monkeys, guinea pigs, rabbits, and rats. AEGL-2 values are supported by other animal studies. Similar microscopic lesions of the olfactory epithelium were observed in rats following a single exposure (Frederick et al. 2002) and in rats and mice following subchronic and chronic exposures. Repair of the lesions was evident in animals exposed to 225 ppm, 6 hours/day, 5 days/week for 6 months and held for 3-6 months (BASF 1989). A monkey survived 28 exposures to 272 ppm for 7 hours each but clinical signs of irritation and slight lethargy were observed (Treon et al. 1949).

Animal data relevant to derivation of AEGL-3 values are limited to 1- and 4-hour LC_{50} studies in rats. These were well conducted studies with analytically determined exposure concentrations and which included mortality ratios at all concentrations. Clinical signs of irritation were observed in animals during exposure and death was attributed to cardiopulmonary collapse. Calculated LC_{50} values were 6493 ppm for 1 hour (Nachreiner and Dodd 1989; Union Carbide 1989) and 2180 ppm for 4 hours (Oberly and Tansy 1985). From these data, 1- and 4-hour $BMCL_{05}$ values were calculated by a log-probit analysis using US EPA Benchmark Dose Software version 1.3.2. The resulting 1-hour $BMCL_{05}$ of 2387 ppm was used to derive the 10-minute, 30-minute, and 1-hour AEGL-3 values. The resulting 4-hour $BMCL_{05}$ of 706 ppm was used to derive the 4- and 8-hour AEGL-3 values. Values were scaled using the equation $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). By combining the 1- and 4- hour LC_{50} data sets in a 3-dimensional probit analysis, the value of n = 1.3 was calculated (Zwart et al. 1992). A total uncertainty factor of 10 was used including a 3 for interspecies extrapolation and 3 for intraspecies extrapolation. Use of greater uncertainty factors was not necessary because the mechanism of irritation is not expected to differ between individuals and similar lesions were found in monkeys, guinea pigs, rabbits, and rats.

The calculated values are listed in the tables below.

Summary of AEGL Values for Ethyl Acrylate

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1 (Nondisabling)	8.3 ppm (34 mg/m^3)	8.3 ppm (34 mg/m^3)	8.3 ppm (34 mg/m^3)	8.3 ppm (34 mg/m^3)	8.3 ppm (34 mg/m^3)	Reversible lesions in the olfactory epithelium (Frederick et al. 2002)
AEGL–2 (Disabling)	66 ppm (270 mg/m^3)	45 ppm (180 mg/m^3)	36 ppm (150 mg/m^3)	19 ppm (78 mg/m^3)	9.4 ppm (39 mg/m^3)	Reversible lesions in the olfactory epithelium (Harkema et al. 1997; Rohm and Haas 1994)
AEGL–3 (Lethal)	950 ppm (3900 mg/m^3)	410 ppm (1700 mg/m^3)	240 ppm (980 mg/m^3)	71 ppm (290 mg/m^3)	41 ppm (170 mg/m^3)	$BMCL_{05}$ (Nachreiner and Dodd 1989; Union Carbide 1989; Oberly and Tansy 1985)

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1. INTRODUCTION

Ethyl acrylate (EA) is a highly flammable, clear liquid. The chemical is a monomer that polymerizes readily to a transparent, elastic substance in the presence of light, heat, or catalysts (Bisesi 2001; ECETOC 1994). EA is used in latex paints, binders, polishes, adhesives, coatings, and as an additive in foods and cosmetics (IARC 1986; ECETOC 1994).

EA is the second largest-volume production commodity acrylate ester behind n-butyl acrylate (Lacson et al. 2001). In 1993, the United States produced 160 million kg EA (HSDB 2004) and production was in the range of >45.5-227 million kg in 2002 (U.S. EPA 2004). The most common manufacturing process is by catalyzed esterification of acrylic acid (ECETOC 1994).

TABLE 1. Chemical and Physical Properties

Parameter	Value	Reference
Synonyms	2-propenoic acid ethyl ester	O'Neil et al. 2001
Chemical formula	$C_5H_8O_2$	O'Neil et al. 2001
Molecular weight	100.12	O'Neil et al. 2001
CAS Reg. No.	140-88-5	
Physical state	liquid	O'Neil et al. 2001
Solubility in water	2 g/100 mL at 20°C	O'Neil et al. 2001
Vapor pressure	38-39.2 hPa at 20°C	ECETOC 1994
Vapor density (air =1)	3.45	O'Neil et al. 2001
Liquid density (water =1)	0.9405	O'Neil et al. 2001
Melting point	-72°C	ECETOC 1994
Boiling point	99.4°C	O'Neil et al. 2001
Flammability limits	1.8-12%	ECETOC 1994
Conversion factors	1 mg/m^3 = 0.245 ppm 1 ppm = 4.1 mg/m^3	AIHA 2000

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No reports of human fatalities from exposure to EA were found.

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold/Odor Awareness

Odor thresholds for EA are 0.00024 ppm for detection and 0.00037 ppm for recognition (ACGIH 1995; U.S. EPA 1992). The odor is described as pungent or acrid (ECETOC 1994; IARC 1986).

2.2.2. Case Reports

Workers exposed to dust of ethyl acrylate polymer noted only itching of the skin when the dust lodged in facial creases, ears, and nose (Cohen and Maier 1974).

2.2.3. Epidemiologic Studies/Occupational Exposure

No epidemiologic studies were found concerning human exposures to EA.

Rohm and Haas, Co. (1987) submitted employee exposure monitoring results for a number of operations during 1978-1987. Average concentrations of EA for full shift ranged from 0.2-2.3 ppm and short-term exposure average concentrations ranged from <0.1-30 ppm. No other information was included in the report.

Time-weighted average concentrations of EA at four job sites in a polystyrene production plant were <1-55 ppb (range: not detected-274 ppb) in the breathing zone of workers and <1-27 ppb (range: not detected-241 ppb) in the atmosphere of the workplaces (Samimi and Falbo 1982). Samples were collected in charcoal tubes from 50 minutes to 7.5 hours and quantitated with a gas chromatograph. No information on worker health status was given.

2.2.4. Clinical Studies

Olfactory function was investigated in chemical workers exposed to acrylates and methacrylates (Schwartz et al. 1989; Rohm and Haas 1988). Specific chemicals were not identified. Workers were administered a standardized smell identification test consisting of an odorant strip and a questionnaire. A dose-responsive relationship was found between olfactory dysfunction and cumulative exposure scores (semi-quantitative indices of life-time exposures to the acrylates) with reversible effects shown with increasing duration since the last exposure.

Dermal irritation and skin sensitization have been reported from exposure to EA (IARC 1986; Bauer 2003).

2.3. Neurotoxicity

Prolonged exposure (not defined) to 50-75 ppm EA has been reported to produce drowsiness, headache, and nausea (IARC 1986); no further details could be found.

2.4. Developmental/Reproductive Toxicity

No reports of developmental or reproductive toxicity in humans from exposure to EA were found.

2.5. Genotoxicity

No reports of genotoxicity in humans from exposure to EA were found.

2.6. Carcinogenicity

An increased risk of mortality from cancers of the colon or rectum was found among workers exposed to both EA and methyl methacrylate (Walker et al. 1991; Rohm and Haas 1989). However, the excess cancer deaths were limited to those who were hired between 1933-1945 and worked in jobs with presumed high exposure to the vapors of both monomers and to volatile by-products of the polymerization process. In addition, the excess cancer mortality did not appear until two decades after the accumulated exposure. Later cohorts (after 1945) and cohorts from similar plants did not have increase deaths due to colo-rectal cancers. Deaths from all causes were slightly lower than expected in all cohorts and the incidence of lung cancer was similar to the expected rate.

Based on sufficient evidence in experimental animals (oral) and no relevant epidemiological data in humans, EA has been classified in Group 2B, possibly carcinogenic to humans (IARC 1999).

2.7. Summary

Very little data concerning human exposures to EA were available. The chemical is irritating on contact with the skin.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Nonhuman Primates

One monkey (sex and species not specified) was exposed in whole-body three times to 1204 ppm EA for 7 hours (Treon et al. 1949). Atmospheres in the dynamic chamber were produced by metering the chemical with an injection pump into a stream of air and were measured by oxidation with chromic acid. The animal died during the third exposure with clinical signs of eye and nose irritation, salivation, prostration, spasmodic respiration, and convulsive movements. Necropsy revealed congestion of the respiratory tract and lungs with areas of hemorrhage and atelectasis, diffuse emphysema, and increased mucus secretion. In addition, edema, congestion, and/or cloudy swelling were observed in the myocardium, liver, kidney, and spleen. Another monkey survived 28 exposures to 272 ppm for 7 hours each but clinical signs of irritation and slight lethargy were observed. No deaths, clinical signs, or pathology occurred in animals (n = 1) exposed to 24.5 or 26.2 ppm, 7 hours/day for 130 exposures in 199 days.

3.1.2. Rabbits

Groups of four rabbits (sex and strain not specified) were exposed whole-body to either 1204 ppm EA for 7 hours, to 501 ppm for 7 hours/day for 4 days, or to 272 ppm for 7 hours/day for 8-17 days (Treon et al. 1949). Exposures were repeated until all animals in the group had died. Atmospheres in the dynamic chamber were produced by metering the chemical with an injection pump into a stream of air and were measured by oxidation with chromic acid. All animals died with clinical signs of eye and nose irritation, salivation, rales, prostration, gasping, convulsive movements, and diarrhea. Necropsy revealed congestion of the respiratory tract and lungs with areas of hemorrhage and atelectasis, diffuse emphysema, and increased mucus secretion. In addition, edema, congestion, and/or cloudy swelling were observed in the myocardium, liver, kidney, and spleen. No deaths, clinical signs, or pathology occurred in animals exposed to either 74.8 ppm for 7 hours/day for 50 exposures in 72 days or to 24.5 ppm, 7 hours/day for 130 exposures in 199 days.

3.1.3. Guinea Pigs

Groups of two guinea pigs (sex and strain not specified) were exposed whole-body to either 1204 ppm EA for 7 hours, to 501 ppm for 7 hours/day for 13 days, or to 272 ppm for 7 hours/day for 28 days (Treon et al. 1949). Exposures were repeated until all animals in the group had died. Atmospheres in the dynamic chamber were produced by metering the chemical with an injection pump into a stream of air and were measured by oxidation with chromic acid. All animals died with clinical signs of eye and nose irritation, salivation, rales, prostration, gasping, and convulsive movements. Necropsy revealed congestion of the respiratory tract and lungs with areas of hemorrhage and atelectasis, diffuse emphysema, and increased mucus secretion. In addition, edema, congestion, and/or cloudy swelling were observed in the myocardium, liver, kidney, and spleen. No deaths, clinical signs, or pathology occurred in animals exposed to either 74.8 ppm for 7 hours/day for 50 exposures in 72 days or to 24.5 or 26.2 ppm, 7 hours/day for 130 exposures in 199 days.

3.1.4. Rats

Male and female Sprague-Dawley rats (n = 5/sex/group) were exposed whole-body for 1 hour to analytically determined concentrations of 5843, 7421, or 8882 ppm EA followed by a 14-day observation period (Nachreiner and Dodd 1989; Union Carbide 1989). The chemical was metered onto an evaporator and carried to the chamber by an air stream; atmospheres were monitored by gas chromatography. Clinical signs on the day of exposure in all treated groups included blepharospasm, lacrimation, perinasal and perioral wetness, and a slow righting reflex. Additionally at the two highest concentrations animals displayed abdominal and/or mouth breathing, audible respiration, tremors, and distended stomachs during exposure. Many of these clinical signs were also observed during the post-exposure period but resolved by day 10 in the 7421 ppm group and by day 6 in the 5843 ppm group. Body weight gain was reduced in both sexes at 7421 ppm during the first week of the post-exposure period. Gross necropsy lesions in animals that died included a dark red or mottled discoloration of the lungs, liver, and kidneys, clear fluid in the trachea and thoracic cavity, and gas-filled stomachs; no lesions were found in survivors. The number of deaths at each concentration was 4, 6, and 10 with an equal number of males and females affected at each concentration. The calculated 1-hour LC_{50} was 6493 ppm for the sexes combined.

Male Sprague-Dawley rats (n = 10/group) were exposed whole-body for 4 hours to 1538, 1991, 2417, 2791, or 3001 ppm EA followed by a 14-day observation period (Oberly and Tansy 1985). Atmospheres were generated by constant infusion of liquid monomer into a heated reaction vessel through which room air was passed at a known constant rate. Vapor concentration was determined by gas chromatography. During exposures animals exhibited normal behavior during the first few minutes followed by irritation of the eyes, nose, and respiratory tract and labored breathing. All deaths occurred within 24 hours and were attributed to cardiopulmonary collapse. The number of deaths at each concentration was 1, 6, 7, 7, and 9, respectively. The 4-hour LC_{50} was calculated as 2180 ppm.

Male Holtzman rats (n = 6/group) were exposed by whole-body to 300-1500 ppm EA for 4 hours (Silver and Murphy 1981). Chamber concentrations generated by a variable speed infusion pump and were measured by gas chromatography. Clinical signs were noted only as nasal and eye irritation during exposure to "higher" concentrations. One animal died 48-72 hours post-exposure to 1500 ppm. However, when rats were pretreated with 125 mg/kg of TOTP (triorthotolyl phosphate, an inhibitor of carboxylesterase), exposures to 750, 1000, or 1500 ppm resulted in deaths of 5/6, 5/6, and 6/6 rats, respectively; all deaths occurred either during exposure or up to 20 hours post-exposure.

In a preliminary report, no deaths occurred in rats exposed to 1000 ppm EA for 4 hours but 80% mortality occurred when animals were pretreated with TOTP; no further details were reported in the abstract (Silver and Murphy 1978).

Groups of two rats (sex and strain not specified) were exposed whole-body to 1204 ppm EA for two exposures of 7 hours each or to 501 ppm for 7 hours/day for 13 days (Treon et al. 1949). Exposures were repeated until all animals in the group had died. Atmospheres in the dynamic chamber were produced by metering the chemical with an injection pump into a stream of air and were measured by oxidation with chromic acid. Both animals died at 1204 ppm and 1/2 died at 501 ppm with clinical signs of eye and nose irritation, salivation, rales, prostration, gasping convulsive movements, and diarrhea. Necropsy revealed congestion of the respiratory tract and lungs with areas of hemorrhage and atelectasis, diffuse emphysema, and increased mucus secretion. In addition, edema, congestion, and/or cloudy swelling were observed in the myocardium, liver, kidney, and spleen. No deaths but clinical signs were observed in animals exposed to 272 ppm for 7 hours/day for 28 days. No deaths, clinical signs, or pathology occurred in animals exposed to either 74.8 ppm for 7 hours/day for 50 exposures in 72 days or to 24.5 or 26.2 ppm, 7 hours/day for up to130 exposures in 199 days.

A saturated vapor (~50,000 ppm) of EA induced gasping within 3 minutes, prostration within 10 minutes, and death of all six Sherman rats (sex not specified) within 15 minutes (Pozzani et al. 1949). Death was attributed to pulmonary damage with congestion and hemorrhage found in the lungs of all decedants. All rats survived a similar exposure to saturated concentration for 5 minutes. Four-hour exposures to calculated concentrations of 1000, 2000, or 4000 ppm resulted in death of 0/6, 5/6, and 6/6 rats, respectively. Respiratory distress was noted at 4000 ppm and pronounced redness of the nose, ears, and feet occurred at all concentrations; for animals that died, gross findings were similar to those described for the saturated vapor. Atmospheres were generated by injecting

the liquid monomer into an evaporator and the required amount of dilution air delivered by a "Rotameter."

Groups of Sherman rats (10-15/sex/group) were exposed whole-body to 70, 300, or 540 ppm EA for 7 hours/day, 5 days/week, for 30 days (Pozzani et al. 1949). Concentrations were measured daily with an interferometer. Exposures to 540 ppm were stopped after 19 days because only 6 animals remained alive and 18/30 animals died from exposures to 300 ppm. For both groups body weight gains were marked reduced in the survivors. Necropsy of animals that died revealed "pneumonic involvement", congestion of the lung, and cloudy swelling of the renal tubules and liver. No effects were observed at 70 ppm.

3.2. Nonlethal Toxicity

3.2.1. Nonhuman Primates

Groups of three Cynomolgus monkeys (males and females randomly distributed) were exposed head-only to 0 or 75 ppm EA for either 3 or 6 hours (Harkema et al. 1997; Rohm and Haas 1994). Atmospheres were generated by passing a stream of nitrogen through the liquid chemical and diluting with fresh air; concentrations were monitored using an infrared spectrophotometer. Following exposure, the animals were sacrificed and the nasal cavity examined microscopically. Lesions consisted of focal degeneration, necrosis, and exfoliation with mild inflammation and were limited to the olfactory epithelium lining the dorsal medial meatus. The distribution and severity of the lesions was greater following the 6-hour exposure compared with the 3-hour exposure with approximately 50% and 15%, respectively, of the olfactory epithelium containing damage.

3.2.2. Dogs

In a study of questionable validity, four dogs (sex and breed not specified) were exposed to variable concentrations of EA for 5 days/week for 12 weeks (DuPont 1946). Generally exposures were for 2 hours/day during weeks 1-4, then for 4 hours/day during weeks 5-12. Daily concentrations for the first week ranged from a trace to over 500 ppm. The estimated concentrations were 180 ppm for weeks 2-4, and over 500 ppm for week 5; no exposures occurred during weeks 6 and 7 and weekly analytical concentrations during weeks 8-12 were 25-60 ppm. Chamber atmospheres were produced by passing a stream of air over a known amount of monomer and mixing with fresh air. The concentrations were monitored colorimetrically. Clinical signs from individual exposures were not reported. However, it was reported that concentrations as low as 25 ppm produced irritation of the eyes with slight conjunctivitis and higher concentrations produced tearing and nasal irritation with watery discharge. In addition, between 60 and 180 ppm changes in blood pressure (defined only as circulatory abnormalities) occurred after exposure compared to pre-exposure measurements. No gross or microscopic pathology was seen at necropsy.

3.2.3. Rats

Male F344/N rats (n = 5/group) were exposed nose only to 0, 5, 25, or 75 ppm EA for 1, 3, or 6 hours (Frederick et al. 2002). Descriptions of vapor generation and concentration monitoring were not given. No effects were seen following exposure to 5 ppm for up to 6 hours or following a 1-hour exposure to any of the concentrations tested. Lesions in the olfactory epithelium were observed after

exposure to 25 or 75 ppm for 3 or 6 hours. After a 3-hour exposure to 25 ppm, two rats had unilateral sustentacular cell necrosis and olfactory neuron degeneration and desquamation located on the lateral wall of the dorsal meatus observed in one section. After a 6-hour exposure to 25 ppm, the lesion was observed in three animals and distributed to two sections. The distribution and severity of the lesions in the olfactory epithelium increased with exposure to 75 ppm and were greatest after 6 hours. Nearly complete recovery of normal olfactory tissue was observed in affected animals in the 25- and 75-ppm groups following a 6-week recovery period.

Male Holtzman rats (n = 5/group) exposed to 100, 300, or 500 ppm EA for 1 hour had concentration-related decreases in respiratory frequency, minute volume, and rectal temperature (Silver et al. 1981). Atmospheres were generated by passing a metered air stream through a sample of chemical followed by dilution with fresh air; chamber concentrations were measured by gas chromatography. Results were given in graphical form such that the magnitude of the effects could not be determined. Pretreatment of rats with 125 mg TOTP/kg significantly potentiated the decreases in respiration and temperature during exposure.

Circulating white blood cells were decreased by approximately 50% in male Sprague-Dawley rats (n = 5/group) exposed whole-body to 122 or 206 ppm EA for 4 hours and were slightly decreased at 102 ppm (Brondeau et al. 1990). Atmospheres were measured by gas-liquid chromatography. Clinical signs were not reported.

Subchronic (30-day) and chronic (2-year) inhalation studies in male and female Fischer 344 rats showed that the primary target is the olfactory epithelium lining the dorsal meatus (BASF 1989). Exposures were for 6 hours/day for 5 days/week. Lesions in the nasal passage consisted of inflammation, degeneration, focal necrosis, and squamous metaplasia. The severity and extent of the lesions were concentration and time dependent and were first observed at 75 ppm at 30 days and at 25 ppm at 6 months. Repair of the lesions was evident in animals exposed to 225 ppm for 6 months and held for 3-6 months.

3.2.4. Mice

The RD_{50} in male Swiss mice (n = 6) was calculated as 315 ppm (de Ceaurriz et al. 1981). Animals were exposed head-only and concentrations measured by gas-liquid chromatography. Clinical signs were not reported and the range of concentrations used was not given.

Subchronic and chronic inhalation studies in male and female $B6C3F_1$ mice show that the primary target is the olfactory epithelium lining the dorsal meatus (BASF 1989). Exposures over a range of concentrations were for 6 hours/day for 5 days/week. Lesions in the nasal passage consisted of inflammation, degeneration, focal necrosis, and squamous metaplasia. The severity and extent of the lesions were concentration and time dependent and were first observed at 75 ppm at 30 days and at 25 ppm at 6 months. Repair of the lesions was evident in animals exposed to 225 ppm for 6 months and held for 3-6 months.

3.3. Neurotoxicity

No information was found on the neurotoxicity of EA in animals following inhalation exposure.

3.4. Developmental/Reproductive Toxicity

Sprague-Dawley rats (n = 17-19) were administered 0, 25, 50, 100, or 200 ppm EA, 6 hr/day on GD 6-20 (Saillenfait et al. 1999). Mean analytically determined concentrations were 25, 51.2, 101.3, and 202.0 ppm, respectively. All animals survived to scheduled sacrifice; clinical signs of toxicity were not reported. Maternal body weight gain was markedly reduced in at the highest concentration during the exposure interval to 67% of the control group level. Food consumption was not measured. The numbers of implantation sites, live fetuses, and resoprtions per litter were not affected. Fetal body weights were significantly reduced in the 200-ppm group. No treatment-related external, visceral, or skeletal malformations were found in any fetus.

In an earlier study, Sprague-Dawley rats (n = 33) were exposed to 0, 50, or 150 ppm EA, 6 hours/day on GD 6-15 (Murray et al. 1981; Dow 1989). Mean analytically determined concentrations were within ±10% of nominal for all days. No clinical signs of toxicity were observed in the dams and all animals survived to scheduled termination. Females in the 150-ppm group had significantly reduced body weight gain on GD 6-7 and 12-15 resulting in lower absolute body weights after GD 8, significantly decreased food consumption during GD 6-14, and significantly increased water consumption on GD 6-20. The numbers of implantation sites, live fetuses, and resoprtions per litter and fetal body weights were not affected by maternal treatment. Although not statistically significant, three fetuses from three 150-ppm litters contained multiple malformations including hypoplastic tail and missing vertebrae.

3.5. Genotoxicity

No DNA adducts were detected in the forestomach of rats administered up to 400 mg/kg by gavage (Ghanayem et al. 1987). However, chromosome damage leading to micronuclei formation in bone marrow polychromatic erythrocytes was induced in Balb C mice administered 225-1800 mg/kg by intraperitoneal injection (Przybojewska et al. 1984). This result was not duplicated in other studies (BIBRA 1996; Loveday et al. 1990) and chromosome effects were not seen in spleen cells from mice administered up to 1000 mg/kg (BIBRA 1996).

EA was shown to be mutagenic in mouse lymphoma cells in the presence and absence of metabolic activation (Amtower et al. 1986, NTP 1986, BIBRA 1996, Ciaccio et al. 1998). Subsequent investigations indicated that the EA-induced mutagenic response correlated with cellular cytotoxicity mediated by non-protein sulfhydryl depletion and mitochondrial membrane impairment (Ciaccio et al. 1998).

A number of reports found EA to be negative for mutagenicity with and without enzymatic activation in *Salmonella typhimurium* (TA1535, TA1537, TA98, TA100) and *Saccharomyces cerevisiae* (D4) but one study reported weakly positive results in TA100 in the presence of metabolic activation (NTP 1986, BIBRA 1996).

3.6. Chronic Toxicity/Carcinogenicity

As part of the chronic study described below, male and female Fischer 344 rats and $B6C3F_1$ (n = 75) were exposed by whole body to 275 ppm EA for 6 hours/day, 5 days/week for 6 months and

held for up to an additional 21 months (Miller et al. 1985). Body weight gains were markedly decreased during the 6-month exposure period with recovery after cessation of treatment. At termination, residual lesions of the olfactory mucosa consisted of diffuse atrophy of the olfactory epithelium lining the dorsal meatus.

In a chronic inhalation study, male and female Fischer 344 rats and $B6C3F_1$ (n = 60-90) were exposed by whole body to 0, 5, 25, or 75 ppm EA for 6 hours/day, 5 days/week for a total of 24-27 months (Miller et al. 1985). Body weight gains were slightly reduced at 75 ppm throughout the study. No clinical signs or other systemic toxicity were observed and no evidence of carcinogenicity was found. Histopathological lesions attributable to chronic irritation were seen in the nasal mucosa of the 25- and 75-ppm groups. Generally lesions were found in the areas of the nasal mucosa lined with olfactory epithelium but not in regions lined with respiratory epithelium.

No epidermal tumors were observed on male C3H/HeJ mice treated with undiluted EA on the dorsal skin 3 times/week for their lifetimes (De Pass et al. 1984).

Male and female F344/N rats and $B6C3F_1$ mice (n = 50) were administered EA by gavage at doses of 0, 100, or 200 mg/kg, 5 days/week for 2 years (NTP 1986). Both dose levels induced squamous cell papillomas and squamous cell carcinomas of the forestomach at the site of application. No evidence of systemic toxicity was observed. Subsequent studies further characterized the forestomach lesions, showed them to be route specific at the site of gavage application, and demonstrated dose-dependent recovery of lesions (Ghanayem et al. 1985a, 1986). In addition, structure-toxicity studies showed similar lesions with methyl acrylate, but not with acrylic acid and *n*-butyl acrylate (Ghanayem et al. 1985b).

3.7. Summary

Clinical signs of irritation were common to all animal species exposed to EA. The target within the respiratory tract from non-lethal exposures was shown to be the olfactory epithelium lining the dorsal meatus in both monkeys (Harkema et al. 1997) and rats (BASF 1989). Both the severity and extent of the lesions were concentration and time dependent. At lethal concentrations, death was attributed to cardiopulmonary collapse, and was accompanied by cloudy swelling and/or congestion of other visceral organs. Developmental toxicity studies show that the fetus is not uniquely sensitive to maternal EA exposure, but may be affected at maternally toxic concentrations (Saillenfait et al. 1999; Murray et al. 1981; Dow 1989). Route specific tumors have been found in the forestomach following oral administration, but none were found following inhalation exposure (Miller et al. 1985; NTP 1986).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Absorption of EA has been shown to be rapid after both inhalation and oral administration. Approximately 65% of the administered EA was absorbed by the intact respiratory tract of anesthetized male Fischer 344 rats exposed nose-only to 225 ppm for up to 2 hours (Stott and McKenna 1984). Absorption reached a plateau within 10 to 20 minutes, then remained relatively

constant for the duration of exposure. Inhibition of carboxylesterase activity by pretreatment with TOCP resulted in lowering the absorption curve such that the authors estimated that approximately 50% of the loss of EA passing through the upper respiratory tract can be accounted for by the enzymatic hydrolysis of the chemical (Stott and McKenna 1984). Following oral administration, greater than 90% of the administered dose was absorbed within 4 hours and EA-derived radioactivity was found in all major tissues mainly bound to proteins and lipids (De Bethizy et al. 1987, Ghanayem et al. 1987).

To further explore the potential enzymatic hydrolysis of EA in the upper respiratory tract, the activity of carboxylesterase recovered from nasal mucosal tissue of B6C3F1/CrlBr mice was studied (Stott and McKenna 1985). Under subsaturating concentrations, EA was hydrolyzed under first-order kinetics with a V_{MAX} of 0.568×10^{-3} M/min and a K_M of 10.5×10^{-3} M. Loss of enzymatic activity occurred at concentrations in excess of 5 mM. Carboxylesterase specific activity was approximately equivalent in the nasal mucosa and liver of mice with ethylene glycol monomethyl ether acetate as substrate. *In vitro* nasal enzyme activity was shown to be similar between mice and dogs, slightly less in rats, and nearly sevenfold less in rabbits. Other studies with both rats and mice (Bogdanffy et al. 1987; Frederick et al. 1994) found that the carboxylesterase activity in olfactory mucosa was much greater than that in respiratory muscosa.

Once absorbed, EA is either hydrolyzed, bound to proteins, or conjugated with glutathione. An *in vitro* study measured the hydrolysis rate in rat liver homogenate and disappearance from whole blood (Miller et al. 1981). The rate of hydrolysis of EA (26.8 nmole•min^{-1}) in liver homogenate directly correlated with the appearance of acrylic acid (33.4 nmoles•min^{-1}) in the medium. In contrast hydrolysis in whole blood (12.0 nmoles•min^{-1}) did not result in any detectable acrylic acid suggesting a different mechanism. This is supported by results in which EA was shown to bind with non-protein sulfhydryls in red blood cells.

Another *in vitro* study with rat tissues also demonstrated hydrolysis of EA in plasma and by homogenates of liver, lung, and kidney. In addition, tissues from rats pretreated with TOTP had dose-related inhibition of EA hydrolysis (Silver and Murphy 1981).

Following a 6-hour inhalation exposure of male Wistar rats to 245-980 ppm EA, <2% of the dose was excreted in the urine as thioethers (Vodička et al. 1990). However, total tissue sulfhydryl groups were significantly decreased in the liver and blood following exposure to 980 ppm and non-protein sulfhydryl groups were decreased in liver and to a lesser extent in blood and brain. Non-protein sulfhydryls were also decreased in lung, liver, and blood following exposure of rats to 480-1000 ppm EA; pretreatment with TOTP markedly potentiated the depletion of non-protein sulfhydryls from these tissues and also resulted in depletion from the kidney (Silver and Murphy 1981). In contrast, after oral administration non-protein sulfhydryls were depleted in the stomach but not in blood or liver (De Bethizy et al. 1987).

The major urinary metabolites from female Wistar rats administered 0.5-2.0 mmol/kg of labeled EA by intraperitoneal injection (Linhart et al. 1994) were 3-hydroxypropanoic acid and two mercapturic acids. Quantitation of the mercapturic acids showed that the absolute amount remained relatively constant while the proportion conjugated was essentially constant over the range of doses used. In addition, characterization of the carboxylic acids found in urine indicated that the acrylic

acid entered intermediary metabolism via propanoic acid catabolism and the tricarboxylic acid cycle (Linhart et al. 1994). Mercapturic acid derivatives were also the main metabolites in urine following oral administration of 100-400 mg EA/kg to male Fisher 344 rats (Ghanayem et al. 1987) and male Sprague-Dawley rats administered 2-200 mg/kg by gavage (De Bethizy et al. 1987).

The major route of excretion of EA following oral administration to rats was as CO_2 in expired air; approximately 60-70% of the administered dose was recovered in expired air with 10-20% in urine and smaller amounts in bile and feces (De Bethizy et al. 1987, Ghanayem et al. 1987).

4.2. Mechanism of Toxicity

EA is a direct irritant to the mucus membranes. The target within the respiratory tract from non-lethal exposures was shown to be the olfactory epithelium lining the dorsal meatus in both monkeys (Harkema et al. 1997) and rats (BASF 1989). Both the severity and extent of the lesions were concentration and time dependent. Metabolism and subsequent removal of the chemical by carboxylesterase in the upper respiratory tract reduces the toxicity (Silver and Murphy 1978, 1981) by reducing systemic uptake and by preventing the chemical from getting to the lower respiratory tract. At lethal concentrations, death was attributed to cardiopulmonary collapse, and was accompanied by cloudy swelling and/or congestion of other visceral organs.

4.3. Structure Activity Relationships

The low molecular weight acrylic acid ester monomers are lacrimators and irritants to the eyes, skin, and mucus membranes (Bisesi 2001, Autian 1975). Acute toxicity based on LC_{50} values for a number of chemicals was determined to be methyl acrylate (1350 ppm) > ethyl acrylate (2180 ppm)> butyl acrylate (2730 ppm) > butyl methacrylate (4910 ppm) > methyl methacrylate 7093 ppm) > ethyl methacrylate (8300 ppm) (Oberly and Tansy 1985). The rapid metabolism and elimination of the low molecular weight esters suggests that cumulative effects will not occur (Autian 1975).

The target within the respiratory tract was also shown to be the olfactory epithelium lining the dorsal meatus following exposure to several other acrylate esters. Similar nasal lesions were observed in laboratory animals after exposure to methacrylic acid (NAC 2004a), methyl methacrylate (NAC 2004b), and acrylic acid (NAC 2004c).

4.4. Other Relevant Information

4.4.1. Species Variability

Little evidence for species variation was seen in the available data. Clinical signs and histopathological lesions were similar between monkeys, dogs, rabbits, rats, and guinea pigs exposed to EA.

4.4.2. Susceptible Populations

No data were available that identified susceptible populations. Developmental toxicity studies show that the fetus is not uniquely sensitive to maternal EA exposure, but may be affected at maternally toxic concentrations.

4.4.3. Concentration-Exposure Duration Relationship

The concentration-exposure duration relationship for an irritant gas such as EA can be described by the equation $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of a chemical-specific, empirically derived exponent, a default value of n = 1 can be used when extrapolating to longer timepoints and a default value of n = 3 can be used when extrapolating to shorter timepoints. This method will yield the most conservative AEGL estimates and was used for extrapolation of AEGL-2 values. For extrapolation of AEGL-3 values n was calculated from lethality data. By combining the 1- and 4- hour LC_{50} data sets in a 3-dimensional probit analysis, the value of n = 1.3 was calculated (Zwart et al. 1992).

Different n values were used in the extrapolation of AEGL-2 and -3. This approach was considered to be appropriate because the mechanism of toxicity for AEGL-2 endpoints differs from that of AEGL-3 endpoints. Under the definition of AEGL-2, lesions in the upper respiratory tract were caused by irritation of the chemical due to direct contact with mucus membranes in conjunction with enzymatic hydrolysis. In contrast, lethality as the basis for AEGL-3 was due to cardiopulmonary collapse as a result of the chemical reaching the lower respiratory tract and the systemic circulation.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No human data relevant to derivation of AEGL-1 values were found. Worker monitoring studies reported up to 30 ppm as a short-term exposure average concentration (Rohm and Haas, Co. 1987), but no health effects were included.

5.2. Summary of Animal Data Relevant to AEGL-1

Male F344/N rats (n = 5/group) exposed nose only to 25 or 75 ppm EA for 3 or 6 hours had lesions in the olfactory epithelium (Frederick et al. 2002). The distribution and severity of the lesions increased with concentration and duration. Nearly complete recovery of normal olfactory tissue was observed in affected animals following a 6-week recovery period.

Monkeys exposed to 75 ppm for 3 or 6 hours had histopathological lesions in the olfactory epithelium that increased in severity with exposure duration (Harkema et al. 1997; Rohm and Haas 1994). No deaths, clinical signs, or pathology occurred in monkeys exposed to 24.5 or 26.2 ppm , 7 hours/day for 130 exposures in 199 days (Treon et al. 1949).

Dogs exposed to concentrations as low as 25 ppm had irritation of the eyes with slight conjunctivitis; however clinical signs from individual exposures were not reported (DuPont 1946).

5.3. Derivation of AEGL-1

Limited data were available upon which to base AEGL-1 values. A concentration of 25 ppm resulted in reversible lesions of the olfactory epithelium in rats (Frederick et al. 2002). This same concentration did not result in any effects in monkeys following repeated exposures (Treon et al. 1949), but slight irritation was reported for dogs (DuPont 1946) at this concentration. Therefore, 25 ppm was chosen as a probable threshold for AEGL-1 effects. Extrapolations were not performed. A total uncertainty factor of 3 was used including a 1 for interspecies extrapolation and 3 for intraspecies extrapolation. Use of greater uncertainty factors was not necessary because the lesion is reversible, the mechanism of irritation is not expected to differ between individuals, and similar lesions were found in monkeys, guinea pigs, rabbits, and rats.

TABLE 2. AEGL-1 Values for Ethyl Acrylate

10-minute	30-minute	1-hour	4-hour	8-hour
8.3 ppm (34 mg/m^3)	8.3 ppm (34 mg/m^3)	8.3 ppm (34 mg/m^3)	8.3 ppm (34 mg/m^3)	8.3 ppm (34 mg/m^3)

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Data in humans relevant to derivation of AEGL-2 values were not found. No serious, long-lasting health effects were reported following exposure to EA. Prolonged exposure (not defined) to 50-75 ppm EA has been reported to produce drowsiness, headache, and nausea (IARC 1986); no further details could be found.

6.2. Summary of Animal Data Relevant to AEGL-2

The best animal data for derivation of AEGL-2 values is the study in which monkeys were exposed head-only to 75 ppm EA for either 3 or 6 hours (Harkema et al. 1997; Rohm and Haas 1994). Following exposure, the animals were sacrificed and the nasal cavity examined microscopically. Lesions consisted of focal degeneration, necrosis, and exfoliation with mild inflammation and were limited to the olfactory epithelium lining the dorsal medial meatus. The distribution and severity of the lesions was greater following the 6-hour exposure compared with the 3-hour exposure with approximately 50% and 15%, respectively, of the olfactory epithelium containing damage.

Lesions in the olfactory epithelium similar to those observed in monkeys were seen in rats exposed to 25 or 75 ppm for 3 or 6 hours (Frederick et al. 2002). The distribution and severity of the lesions increased with exposure to 75 ppm compared with exposure to 25 ppm and were greatest after 6 hours. Recovery was evident at both concentrations after 6 weeks.

Microscopic lesions of the olfactory epithelium were observed in rats and mice following subchronic and chronic exposures. Repair of the lesions was evident in animals exposed to 225 ppm, 6 hours/day, 5 days/week for 6 months and held for 3-6 months (BASF 1989).

A monkey survived 28 exposures to 272 ppm for 7 hours each but clinical signs of irritation and slight lethargy were observed (Treon et al. 1949).

6.3. Derivation of AEGL-2

Exposure of monkeys to 75 ppm for 3 hours, which resulted in damage to 15% of the olfactory epithelium (Harkema et al. 1997; Rohm and Haas 1994), was used to derive AEGL-2 values. The effects after the 6-hour exposure were considered too severe for AEGL-2. Values were scaled using the equation $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed using n = 3 for extrapolating to the 10- and 30-minute time points and n = 1 for the 4- and 8-hour time points. A total uncertainty factor of 3 was used including a 1 for interspecies extrapolation and 3 for intraspecies extrapolation. Use of greater uncertainty factors was not necessary because the lesion is reversible, the mechanism of irritation is not expected to differ between individuals, and similar lesions were found in monkeys, guinea pigs, rabbits, and rats. The AEGL-2 values are less than those reported to produce drowsiness, headache, and nausea in humans.

TABLE 3. AEGL-2 Values for Ethyl Acrylate

10-minute	30-minute	1-hour	4-hour	8-hour
66 ppm (270 mg/m^3)	45 ppm (180 mg/m^3)	36 ppm (150 mg/m^3)	19 ppm (78 mg/m^3)	9.4 ppm (39 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

Human exposure data relevant to derivation of AEGL-3 values were not available. No reports of human lethality from exposure to EA were found in the literature.

7.2. Summary of Animal Data Relevant to AEGL-3

Animal data relevant to derivation of AEGL-3 values are limited to 1- and 4-hour LC_{50} studies in rats. These were well conducted studies with analytically determined exposure concentrations. Clinical signs of irritation were observed in animals during exposure and death was attributed to cardiopulmonary collapse. Calculated LC_{50} values were 6493 ppm for 1 hour (Nachreiner and Dodd 1989; Union Carbide 1989) and 2180 ppm for 4 hours (Oberly and Tansy 1985).

7.3. Derivation of AEGL-3

The LC_{50} studies (Nachreiner and Dodd 1989; Union Carbide 1989; Oberly and Tansy 1985) were well conducted and included mortality ratios at all concentrations. From these data, 1- and 4-hour $BMCL_{05}$ values were calculated by a log-probit analysis using US EPA Benchmark Dose Software version 1.3.2. The resulting 1-hour $BMCL_{05}$ of 2387 ppm was used to derive the 10-minute, 30-minute, and 1-hour AEGL-3 values. The resulting 4-hour $BMCL_{05}$ of 706 ppm was used to derive the 4- and 8-hour AEGL-3 values. Values were scaled using the equation $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). By combining the 1- and 4- hour LC_{50} data sets in a 3-dimensional probit analysis, the value of n = 1.3 was calculated (Zwart et al. 1992). A total uncertainty factor of 10 was used including a 3 for interspecies extrapolation and 3 for intraspecies extrapolation. Use of greater uncertainty factors was not necessary because the mechanism of irritation is not expected to differ between individuals and similar lesions were found in monkeys, guinea pigs, rabbits, and rats.

TABLE 4. AEGL-3 Values for Ethyl Acrylate

10-minute	30-minute	1-hour	4-hour	8-hour
950 ppm (3900 mg/m^3)	410 ppm (1700 mg/m^3)	240 ppm (980 mg/m^3)	71 ppm (290 mg/m^3)	41 ppm (170 mg/m^3)

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity Endpoints

The derived AEGL values for various levels of effects and durations of exposure are summarized in Table 5. AEGL-1 and -2 were based reversible histopathology of the olfactory epithelium. The basis for AEGL-3 was a calculated 1- or 4-hour $BMCL_{50}$ value in the rat.

TABLE 5. Summary of AEGL Values

Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	8.3 ppm (34 mg/m^3)	8.3 ppm (34 mg/m^3)	8.3 ppm (34 mg/m^3)	8.3 ppm (34 mg/m^3)	8.3 ppm (34 mg/m^3)
AEGL-2 (Disabling)	66 ppm (270 mg/m^3)	45 ppm (180 mg/m^3)	36 ppm (150 mg/m^3)	19 ppm (78 mg/m^3)	9.4 ppm (39 mg/m^3)
AEGL-3 (Lethal)	950 ppm (3900 mg/m^3)	410 ppm (1700 mg/m^3)	240 ppm (980 mg/m^3)	71 ppm (290 mg/m^3)	41 ppm (170 mg/m^3)

8.2. Comparison with Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures are listed in Table 6. The ACGIH recommends a STEL of 15 ppm for workers (ACGIH 2003) while the OSHA PEL is 25 ppm (OSHA, 1999). NIOSH (2003a) considers EA to be a potential occupational carcinogen and, thus, has not established a REL. The NIOSH IDLH is 300 ppm based on toxicity data in humans and animals (NIOSH 2003b). ERPG-3 and -2 values were based on the RD_{50} in mice and the ERPG-1 is based on odor recognition (AIHA 2000). The occupational exposure limits from ACGIH, Germany, The Netherlands, and Sweden are 5 ppm.

TABLE 6. Extant Standards and Guidelines for Ethyl Acrylate

Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	8.3 ppm	8.3 ppm	8.3 ppm	8.3 ppm	8.3 ppm
AEGL-2	66 ppm	45 ppm	36 ppm	19 ppm	9.4 ppm
AEGL-3	950 ppm	410 ppm	240 ppm	71 ppm	41 ppm
ERPG-1 (AIHA)[a]			0.01 ppm		
ERPG-2 (AIHA)			30 ppm		
ERPG-3 (AIHA)			300 ppm		
PEL-TWA (OSHA)[b]					25 ppm
IDLH (NIOSH)[c]		300 ppm			
TLV-TWA (ACGIH)[d]					5 ppm (A4)
TLV-STEL (ACGIH)[e]	15 ppm (A4)				
MAK (Germany)[f]					5 ppm
MAK Peak Limit (Germany)[g]	5 ppm				
MAC (The Netherlands)[h]					5 ppm
OEL-TWA (Sweden)[i]					5 ppm
OEL-STEL (Sweden)[j]	10 ppm				

[a]**ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association** (AIHA 2000)

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 protection action.

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

[b]**OSHA PEL-TWA (Occupational Safety and Health Administration, Permissible Exposure Limits - Time Weighted Average)** (OSHA 1999) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[c]**IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** (NIOSH 2003b) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

[d]**ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH 2003) 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. A4: not classifiable as a human carcinogen.

[e]**ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit)** (ACGIH 2003) 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. A4: not classifiable as a human carcinogen.

[f]**MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration])** (Deutsche Forschungsgemeinschaft [German Research Association] 2002) is defined analogous to the ACGIH-TLV-TWA.

[g]**MAK Spitzenbegrenzung (Peak Limit [I(2)])** (German Research Association 2002) constitutes the maximum average concentration to which workers can be exposed for a period up to 30 minutes with no more than 2 exposure periods per work shift; total exposure may not exceed 8-hour MAK.

[h]**MAC (Maximaal Aanvaaarde 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]**OEL-TWA (Occupational Exposure Limits - Time-weighted-average)** (IPCS 2003) is an occupational exposure limit value for exposure during one working day.

[j]**OEL-STEL (Occupational Exposure Limits - Short-term exposure limit)** (IPCS 2003) is an occupational exposure limit value for exposure during a reference period of fifteen minutes.

8.3. Data Adequacy and Research Needs

No human data were available. Worker monitoring studies did not report potential individual exposure or effects. Limited animal data were available for derivation of AEGL-1. However, AEGL-2 and -3 were based on well-conducted studies with adequate information.

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APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1

Key Studies:	Frederick et al. 2002
Toxicity endpoint:	Reversible lesions in the olfactory epithelium following exposure to 25 ppm for 3 hours; severity and distribution increased with increasing duration and concentration.
Time scaling:	None
Uncertainty factors:	3 (3 for intraspecies variability and 1 for interspecies variability)
Modifying factor:	None
Calculations:	C/UFs = 25 ppm/3 = 8.3 ppm
10-minute AEGL-1:	8.3 ppm
30-minute AEGL-1:	8.3 ppm
1-hour AEGL-1:	8.3 ppm
4-hour AEGL-1:	8.3 ppm
8-hour AEGL-1:	8.3 ppm

Derivation of AEGL-2

Key Study:	Harkema et al. 1997; Rohm and Haas 1994
Toxicity endpoints:	Microscopic lesions covering 15% of the olfactory epithelium of monkeys exposed to 75 ppm for 3 hours.
Time scaling	$C^n \times t = k$ (ten Berge et al. 1986) n = 3 for extrapolating to the 10-min, 30-min, and 1-hr time points; n = 1 for extrapolating to the 4- and 8-hr time point
Uncertainty factors:	3 (3 for intraspecies variability and 1 for interspecies variability)
Modifying factor:	None
Calculations:	*10-min, 30-min, and 1-hr time points* $(C/UFs)^3 \times t = k$ $(75 \text{ ppm}/3)^3 \times 3 \text{ hr} = 46875 \text{ ppm}^3 \cdot \text{hr}$ *4- and 8-hr time point* $(C/UFs)^1 \times t = k$ $(75 \text{ ppm}/3)^1 \times 3 \text{ hr} = 75 \text{ ppm}^1 \cdot \text{hr}$
10-minute AEGL-2:	$(46875 \text{ ppm}^3 \cdot \text{hr}/0.1667 \text{ hr}) = 66 \text{ ppm}$
30-minute AEGL-2:	$(46875 \text{ ppm}^3 \cdot \text{hr}/0.5 \text{ hr}) = 45 \text{ ppm}$
1-hour AEGL-2:	$(46875 \text{ ppm}^3 \cdot \text{hr}/1 \text{ hr}) = 36 \text{ ppm}$
4-hour AEGL-2:	$(75 \text{ ppm}^1 \cdot \text{hr}/4 \text{ hr}) = 19 \text{ ppm}$
8-hour AEGL-2:	$(75 \text{ ppm}^1 \cdot \text{hr}/8 \text{ hr}) = 9.4 \text{ ppm}$

Derivation of AEGL-3

Key Studies:	Nachreiner and Dodd 1989; Union Carbide 1989; Oberly and Tansy 1985
Toxicity endpoint:	The 1- and 4-hour LC_{50} values of 6493 and 2180 ppm, respectively, in rats were used for derivation of AEGL-3 values. From these data, 1- and 4-hour $BMCL_{05}$ values were calculated by a log-probit analysis. The resulting 1-hour $BMCL_{05}$ of 2387 ppm was used to derive the 10-minute, 30-minute, and 1-hour AEGL-3 values. The resulting 4-hour $BMCL_{05}$ of 706 ppm was used to derive the 4- and 8-hour AEGL-3 values.
Time scaling	$C^n \times t = k$ (ten Berge et al. 1986) n = 1.3 derived from a 3-dimensional analysis of the 1- and 4-hour LC_{50} data sets
Uncertainty factors:	10 (3 for intraspecies variability and 3 for interspecies variability)
Modifying factor:	None
Calculations:	*10- and 30-min time points* $(C/UFs)^{1.3} \times t = k$ $(2387 \text{ ppm}/10)^{1.3} \times 1 \text{ hr} = 1233.696 \text{ ppm}^{1.3}\cdot\text{hr}$ *8-hr time point* $(C/UFs)^{1.3} \times t = k$ $(706 \text{ ppm}/10)^{1.3} \times 4 \text{ hr} = 1012.758 \text{ ppm}^{1.3}\cdot\text{hr}$
10-minute AEGL-3:	$(1233.696 \text{ ppm}^{1.3}\cdot\text{hr}/0.1667 \text{ hr}) = 950 \text{ ppm}$
30-minute AEGL-3:	$(1233.696 \text{ ppm}^{1.3}\cdot\text{hr}/0.5 \text{ hr}) = 410 \text{ ppm}$
1-hour AEGL-3:	$(2387 \text{ ppm}/10) = 240 \text{ ppm}$
4-hour AEGL-3:	$(706 \text{ ppm}/10) = 71 \text{ ppm}$
8-hour AEGL-3:	$(1012.758 \text{ ppm}^{1.3}\cdot\text{hr}/8 \text{ hr}) = 41 \text{ ppm}$

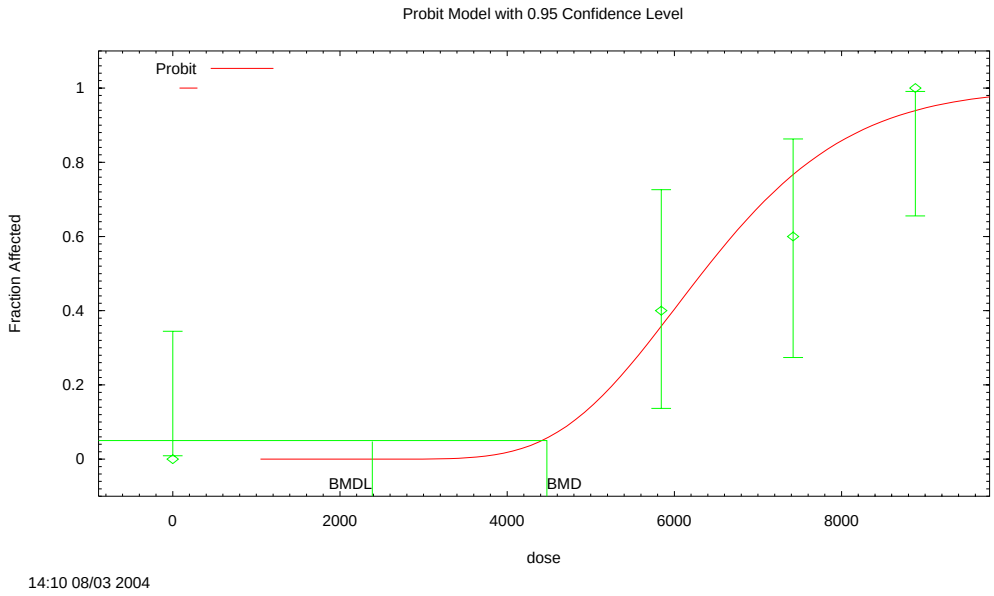
APPENDIX B: Benchmark Calculations

Benchmark Calculations

1. 1-Hour Calculations

The benchmark calculations are based on the study by Nachreiner and Dodd (1989) using a range of three concentrations in rats to determine a 1-hour LC_{50}. For the derivation of 10-minute, 30-minute, and 1-hour AEGL-3 values, a $BMCL_{05}$ of 2387 ppm, derived with the Log-Probit model, was used.

$BMCL_{05}$ = 2387 ppm
BMC_{01} = 3855 ppm

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    Gnuplot Plotting File:  C:\BMDS\DATA\EA-1HR.plt
    Tue Aug 03 14:10:36 2004
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 BMDS MODEL RUN
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The form of the probability function is:
P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)), where CumNorm(.) is the cumulative normal distribution function

Dependent variable = Mortality
Independent variable = Conc.
Slope parameter is not restricted

Total number of observations = 4
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
background = 0
intercept = -39.5121
slope = 4.50679

Asymptotic Correlation Matrix of Parameter Estimates
(*** The model parameter(s) -background have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix)

	intercept	slope
intercept	1	-1
slope	-1	1

Parameter Estimates		
Variable	Estimate	Std. Err.
background	0	NA
intercept	-40.0425	15.0216
slope	4.56769	1.69918

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table				
Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-13.4602			
Fitted model	-14.7819	2.64331	2	0.2667
Reduced model	-27.7259	28.5313	3	<.0001

AIC: 33.5638

Goodness of Fit					
Dose	Est. Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	10	0
5843.0000	0.3347	3.347	4	10	0.4374
7421.0000	0.7470	7.470	6	10	-1.069
8882.0000	0.9314	9.314	10	10	0.8585
Chi-square = 2.07		DF = 2		P-value = 0.3549	

Benchmark Dose Computation

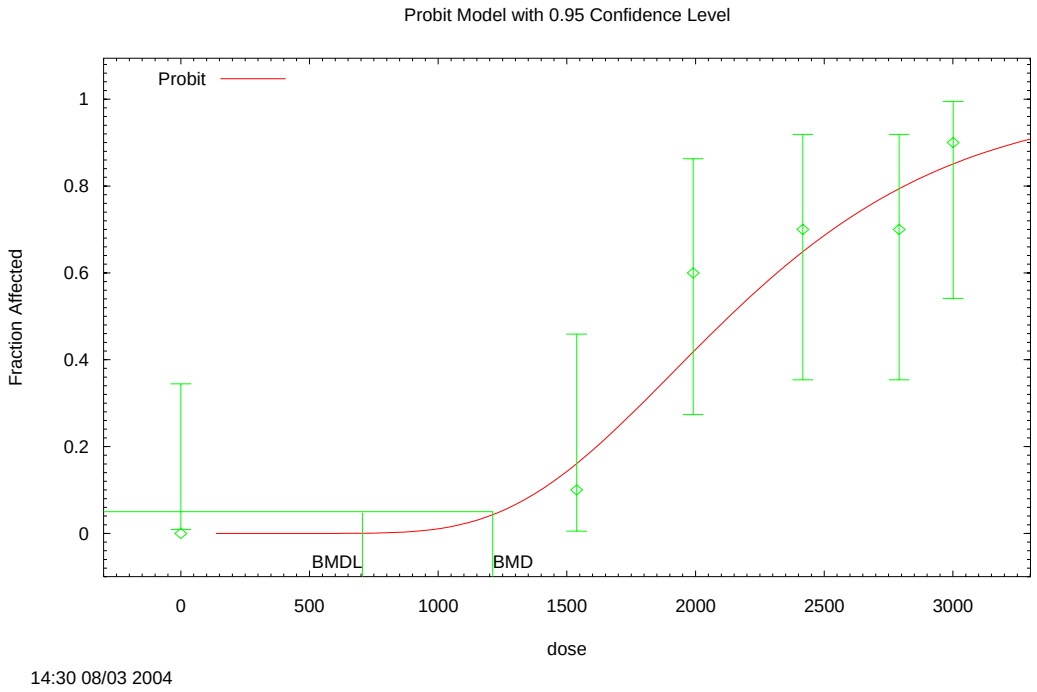
Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95

BMD = 4475.4
BMDL = 2386.81

2. 4-Hour Calculations

The benchmark calculations are based on the study by Oberly and Tansy (1985) using a range of five concentrations in rats to determine a 4-hour LC_{50}. For the derivation of 4- and 8-hour AEGL-3 values, a $BMCL_{05}$ of 706 ppm, derived with the Log-Probit model, was used.

$BMCL_{05}$ = 706 ppm
BMC_{01} = 969 ppm



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Tue Aug 03 14:30:53 2004

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BMDS MODEL RUN

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The form of the probability function is:
P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)), where CumNorm(.) is the cumulative normal distribution function
~~~~~~

Dependent variable = Mortality
Independent variable = Conc.
Slope parameter is not restricted

Total number of observations = 6
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
background = 0
intercept = -24.9945
slope = 3.26579

Asymptotic Correlation Matrix of Parameter Estimates
(*** The model parameter(s) -background have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix)

	intercept	slope
intercept	1	-1
slope	-1	1

Parameter Estimates		
Variable	Estimate	Std. Err.
background	0	NA
intercept	-23.2567	6.75099
slope	3.04404	0.873355

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table				
Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-25.4491			
Fitted model	-26.609	2.31979	4	0.6772
Reduced model	-41.5888	32.2795	5	<.0001

AIC: 57.2179

Goodness of Fit					
Dose	Est. Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.0000	0	10	0
1538.0000	0.1791	1.791	1	10	-0.6523
1991.0000	0.4471	4.471	6	10	0.9725
2417.0000	0.6762	6.762	7	10	0.1605
2791.0000	0.8147	8.147	7	10	-0.9331
3001.0000	0.8678	8.678	9	10	0.3007
Chi-square = 2.36		DF = 4		P-value = 0.6702	

Benchmark Dose Computation

Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95

BMD = 1211.64
BMDL = 706.083

APPENDIX C: Derivation Summary for Ethyl Acrylate AEGLs

ACUTE EXPOSURE GUIDELINE LEVELS FOR ETHYL ACRYLATE (CAS Reg. No. 140-88-5) DERIVATION SUMMARY

AEGL-1 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
8.3 ppm	**8.3 ppm**	**8.3 ppm**	**8.3 ppm**	**8.3 ppm**

Key Reference: Frederick, C.B., L.G. Lomax, K.A. Black, L. Finch, H.E. Scribner, J.S. Kimbell, K.T. Morgan, R.P. Subramaniam, and J.B. Morris. 2002. Use of a hybrid computational fluid dynamics and physiologically based inhalation model for interspecies dosimetry comparisons of ester vapors. Toxicol. Appl. Pharmacol. 183:21-40.

Test Species/Strain/Number: rat/F344/N/5

Exposure Route/Concentrations/Durations: Inhalation: 5, 25, 75 ppm for 1, 3, or 6 hours

Effects:
- 5 ppm: no effects at any time.
- 25 ppm: lesions in the olfactory epithelium in 2/5 after 3 hours and in 3/5 after 6 hours; reversible.
- 75ppm: lesions in the olfactory epithelium in 5/5; increase in severity and distribution with time; reversible.

Endpoint/Concentration/Rationale: 25 ppm for 3 hours resulted in reversible lesions in the olfactory epithelium.

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
- Interspecies: 1, similar lesions were found in monkeys and rats.
- Intraspecies: 3, mechanism of irritation is not expected to differ between individuals.

Modifying Factor: None

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: Extrapolation to time points was not conducted.

Data Adequacy: No human data and only limited animal data were available.

AEGL-2 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
66 ppm	**45 ppm**	**36 ppm**	**19 ppm**	**9.4 ppm**

Key References:

Harkema, J.R., J.K. Lee, K.T. Morgan, and C.B. Frederick. 1997. Olfactory epithelial injury in monkeys after acute inhalation exposure to acrylic monomers. Toxicologist 36:113.

Rohm and Haas, Co. 1994. Single dose inhalation toxicity study of ethyl acrylate (EA) and acrylic acid (AA) in monkeys, interim report from pharmacokinetic study, with cover letter dated 12/08/94. Doc. ED 86-950000051.

Test Species/Strain/Number: Monkey/Cynomolgus/3

Exposure Route/Concentrations/Durations: Inhalation, 75 ppm for 3 or 6 hours

Effects:

75 ppm for 3 hr: lesions covering 15% of the olfactory epithelium

75 ppm for 6 hr: lesions covering 50% of the olfactory epithelium

Endpoint/Concentration/Rationale: Microscopic lesions/75 ppm/Exposure of monkeys to 75 ppm for 3 hours resulted in reversible lesions, the extent and severity of which are below the definition of AEGL-2 effects.

Uncertainty Factors/Rationale:

Total uncertainty factor: 3

Interspecies: 1, reversible lesion below the definition of AEGL-2; similar lesions were found in monkeys and rats; all species have some degree of protection from carboxylesterase activity.

Intraspecies: 3, mechanism of irritation is not expected to differ between individuals.

Modifying Factor: None

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed using n = 3 for extrapolating to the 10-minute, 30-minute, and 1-hour time points and n = 1 for the 4-hour and 8-hour time point.

Data Adequacy: This was a well-conducted study with sufficient detail for analysis. Values are supported by repeated exposure studies in monkeys, rats, and mice.

AEGL-3 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
950 ppm	**410 ppm**	**240 ppm**	**71 ppm**	**41 ppm**

Key Reference: Nachreiner, D.J. and D.E. Dodd. 1989. Ethyl acrylate: acute vapor inhalation toxicity test in rats. Bushy Run Research Center, Project Report 51-569.

Union Carbide, Corp. 1989. Ethyl acrylate acute vapor inhalation toxicity test in rats with attachments and cover sheet dated 081089 (sanitized). Doc. ID 86-890001494S.

Oberly, R. and M.F. Tansy. 1985. LC50 values for rats acutely exposed to vapors of acrylic and methacrylic acid esters. J. Toxicol. Environ. Health 16:811-822.

Test Species/Strain/Number: Rat/Sprague-Dawley/5 or 10

Exposure Route/Concentrations/Durations: Inhalation
5843, 7421, or 8882 ppm for 1 hour
1538, 1991, 2417, 2791, or 3001 ppm for 4 hours

Effects: 6493 ppm 1-h LC_{50}
2180 ppm 4-hr LC_{50}
Clinical signs of irritation during exposures; death due to cardiopulmonary collapse.

Endpoint/Concentration/Rationale: 1- and 4-hour $BMCL_{05}$ values were calculated by a log-probit analysis. The resulting 1-hour $BMCL_{05}$ of 2387 ppm was used to derive the 10-minute, 30-minute, and 1-hour AEGL-3 values. The resulting 4-hour $BMCL_{05}$ of 706 ppm was used to derive the 4- and 8-hour AEGL-3 values.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, similar lesions were found in monkeys and rats; all species have some degree of protection from carboxylesterase activity.
Intraspecies: 3, mechanism of irritation is not expected to differ between individuals.

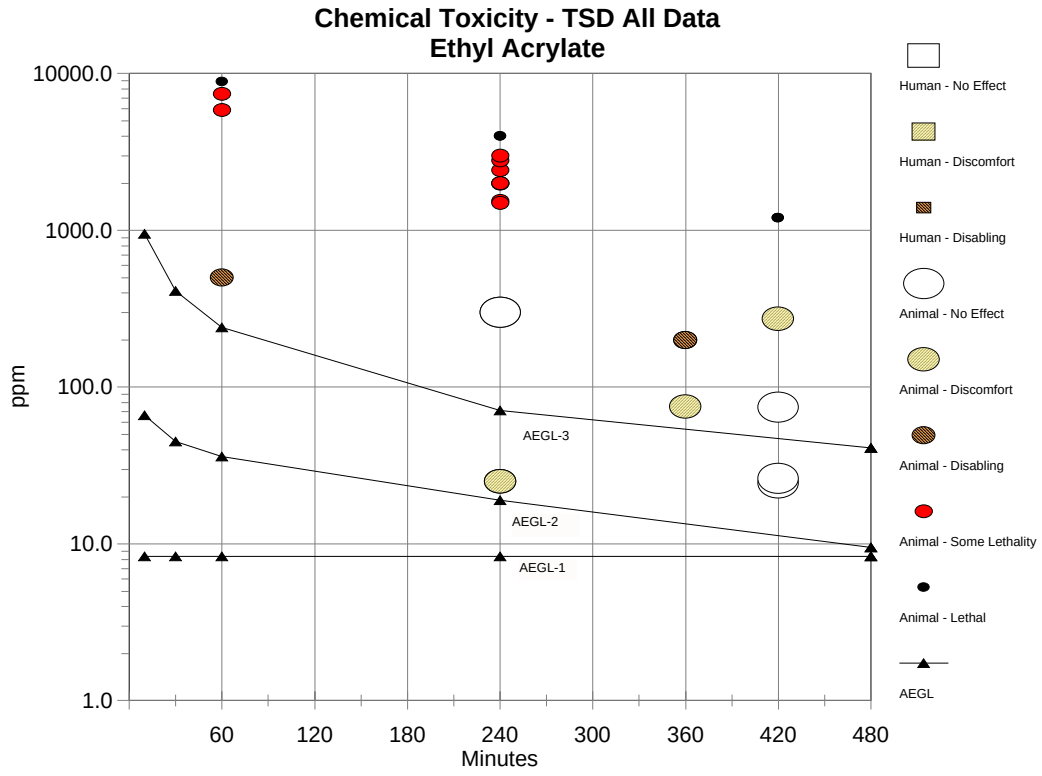
Modifying Factor: None

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). By combining the 1- and 4- hour LC_{50} data sets in a 3-dimensional probit analysis, the value of n = 1.3 was calculated.

Data Adequacy: The LC_{50} studies were well conducted and included mortality ratios at all concentrations.

APPENDIX D: Time-scaling Category Plot for Ethyl Acrylate



No effect = No effect or mild discomfort
Discomfort = Notable transient discomfort/irritation consistent with AEGL-1 level effects
Disabling = Irreversible/long lasting effects or an impaired ability to escape
Some lethality = Some, but not all, exposed animals died
Lethal = All exposed animals died