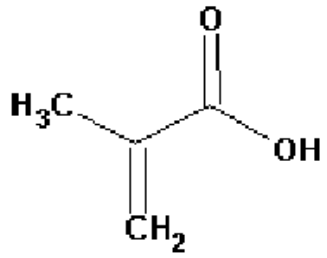
United States Environmental Protection Agency
Office of Pollution Prevention and Toxics

METHACRYLIC ACID
(CAS Reg. No. 79-41-4)



INTERIM ACUTE EXPOSURE GUIDELINE LEVELS
(AEGLs)

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PREFACE

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

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

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

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

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

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

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EXECUTIVE SUMMARY

Methacrylic acid (MAA) is a clear, colorless liquid with an acrid, repulsive odor. An odor detection limit of 0.17 ppm has been reported.

MAA is miscible with most organic solvents and moderately soluble in water.

MAA is used for the production of methacrylic esters and as a co-polymer in different kinds of applications. Exposure can occur at sampling, filling, drumming, cleaning, maintenance, and repair work, as well as during use.

Methacrylic acid is irritating and corrosive to eyes, skin and the respiratory tract. No metabolites were identified that contribute to the toxic effects. MAA is converted to its Coenzyme A ester by enoyl-CoA hydratase and then enters the citric acid cycle as the Coenzyme A ester.

Data on acute effects in humans are limited. None of the reported effects can be related to a specific exposure duration. An acute workplace exposure to 113 ppm was reported to cause skin toxicity and a severe corneal burn (Dow Chemicals 1977). No information on systemic toxic effects in humans has been located.

In animal studies, a 4-hour LC_{50} of 1980 ppm was established by DuPont (1993a). At inhalation concentrations above 1000 ppm MAA for up to 6 hours, increased motor activity, lethargy, respiratory effects, discharge, and corrosive effects to the eyes have been reported during exposure (Food and Drug Research Laboratory 1973; DuPont 1993a; CIIT 1983). Pathological examination revealed severe pulmonary edema, hemorrhage, and discoloration. DuPont (1993b) reported a RD_{50} of 22000 ppm. Concentrations between 20 ppm and 500 ppm result in degeneration of olfactory epithelium, rhinitis, ulceration, inflammation, hyperplasia, and metaplasia of nasal mucosa (CIIT 1983, 1984). No information on systemic toxic effects in experimental animals has been located, except an indication of effects on the cardiovascular system and respiration, e.g. increased motor activity, lethargy, effects on blood pressure, increased respiratory rate (Mir et al. 1974; CIIT 1983; Du Pont 1993a).

No carcinogenicity studies are available for MAA. There is one negative mutagenicity test in Salmonella. The ester of methacrylic acid, methyl methacrylate, does not express a genotoxic potential in vivo. There is evidence suggesting lack of carcinogenicity of methyl methacrylate in experimental animals.

No suitable single exposure studies for derivation of AEGL-1 or AEGL-2 were available.

The AEGL-1 values are based on rhinitis, inflammation, and slight degeneration of the olfactory epithelium observed in Fischer 344 and Sprague-Dawley rats exposed to 20 ppm for 6 hours for 4 days (CIIT, 1984). An uncertainty factor of 3 was used for intraspecies variability. For effects in the nasal cavity, there is evidence that humans are less susceptible than rats. Therefore, an uncertainty factor of 1 was used for interspecies variability. Because no major increase in severity of effects over time is expected, the derived value of 6.7 ppm is used for all points.

The AEGL-2 values are based on inflammation, exudate, and ulceration of the olfactory epithelium (CIIT, 1984). These effects were observed after four 6 hour exposures to 300 ppm in Fischer 344 and Sprague-Dawley rats and B6C3F1 mice. These effects were not seen at 100 ppm. An uncertainty factor of 3 was used for intraspecies variability. For effects in the nasal cavity, there is evidence that humans are less susceptible than rats. Therefore, an uncertainty factor of 1 was used for interspecies variability. No suitable data were available to derive a substance specific value of n. Thus, the default value of n = 3 was used for extrapolation from the 6 hour exposure to shorter durations and n = 1 was used for the 8 hour duration. Because extrapolation from 6 hours to durations of less than 30 minutes lead to very high uncertainty, the value for 10 minutes was set equal to the value for 30 minutes.

The AEGL-3 values are based on a $BMCL_{05}$ of 1414 ppm for 4 hours calculated from a study by DuPont (1993a). At the LC_0 of 1200 ppm, irregular respiration, lethargy, lung noise and colored discharge were observed in CrlCDBR rats. The next higher exposure of 1650 ppm led to lethal effects in 1 of 10 animals. An uncertainty factor of 3 was used for intraspecies variability. Because no information is available concerning species susceptibility in the lower respiratory tract, an interspecies uncertainty factor of 3 was used. An overall uncertainty factor of 10 was used. No suitable data were available to derive a substance specific value of n. Thus, the default value of n = 3 was used for extrapolation from the 4 hour exposure to shorter durations and n = 1 was used for the 8 hour duration. Because extrapolation from 4 hours to durations of less than 30 minutes lead to very high uncertainty, the value for 10 minutes was set equal to the value for 30 minutes.

The calculated values are listed in the Table 1.

TABLE 1. Summary of AEGL Values for Methacrylic Acid [ppm (mg/m3)]*

Classification	10-min	30-min	1-h	4-h	8-h	Endpoint / Species	Reference
AEGL-1 (Nondisabling)	**6.7 (24)**	**6.7 (24)**	**6.7 (24)**	**6.7 (24)**	**6.7 (24)**	**Inflammation; rhinitis, slight degeneration of olfactory epithelium rats**	**CIIT (1984)**
AEGL-2 (Disabling)	**76 (270)**	**76 (270)**	**61 (220)**	**38 (140)**	**25 (90)**	**Inflammation, exudate and ulceration of olfactory epithelium rats and mice**	**CIIT (1984)**
AEGL-3 (Lethal)	**280 (1000)**	**280 (1000)**	**220 (790)**	**140 (500)**	**71 (250)**	**$BMCL_{05}$; respiratory failure at lethal concentration rats**	**DuPont (1993a)**

***Relevant skin uptake of methacrylic acid can not be excluded.**

The reported odor threshold is not adequate to derive a level of odor awareness (LOA) Grudzinskii (1988) reported an odor detection limit of 0.17 ppm.

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1. INTRODUCTION

Methacrylic acid (MAA) is a clear, colorless liquid with an acrid, repulsive odor (ECETOC 1996). An odor threshold concentration of 0.17 ppm (0.6 mg/m^3) is reported by Grudzinskii (1988).

TABLE 2. Chemical and Physical Properties

Parameter	Value	Reference
Synonyms	2-Methylpropenoic acid; p-Methylacrylic acid; 2-Methylacrylic acid; 2-Propenoic acid; 2-methyl methacrylic acid alpha-Methylacrylic acid	ECB (2002) IPCS (2001)
Chemical formula	$C_4H_6O_2$	ECB (2002)
Molecular weight	86.09 g/mol	ECB (2002)
CAS Reg. No.	79-41-4	ECB (2002)
Physical state	liquid at 20 °C	ECB (2002)
Solubility in water	89 g/l at 25 °C	ECB (2002)
Vapor pressure	0.9 hPa at 20 °C	ECB (2002)
Vapor density (air =1)	2.97	IPCS (1996)
Liquid density (water =1)	1.015 - 1.02 at 20 °C	ECETOC (1996)
Melting point	14 - 16 °C	ECB (2002)
Boiling point	159 - 163 °C at 1,013 hPa	ECB (2002)
Conversion factors	mg/m^3 = 3.58 x ppm 1000 ppm = 3.58 mg/l	ECETOC (1996)

MAA is used in the preparation of ethyl methacrylate and higher homologues, for the production of resins, methylacrylic acid esters, carboxylated polymers and polymers for paints, adhesives and textile applications (e.g. carpets) (ECB 2002; ECETOC 1996). In addition it is used as crosslinking co-monomer in different kinds of polymers, e.g. surface coatings, flocculants or soil improvers, and as a primer before applying artificial fingernails. A cumulative production volume of 120,000 tonnes/annum were reported by ECB (2002).

Exposure can occur during sampling, filling, drumming, cleaning, maintenance, and repair work. Contact to MAA via inhalation and dermal exposure in the most likely for workers and consumers. In emergency situations, the vapor exposure might have a higher importance than the aerosol exposure.

MAA is miscible with most organic solvents, and moderately soluble in water (ECETOC 1996).

MMA polymerizes readily and spontaneously when exposed to light or at elevated temperatures. To prevent polymerization, MAA is stabilized with hydroquinone (< 100 ppm) or hydroquinone monomethyl ether (< 250 ppm) (ECETOC 1996)..

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No human data on acute lethality following exposure to MAA are available.

2.2. Nonlethal Toxicity

2.2.1. Case Reports

No case reports following exposure to MAA are available.

2.2.2. Human Studies

Eye and upper respiratory tract irritation have been observed by Grudzinskii (1988) in 21 volunteers exposed to MAA concentrations of 1.4 - 10.7 ppm. No information on exposure duration is given. Exposure concentrations could not be validated by ECETOC (1996).

Acute workplace exposures to a peak concentration of 113 ppm caused skin toxicity and a severe corneal burn (Dow Chemicals 1977). At this concentration no respiratory effects had been observed. No information on exposure duration is provided.

Rumyantsev et al. (1981) conclude from investigations in a MAA manufacturing facility that the no-effect concentration for continuous inhalation of MAA is less than 0.44 mg/m^3 (0.123 ppm). No further details are available.

2.3. Mutagenicity/Genotoxicity

No investigations concerning mutagenic or genotoxic potential of MAA in humans have been conducted.

2.4. Carcinogenicity

No studies on carcinogenicity of MAA have been conducted.

2.5. Summary

Little evidence on toxic effects observed in humans is available. None of the observed effects can be related to a specific exposure duration. However, it is known that MAA is irritating to skin and respiratory tract and corrosive to eyes. No information on systemic toxic effects in humans has been found.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Lethality after inhalation exposure

Food and Drug Research Laboratory (1973) reported that 6 adult albino rats died within 19 minutes following inhalation exposure to 57000 ppm MAA (indicated as 204 mg/l). The animals showed increased motor activity, respiratory distress, and corrosive effects to the eyes. The pathological examination revealed severe pulmonary edema with some hemorrhage and corneal opacity. No information on concentration measurement, e.g. analytics, vapor/aerosol exposure, or whole body/nose-only exposure, is given.

DuPont (1993a) conducted an inhalation study of MAA in CrlCD®BR rats . Four groups of 5 young adult animals of each sex were exposed (nose only) for 4 hours to mean MAA concentrations of 1200, 1650, 2040, or 2290 ppm in perforated, stainless steel polycarbonate cylinders with conical nose pieces. The concentrations of the aerosol-vapor mixture in the 29-l glass exposure cylinder were determined by gas chromatography. The particle size distribution was determined once. The percentage of aerosol/vapor was 21/79 at1200 ppm, 37/63 at 1650 ppm, 50/50 at 2040 ppm, and 57/43 at 2290 ppm. Following exposure the animals were observed for a 14 day-period for clinical signs of toxicity. Death occurred at concentrations of 1650 ppm and above. At the highest concentration, all animals died during exposure. At 2040 ppm the animals died 1 to 7 days after exposure. The death of 1 animal at 1650 ppm occurred during exposure. Lethality incidences are summarized in Table 3. At lethal concentrations, dose-related signs of toxicity included corneal opacity, gasping, irregular respiration, lethargy, lung noises, stained and wet fur, and nasal, ocular and vaginal discharge. During recovery period sores and alopecia on the nose, closed eyes, hunched posture, pallor, ruffled fur, weakness, and slight to severe body-weight losses developed. A LC_{50} of 1980 ppm (7.1 mg/l) for a 4-hour exposure was calculated.

CIIT (1983) conducted a two week study in Fischer 344 and Sprague-Dawley rats (5 animals of each strain and sex). No rats died after the first exposure to 1000 ppm. All rats exposed to 1000 ppm died during the study. For study details see Section 3.3 (Repeated Exposure).

Lethality after oral exposure

Rohm and Haas (1957) reported an oral LD_{50} of 2210 mg/kg for male albino rats. Eastman Kodak (1979) reported an oral LD_{50} of 2260 mg/kg. Elf Atochem (1977) reported an oral LD_{50} of 1320 mg/kg for male Wistar rats.

Mastri (1973) reported an oral LD_{100} of 5000 mg/kg for male albino rats. At necropsy gastrointestinal hemorrhages, ruptured stomachs and chemical burns on abdominal organs were observed.

3.1.2. Mice

Lethality after inhalation exposure

CIIT (1983) conducted a two week study in B6C3F1 mice. At 1000 ppm three of 10 mice died after the first 6 hour exposure. All of the mice exposed at 1000 ppm died within 4 days. For study details see Section 3.3 (Repeated Exposure).

Lethality after oral exposure

Eastman Kodak (1979) reported an oral LD_{50} of 1600 mg/kg. Clinical signs included weakness and rough hair coat.

3.1.3. Guinea Pigs

Lethality after dermal exposure

ECB (Eastman Kodak, 1979) reported a dermal LD_{50} of 1000 - 5000 mg/kg (indicated as 1 - 5 mL/kg).

3.1.4. Rabbits

Lethality after oral exposure

ECB (2000) reported an oral LD_{50} of 1200 mg/kg bw (15 animals).

Lethality after dermal exposure

ECB (2000) reported a dermal LD_{50} between 500 mg/kg bw and 1000 mg/kg from a screening test for dermal toxicity.

Food and Drug Research Laboratory (1973) reported that 2000 mg/kg on intact skin for a 24-hour was lethal for 2 of 3 animals, and 2000 mg/kg on abraded skin was lethal for 3 of 3 animals. Examinations revealed severe erythema and edema at application site, however no abnormalities were observed at gross necropsy.

Dow Chemical (1956) reported that exposure to 100% MAA for 5 minutes to intact skin led to a moderate damage. A 30 second exposure resulted in slight erythema, very slight edema, and necrosis.

Mastri (1973) reported a dermal LD_{100} of 3000 mg/kg in albino rabbits. All animals revealed hypoactivity, blood in excreta, vocalization and a total destruction at skin sites. The animals died within 6 hours to 7 days.

Elf Atochem (1980) reported severe edema, erythema and necrosis in New Zealand White rabbits following dermal application of 0.5 mL MAA to the intact and abraded skin. A primary irritation score of 8.0 was obtained and MAA was classified as corrosive to the skin.

TABLE 3. Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Conc. (ppm)	Exposure	Result	Number of animals Most important effects	Reference
Rat	57000	19 min	LC_{100}	6 Animals died within 19 min severe pulmonary edema, hemorrhage; corneal opacity	Food & Drug Research Laboratory (1973)
Rat	1200 1650 2040 2290 1980 1414	4 h	LC LC_{50} $BMCL_{05}$	0/10 Animals died 1/10 Animals died 4/10 Animals died 10/10 animals died Nose-only; analytical conc.; mixed Vapor/aerosol Corneal opacity, effects on respiration, lethargy, discharge Calculated Calculated	DuPont (1993a) See Appendix B
rat	1000	6 h	LC_0	0/10 Died after first exposure (repeated exposure study) Whole-body; analytical concentration; vapor	CIIT (1983) See Section 3.3
rat	2000	7 h	LC_0	3 Animals Whole-body; nominal conc.; eye irritation; weight loss no further information	Dow Chemicals (1956) See Section 3.2.1
mouse	1000	6 h	LC	3/10 Died after first exposure (repeated exposure study) Whole-body; analytical concentration; vapor	CIIT (1983) See Section 3.3

3.2. Nonlethal Toxicity

3.2.1. Rats

Nonlethal toxicity after inhalation exposure

Dow Chemicals (1956) conducted a range-finding inhalation study at saturated vapor concentration of 2000 ppm (as calculated by the authors). Three female rats exposed for 7 hours (single exposure, whole body) showed definite eye irritation and slight to moderate weight loss. No information on a post-exposure observation period is given.

DuPont (1993a) reported no lethality following a single 4-hour exposure to 1200 ppm in a LC_{50}-study with CrlCD®BR rats (5/sex and concentration) already described above (see Section 3.1.1 - Rats, Acute Lethality). Signs of toxicity observed were nasal, ocular and vaginal discharge, gasping, irregular respiration, lethargy, lung noise, and stained fur. Alopecia, hunched posture and slight to severe weight loss have been observed during the recovery period of 14 days.

CIIT (1983) conducted a repeated exposure study in Fischer-344 rats, Sprague-Dawley rats, and B6C3F1 mice. The animals were whole-body exposed 100, 500, and 1000 ppm for 2 weeks (10 exposures; 6 h/d). For details see Section 3.3. (Repeated Exposure). During the first day of exposure, animals of all strains showed increased activity at 1000 ppm. Sprague-Dawley

rats showed lacrimation, crusty eyes, and a clear nasal discharge. No obvious treatment-related clinical signs were noticed at 100 and 500 ppm after the first exposure.

Morris and Frederick (1995) and Morris (1992) investigated the biochemical responses in the surgically isolated upper respiratory tract (URT) of 5 male Fischer-344 rats exposed (nose only) to 21 ppm, 133 ppm, and 410 ppm MAA (vapor; analytical concentrations). The experiments were conducted using the unidirectional respiratory flow technique with an exposure duration of 60 min. The animals were sacrificed immediately after exposure. Increases in albumin and/or total protein in nasal lavage would indicate mucous hypersecretion, cytotoxicity and transudation of blood proteins. Changes in non-protein sulfhydryl levels would indicate a direct reactivity of toxicants with reduced sulfhydryl compounds. No significant biochemical effects were observed at any exposure that would indicate an irritation of the upper respiratory tract.

3.2.2. Mice

Nonlethal toxicity after inhalation exposure

Dupont (1993b) determined the RD_{50} in male Swiss Webster mice. Animals (four in each group) were exposed for 30 minutes to 5 different concentrations of MAA (4900, 9400, 18000, 27000, and 42000 ppm). Respiratory rates were monitored with plethysmographs before, during and after exposure (10 minutes pre- and post exposure). Vapor concentration was measured by gas chromatography. Respiratory rates (in breaths/min) were recorded every 15 seconds and compared with baseline respiratory rates during preexposure period. The decrease in respiratory frequency was dose-dependent (for details see Table 4). A slight sensory irritation, indicated by an altered breathing pattern, was observed at 4900 ppm during the first minutes of exposure. At higher exposures to MAA, moderate to severe sensory irritation occurred almost immediately after onset of exposure. They persisted for the whole exposure duration. The authors conclude that MAA has only a slight sensory irritating potential. A RD_{50} of 22000 ppm was determined. No substance-related mortality occurred. At concentrations of 18000 ppm or higher, ocular discharge during and/or following exposure was observed.

CIIT (1983) conducted a repeated exposure study in B6C3F1 mice. The animals were exposed (whole body) to 100, 500, and 1000 ppm for 2 weeks (10 exposures; 6 h/d). For details see Section 3.3. (Repeated Exposure). During the first day of exposure, animals showed increased activity at 1000 ppm. Hypoactivity and prostration occurred in one male mouse. Severe necrosis of the nasal mucosa and submucosa were observed after first exposure. No treatment-related clinical signs were noticed at 100 and 500 ppm after the first exposure.

TABLE 4. Summary of Nonlethal Inhalation Data in Laboratory Animals

Species	Conc. (ppm)	Exposure	Number of animals Most important effects	Reference
Rat	1200	4 h	10 Animals; nose-only; analytical conc.; aerosol/vapor; irregular respiration, lethargy, discharge	DuPont (1993a)
Rat	2000	7 h	3 Animals; whole-body; nominal conc.; definite eye irritation; weight loss	Dow Chemicals (1956)
Rat	20	6 h/d 4 d	10 Animals; repeated exposure whole-body; analytical conc.; vapor; minimal to slight degeneration of olfactory epithelium, rhinitis, larynx lymphocyte infiltration, hyperkeratosis	CIIT (1984) See Section 3.3
Rat	100	6 h/d 4 d	As at 20 ppm; slightly increasing effect size and/or number of affected animals	CIIT (1984) See Section 3.3
Rat	300	6 h/d 4 d	10 Animals; repeated exposure whole-body; analytical conc.; vapor; degeneration of olfactory epithelium, rhinitis, ulceration	CIIT (1984) See Section 3.3
Rat	1300	5 h/d 5 d	4 Animals; repeated exposure nose and eye irritation	Gage (1970) See Section 3.3
Rat	100	6 h/d 5 d/wk, 2 wk	10 Animals; repeated exposure whole-body; analytical conc.; vapor hyperplasia, metaplasia, acute inflammation	CIIT (1983) See Section 3.3
Rat	500	6 h/d 5 d/wk, 2 wk	10 Animals; repeated exposure whole-body; analytical conc.; vapor; necrosis, inflammation, hyperplasia, metaplasia, hyperkeratosis of eyelid	CIIT (1983) See Section 3.3
Rat	1000	6 h/d 5 d/wk, 2 wk	10 Animals; repeated exposure whole-body; analytical conc.; vapor; nasal discharge; severe necrosis of nasal mucosa /submucosa; cornea keratitis	CIIT (1983) See Section 3.3
Rat	300	6 h/d 15 days	23 Pregnant females; repeated exposure whole-body exposure; analytical conc.; decreased weight gain and food consumption	Saillenfait (1999) See Section 3.3
Mouse	4900 9400 18000 27000 42000 22000	30 min	8.1% Decrease in respiratory rate 39.6% Decrease in respiratory rate 44.8% Decrease in respiratory rate 52.0/57.6% Decrease in respiratory rate 62.8% Decrease in respiratory rate Head/nose exposure; analytical conc. Ocular discharge at and above 18000 ppm RD_{50} calculated	DuPont (1993b)
Mouse	20	6 h/d 4 d	10 Animals; repeated exposure whole-body; analytical conc.; vapor; no effects reported	CIIT (1984) See Section 3.3
Mouse	100	6 h/d 4 d	10 Animals; repeated exposure whole-body; analytical conc.; vapor; no effects reported	CIIT (1984) See Section 3.3
Mouse	300	6 h/d 4 d	10 Animals; repeated exposure whole-body; analytical conc.; vapor; degeneration of olfactory and necrosis of respiratory epithelium	CIIT (1984) See Section 3.3

TABLE 4. Summary of Nonlethal Inhalation Data in Laboratory Animals

Species	Conc. (ppm)	Exposure	Number of animals Most important effects	Reference
Mouse	100	6 h/d 5 d/wk, 2 wk	10 Animals; repeated exposure whole-body; analytical conc.; vapor; no clinical signs and injuries	CIIT (1983) See Section 3.3
Mouse	500	6 h/d 5 d/wk, 2 wk	10 Animals; repeated exposure whole-body; analytical conc.; vapor; necrosis, acute inflammation	CIIT (1983) See Section 3.3
Mouse	1000	6 h/d 5 d/wk, 2 wk	10 Animals; repeated exposure 3 animals died after first exposure whole-body; analytical conc.; vapor; severe necrosis of nasal mucosa/submucosa	CIIT (1983) See Section 3.3

3.3. Repeated Exposure

Gage (1970) reported nose and eye irritation in rats (2 of each sex) exposed to 1300 ppm for 5 days (5 h/day). After exposure a weight loss was observed. Blood and urine tests, as well as pathological examinations revealed no alterations. Exposure to 300 ppm for 20 days resulted in a slight congestion of kidneys, which was, however, indicated as doubtful by the author. No further information was given.

CIIT (1983) conducted a two week study in rats (Fischer-344 and Sprague-Dawley) and in mice (B6C3F1). Five animals of each species/strain and sex were exposed (whole body) to 100, 500, or 1000 ppm (6 h/d, 5 d/wk). Measurement of concentration was conducted by HPLC. The animals were thoroughly evaluated every day before and after exposure and periodically observed during the exposure period. Examination for gross lesions and histopathology after 10 exposures was conducted on nasal turbinates (4 sections), trachea, and lungs.

During the first day of exposure, animals of all strains developed increased activity at 1000 ppm. Hypoactivity and prostration was observed in one male mouse. Sprague-Dawley rats showed lacrimation, crusty eyes, and a clear nasal discharge. No obvious treatment-related clinical signs were noticed at 100 and 500 ppm after the first exposure.

No mortality was observed at 100 ppm and 500 ppm. At 1000 ppm all mice (day 1 - 4, 3 after the first exposure), all Fischer-344 (days 4 and 5) and 1 Sprague-Dawley rat (following 11th exposure) died. After 10 exposures at 100 ppm, animals of the three strains were virtually free of abnormal clinical observations. Histopathology of the 100 ppm-groups revealed changes of the nasal mucosa in rats, i.e. minimal to moderate hyperplasia (Fischer-344 and Sprague-Dawley), mild to minimal metaplasia of the respiratory epithelium (Sprague-Dawley), or acute inflammation (Fischer-344). No treatment-related lesions were present in mice.

At 500 ppm histological lesions in the nasal turbinates were evident in all rat strains and mice. For mice these lesions consisted of slight acute necrosis with associated inflammation of the nasal mucosa. For Fischer 344 rats these lesions consisted of mild necrosis of the nasal mucosa accompanied by acute inflammation, metaplasia of the respiratory epithelium, and mild

hyperkeratosis of the eyelid. For Sprague-Dawley rats these lesions consisted of hyperplasia and metaplasia of the nasal mucosa, as well as small focal areas of necrosis.

At 1000 ppm severe necrosis of the nasal mucosa and submucosa was observed after the first exposure in mice. Fischer-344 and Sprague-Dawley rats showed acute necrosis of the nasal mucosa and submucosa and mild keratitis of cornea.

Occasionally, irregular breathing, crusty nose, eyes and muzzle were observed at exposure concentrations of 500 ppm and 1000 ppm.

CIIT (1984) conducted a 90-day inhalation study with B6C3F1 mice, Sprague-Dawley rats, and Fischer-344 rats. Twenty animals each species/strain and sex were exposed (whole body) to 20, 100, or 300 ppm for 6 hr/d, 5 days/wk. A control group of 20 animals of each species/strain and sex was exposed to clean air and handled in similar matter to the exposed animals. Measurement of concentration was conducted by HPLC. After the fourth exposure, animals were examined and an interim sacrifice was conducted on 10 animals on day 5. At all concentrations after 4 exposures, minimal to mild dose-related rhinitis, inflammation of respiratory epithelium, and degeneration of the olfactory epithelium in both male and female rats were observed . Eosinophilic globules were found in the sustentacular cells of the olfactory epithelium in mice. Mice appeared most susceptible regarding incidence and severity of histopathological findings at 300 ppm, followed by Fischer-344 rats and Sprague-Dawley rats. Mice, but not rats, showed additional necrosis of the respiratory epithelium at 300 ppm. The males of each species were affected more than the females. Some of these local effects have been also observed in control animals, however with lower incidences. Effects are summarized in Table 5. Pathological and histopathological findings after 90-day exposure are not described.

Labonova et al. (1979) conducted a 4month study in rats and mice at 0.12, 2.5, or 61.7 ppm. The animals revealed reversible, dose-dependent “dystrophic and destructive changes” in the lungs. No further data are available. According to ECETOC (1996), the results are of questionable validity.

TABLE 5. Respiratory effects in rats and mice after 4 exposures to MAA (CIIT, 1984)

ppm	0		20		100		300		Species/Strain
Effects, Respiratory	M	F	M	F	M	F	M	F	
Rhinitis	0	0	4	2	2	4	9	7	F344 Rats; 10/sex/concentration examined
Hyperplasia, goblet	0	0	0	0	0	0	3	6	
Ulceration	0	0	0	0	0	0	3	1	
Necrosis	0	0	0	0	0	0	1	0	
Hyperkeratosis	0	0	0	0	0	0	1	3	
Exudate	0	0	0	0	0	0	3*	4	
Rhinitis	2	0	3	2	4	4	6	6	S-D Rats 10/sex/concentration examined
Exudate	0	0	1	0	0	0	3	3	
Ulceration	0	0	0	0	0	0	1	1	
Hyperkeratosis	0	0	0	1	2	3	2	7	
Lung lymphocytes	3	4	7	3	8	6	7	6	
Larynx lymphocytic infiltrate	0	0	1	1	1	2	1	2	
Rhinitis	0	0	0	0	0	0	5	6*	B6C3F1 -Mice 10/sex/concentration examined
Necrosis	0	0	0	0	0	0	7*	6	
Exudate	0	0	0	0	0	0	2*	1*	
Ulceration	0	0	0	0	0	0	0	1	
Larynx inflamm	0	0	0	0	0	0	0	1	

* Effects not restricted level A of the turbinates (most anterior), but also observed at level B,C, or D (posterior sections)

3.4. Developmental / Reproductive Toxicity

Saillenfait et al. (1999) investigated the developmental toxicity of MAA following inhalation exposure in Sprague-Dawley rats. Groups of 19 - 25 pregnant females were exposed (whole body) to 50, 100, 200, and 300 ppm for 6 hours per day from day 6 to day 20 of gestation. The exposure was conducted in a 200 L glass/stainless-steel inhalation chamber. MAA was delivered at a constant rate of the liquid with an infusion pump at the top of a heated glass column filled with glass beads. Compressed heated air was introduced at the bottom of the glass column. MAA concentrations were monitored by gas chromatography. At 300 ppm significant decreases in maternal weight gain and food consumption during the 15 days of exposure were noticed. No effects were observed within the other dose groups. No signs of toxicity related to embryolethality or teratogenicity were observed.

3.5. Sensitization

Parker and Turk (1983) observed no contact sensitivity in guinea pigs (outbred Hardley strain) using the Polak test protocol.

3.6. Mutagenicity/Genotoxicity

A Salmonella mutagenicity test with the strains TA1535, TA1537, TA98, and TA100 was negative with and without metabolic activation (rat and hamster S-9 mix) (Haworth et al. 1983). Cytotoxicity was observed at 4000 mg/plate .

No other tests on mutagenicity and genotoxicity are available. However, it is expected that MAA, like methyl methacrylate, is not genotoxic in vivo (see TSD for methyl methacrylate).

3.7. Carcinogenicity

No carcinogenicity studies are available. However, studies with methyl methacrylate are applicable for the assessment of carcinogenicity following MAA exposure., These studies include a comprehensive carcinogenicity study in rats and mice conducted by NTP (1986) and revealed no carcinogenic potential (see TSD for methyl methacrylate).

3.8. Summary

The effects of MAA include irritation and corrosion to respiratory tract, eyes and skin (Food and Drug Research Laboratories 1973; Greim et al. 1995).

At 1000 ppm and above for up to 6 hours of exposure, MAA caused increased motor activity, lethargy, respiratory distress, lung noises, nasal, ocular and vaginal discharge, and corrosive effects to the eyes (Food and Drug Research Laboratory 1973; DuPont 1993a; Gage 1970; CIIT 1983). Pathological examination revealed severe pulmonary edema, hemorrhage, and discoloration. DuPont (1993a) reported an LC_{50} of 1980 ppm for a 4-hour exposure.

For the concentration range below 1000 ppm, data on effects are sparse. Repeated exposure of 6 hours (4 or 10 exposures) to concentrations below 500 ppm led to degeneration of olfactory epithelium, rhinitis, ulceration, inflammation, hyperplasia, and metaplasia of nasal mucosa (CIIT 1983, 1984).

As described by DuPont (1993a), lethality and other toxic effects (closed eyes, sores, weakness, and body-weight loss) can develop after exposure. Delayed effects were also reported by CIIT (1984), where an aggravation of olfactory epithelium ulceration following 4 exposures was observed.

Using biochemical investigations in the isolated upper respiratory tract after exposure of rats to 410 ppm for 60 minutes, no indications of irritation were observed by Morris and Frederick (1995) and Morris (1992). The measured biochemical parameters were nasal albumin, protein and NPSH (Non-protein sulfhydryl) levels. The no-effect concentration of 410 ppm must be regarded in context with the respective results from the exposure to the less toxic MAA ester, methyl methacrylate, where 500 ppm already cause a significant decrease in NPSH levels of

approximately 25% (see TSD for methyl methacrylate). Moreover, cyclic flow studies do not perfectly mimic the normal breathing (Morris 1992). Therefore, the study design seems difficult to interpret and not suitable for absolute potency quantification.

DuPont (1993b) reported a RD_{50} of 22000 ppm.

There are no indications for sensitizing properties of MAA.

No carcinogenicity studies are available for MAA. There is one negative mutagenicity test. However, the ester of MAA, methyl methacrylate, does not express a genotoxic and mutagenic potential in vivo, and there is evidence suggesting lack of carcinogenicity of methyl methacrylate in experimental animals (IARC 1994).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

MAA is rapidly absorbed following inhalation and oral exposure (ECB 2002). Although no specific investigations were conducted, a dermal absorption can be assumed as lethality is demonstrated after dermal exposure to MAA. NIOSH (1992) provided the REL-TWA value with a skin“ notation.

There are no studies that address the toxicokinetics of MAA in vivo. Most of the available data are derived from metabolism studies with its methyl ester, methyl methacrylate. Methyl methacrylate is metabolized to MAA by carboxylesterase.

From investigations on the surgically isolated upper respiratory tract (URT) of anaesthetized rats, Morris and Frederick (1995) and Morris (1992) concluded that most of the MAA does not reach the lung. A deposition efficiency of 95% was measured in the URT of rats following exposure to 133 ppm. However at exposures above 1000 ppm, lung effects (lung noises and edema) have been reported for the rat (Food & Drug Research 1973; DuPont 1993a). Therefore it can be assumed that with increasing exposure MAA is not totally removed by the upper respiratory tract.

After single administration of 8 mmol/kg methyl methacrylate (equivalent 800 mg/kg bw) by stomach tube, MAA was detected in rat blood serum after 5 minutes at a concentration of 0.5 mmol (Bereznowski 1995). The concentration peak was reached after 10 to 15 minutes leading to about 0.8 mmol in serum, followed by a decrease to nearly undetectable concentrations after 1 hour. The author assumes that MAA is removed efficiently from blood serum by liver uptake.

Bratt and Hathway (1977) and Crout et al. (1982) investigated the metabolism of MAA. The Coenzyme A ester of MAA is a normal intermediate in the catabolism of valine (Crout et al. 1979). The enzyme enoyl-CoA-hydratase, that converts MAA into the coenzyme A ester (ECB 2002), would permit MAA to enter a normal catabolic pathway leading to CO_2. Bratt and Hathway (1977) found that up to 65% of administered methyl methacrylate is exhaled as CO_2 within 2 hours in rats. MAA is metabolized through the same pathway as the amino acid valine, irrespective of the route of administration, both leading to methylacrylyl-CoA which enters the citric acid cycle (Maclaine Pont 1991). Methacrylyl-CoA is converted into methylmalonyl-CoA

which is rearranged into succinyl-CoA (Crout et al. 1982). Succinyl-CoA enters the tricarboxylic acid cycle and is oxidized to carbon dioxide.

4.2. Mechanism of Toxicity

MAA acts locally with irritating and corrosive properties at the site of .exposure. The toxicity of MAA is presumably completely due to the intact molecule. No metabolites were identified that contribute to the toxic effects. Inhalation of MAA results in the deposition at the upper respiratory tract, where it causes necrosis of the nasal mucosa and submucosa, degeneration of olfactory epithelium, inflammation, rhinitis, and breathing problems (DuPont 1993a,b; Gage 1970; CIIT 1983, 1984). Additionally, effects on the eyes, e.g. lacrimation, discharge, keratitis, and corneal opacity, have been reported following inhalation exposure (Gage 1970; CIIT 1983; DuPont 1993a). At concentrations above 1000 ppm effects on the lower respiratory tract, e.g. lung noises and edema, have been observed in the rat (Food & Drug Research 1973; DuPont 1993a).

MAA is considered a weak sensory irritant with a RD_{50} of 22000 ppm (DuPont 1993b).

No information is available on specific systemic effects of inhalation exposure to MAA. Effects as weakness, lethargy, body-weight decrease, reported in several studies, can not be attributed to a definite toxic mechanism. An indication of systemic effects of MAA on the cardiovascular system and respiration is provided by Mir et al. (1974), who observed changes in blood pressure, heart rate, and respiratory rate after i.v. administration to dogs, as well as by CIIT (1983), where hyper- and hypoactivity have been reported.

4.3. Structure Activity Relationships

Morris and Frederick (1995) assume that the acid metabolite of various esters is responsible for toxicity as exposure to acid vapors produces similar lesions. Ester exposure lead to acid production intracellularly, whereas inspired acid initially deposits on the mucous lining layer and diffuses through the layer after interacting with the epithelium. The authors expect that the acid metabolite is responsible for the toxicity and that the acid vapors would be more potent than the parent compound in producing respiratory toxicity. By comparing 4-hour LC_{50} values of methyl methacrylate (7093 ppm) and MAA (1980 ppm), this effects seems to be true for this ester/acid pair.

For both acrylic acid and MAA, similar mechanisms of toxicity are assumed. The toxic effects following inhalation exposure to acrylic acid are focused on the olfactory epithelium, where irritative and corrosive injuries occur (o. V. 2003). At higher exposure the lower respiratory tract is affected. Similarly to MAA no metabolite of acrylic acid was identified that contributes to the toxic effects. Therefore toxicodynamic and toxicokinetic mechanism are comparable for both substances.

In a non-published report, a hybrid computational fluid dynamics and physiologically-based pharmacokinetic (CFD-PBPK) inhalation model for MAA has been constructed based on modification of a CFD-PBPK model for acrylic acid (Frederick 1998). Results relate to species differences (see section 4.4.1.).

4.4. Other Relevant Information

MAA has an acrid, repulsive odor and therefore shows good warning properties. Odor threshold concentrations of 0.032 ppm and of 0.17 ppm have been reported (Klimkina et al. 1973; Grudzinskii 1998, as quoted in secondary literature).

Grudzinskii (1988) report some odor detection limits on other acrylates, e.g., methyl methacrylate (0.2 to 1.2 mg/m^3) and describe the testing on MAA: In this study 6 concentrations were used (0.4, 0.6, 1.0, 1.5, 2.0, 3.0 mg/m^3). Twenty-one healthy persons from 22 to 30 years of age were asked to report the odor detection threshold. This ranged between 0.6 to 3 mg/m^3, The lowest concentration was only detected by a few persons. An EC_{16} of 1.8 mg/m^3 was calculated and a limit value of 0.25 mg/m^3 was derived. (For comparison, acrylic acid was assigned an EC_{16} of 0.24 mg/m^3 and a limit value of 0.08 mg/m^3) [personal translation of Russian original article]. The data are not sufficiently detailed to derive a level of odor awareness (LOA) using the procedure of Doorn et al. (2002).

4.4.1. Species Variability

Regarding the relevant endpoints of toxicity, no major differences in toxicokinetic and toxicodynamic are to be expected. MAA is an irritating and corrosive contact-site acting substance, and the local toxicity does not require metabolism of MAA. The different breathing patterns between humans and rats (nose/mouth breathers versus nose-breathers) may be taken into account for species variability.

From studies with the ester of MAA, methyl methacrylate, it is assumed, that humans are less susceptible against vapors than experimental animals, e.g. rats and mice. The nasal cavity anatomy differs between rats an humans (Muttray et al. 1997; Lomax et al. 1997; Andersen and Sarangapani 1999). In rats, the nasal cavity has a greater capacity for reaction with MAA. Additionally, in humans, only 8% of the nasal mucous membranes consist of olfactory epithelium, however 50% of the nasal mucous membranes consist of olfactory epithelium in rats. The olfactory epithelium in humans is located in the secondary air flow, whereas the olfactory epithelium is in the primary air flow in rats. Consequently, in rats more of MAA is delivered to target tissues compared to humans. Because toxic effects following exposure to methyl methacrylate are due to the formation of MAA it can be assumed, that susceptibilities would be similar following direct exposure to MAA.

Frederick (1998) and Frederick et al. (1998) stated that the dominant factor influencing interspecies differences in susceptibility to inhaled irritants would be the olfactory dose. Based on a mathematic model that includes computational fluid dynamics and physiologically-based pharmacokinetic modeling, the authors determined, that the olfactory epithelium in the dorsal meatus region of the rat nasal cavity is exposed to two- to threefold greater concentrations of acrylic acid in the mucus than the human olfactory epithelium. The similar mode of action between acrylic acid and MAA permit the conclusion that the same relationship applies for MAA. However, in this calculation increased activity levels in humans have not been taken into account and may result in similar sensitivity of both species (Frederick 1998).

Comparable studies conducted with rats and mice show a higher susceptibility at lethal exposure concentrations of MAA in mice. At nonlethal concentrations, varying susceptibilities

for rats and mice have been observed. Regarding the species differences among rodents, Barrow et al. (1986) calculated the dose of acrylic acid delivered to the nasal epithelium as about 2 times higher in mice compared to rats, resulting in more severe lesions at upper respiratory tract observed at 75 ppm.

4.4.2. Susceptible Populations

No indications for a higher susceptibility to MAA within the population are available. MAA is a local acting substance and no metabolite contributes to the toxic effect. Therefore, it is likely that there is little difference between individuals in the reaction of the respiratory tract to MAA.

4.4.3. Concentration-Exposure Duration Relationship

As demonstrated by CIIT (1984), corrosion and irritative effects on the respiratory tract and eyes increased with increasing exposure duration as shown by the comparison of effects from a 4 day and 90 day exposure. During single exposures to low, non cytotoxic concentrations of MAA, no marked increase in effects with time is expected for the very slight irritative effects relevant for AEGL-1 by analogy with acrylic acid (o.V. 2003). At higher concentrations relevant for AEGL- 3, an increasing proportion of MAA is not removed by the upper respiratory tract but reaches the lung. For effects on the lower respiratory tract and for pronounced effects on the nasal passages (AEGL-2-level), a concentration - exposure duration relationship is assumed for MAA by analogy with acrylic acid (o. V. 2003).

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

There are no valid human data to be used for the derivation of AEGL-1. The effect concentration of 113 ppm reported from acute workplace exposure showed no effect on the respiratory tract, but showed severe effects on the eye (corneal burn). Such effects are above AEGL-1.

Exposure concentrations reported in studies with limited validity revealed irritation of respiratory tract and eyes below 1 ppm (Grudzinskii 1988; Rumyantsev et al. 1981). The occurrence of these effects seem questionable for the reported exposure concentration.

5.2. Summary of Animal Data Relevant to AEGL-1

No adequate data on single exposure are available that would be suitable for AEGL-1 derivation.

A study with repeated exposure (4 days, 6 hours/day) to 20 ppm showed rhinitis, discharge, inflammation and slight degeneration of olfactory epithelium in 2 strains of rats (CIIT 1984). These effects were dose-related and showed a higher severity at 100 ppm and 300 ppm (see table 5). At 300 ppm mice were similarly affected.

In a study with repeated exposure (10 days, 6 hours/day, 5 animals/sex/strain/exposure level) with 2 strains of rat and 1 strain of mice (Sprague-Dawley rats, Fischer-344 rats, and

B6C3F1 mice) no obvious clinical effects have been observed after first day exposure to 100 or 500 ppm, but were seen after exposure to 1000 ppm (CIIT 1983). After 10 exposures, necrosis, acute inflammation, hyperplasia and metaplasia of the olfactory epithelium were reported at 100 ppm in rats, but not in mice. Necrosis of nasal mucosa as well as hyperkeratosis were reported at 500 ppm (CIIT 1983).

A RD_{50} of 22000 ppm was established by DuPont (1993b).

5.3. Derivation of AEGL-1

The effects in rats, i.e. rhinitis, inflammation and minimal to light degeneration of olfactory epithelium observed following exposure to 20 ppm for a duration of 6 hours for 4 successive days (CIIT 1984) are judged as relevant for the AEGL-1 derivation. Although degenerative effects on mucosa are regarded as above AEGL-1 level, these effects have only been documented after repeated exposure.

Alternatively, the no observed effect concentration of 100 after first 6 hour exposure (CIIT 1983) could be used as a starting point. An additional modifying factor of 3 would be used because of the lack of appropriate histopathology in this study. This approach would result in a very similar starting point and very similar AEGL-1 values.

As demonstrated in Sections 4.4.1 and 4.4.2, no major differences in interspecies and intraspecies variability are to be expected due to the local acting irritative and corrosive properties of MAA. By comparing MAA with its ester, methyl methacrylate, as well as with acrylic acid it can be assumed that humans are less susceptible to MAA vapors than rats or mice regarding effects at the upper respiratory tract. This is confirmed by unpublished calculations from Frederick (1998). Based on a mathematical model that includes computational fluid dynamics and physiologically-based pharmacokinetic modeling, the author determined that the olfactory epithelium in the dorsal meatus region of the rat nasal cavity is exposed to two- to threefold greater concentrations of MAA compared to humans (no physical activity assumed). Therefore, an interspecies uncertainty factor of 1 was applied. No major toxicokinetic and toxicodynamic differences for a direct and mainly locally acting substance are to be expected. Therefore an intraspecies uncertainty factor of 3 was applied, leading to an overall uncertainty factor of 3.

As discussed in Section 4.4.3, an increase in severity of slight irritative effects on the upper respiratory tract with increasing exposure duration is not expected . Therefore, the experimental derived exposure value of 20 ppm was used for all time points. This approach is in accordance with the Standing Operating Procedures (NRC 2001) for slight irritating effects.

The AEGL-1 (6.7 ppm) for MAA is between those for acrylic acid (1.5 ppm) and methyl methacrylate (17 ppm) and is, thus, supported by plausibility considerations on irritating potency (see Appendix C for a more complete comparison of acrylates and acrylate esters).

MAA has an acrid, repulsive odor and therefore shows good warning properties. Odor threshold concentrations of 0.17 ppm have been reported (Grudzinskii 1988).

TABLE 6. AEGL-1 Values for Methacrylic Acid*				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)

* Relevant skin uptake of methacrylic acid can not be excluded.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

There are no valid human data to be used for the derivation of an AEGL-2.

Medical examinations of workers exposed to 113 ppm revealed no respiratory effects, but corrosive effects on eyes and skin toxicity (Dow Chemicals 1977). An exposure duration was not reported, therefore these data are not suitable for the derivation of AEGL-values.

6.2. Summary of Animal Data Relevant to AEGL-2

No studies with single inhalation exposure to MAA are available that would be suitable for AEGL-2 derivation. At the lowest non-lethal concentration of 1200 ppm (4 hours), irregular respiration, lung noises, gasping and lethargy have been observed (DuPont, 1993a). These effects are above AEGL-2.

A study with four 6-hour exposures to 100 and 300 ppm showed mild rhinitis, exudate as well as inflammation of respiratory epithelium and ulceration of olfactory epithelium in two rat strains (Fischer-344 and Sprague-Dawley) and one mouse strain (B6C3F1) at 300 ppm (CIIT, 1984). These effects were less pronounced and reversible at 100 ppm. Corrosion and irritative effects on the respiratory tract and eyes increase in severity with increasing exposure duration. An exposure of 500 ppm for 2 weeks (10 6-hour exposures) resulted in metaplasia, hyperplasia and necrosis with inflammation of the nasal mucosa in Fischer-344 rats, Sprague-Dawley rats, and B6C3F1 mice (CIIT 1983). In this study, 1000 ppm were partially lethal for mice after the first 6-hour exposure, but not for rats. Severe necrosis of nasal mucosa and submucosa, as well as keratitis was also observed at this concentration.

Pregnant Sprague-Dawley rats showed significant decreases in weight gain and food consumption at 300 ppm, but not at 200 ppm, following 15 exposures for 6 hours/day (Saillenfait et al. 1999).

A RD_{50} of 22000 ppm was established by DuPont (1993b).

6.3. Derivation of AEGL-2

The effects observed at 100 ppm and 300 ppm in the repeated exposure study (4 x 6 hours) conducted by CIIT (1984) are seen as relevant for AEGL-2 derivation. The effects observed at 100 ppm, rhinitis and inflammation of the respiratory epithelium are reversible. At 300 ppm more severe effects (irreversible ulceration of olfactory epithelium) were observed. Therefore, the 100 ppm concentration was chosen for the AEGL-derivation.

As demonstrated in Sections 4.4.1 and 4.4.2, no major differences in interspecies and intraspecies variability are to be expected due to the local acting irritative and corrosive properties of MAA. By comparing MAA with the similar acting acrylic acid, it can be assumed that humans are less susceptible than rats to effects of MAA in the upper respiratory tract. Therefore, an interspecies factor of 1 was applied. An uncertainty factor of 3 was applied for intraspecies variability. This factor is used to cover the toxicodynamic and toxicodynamic differences between individuals.

The experimental derived exposure value of 100 ppm was scaled using the equation $C^n \times t = k$ (ten Berge et al. 1986). No suitable data to derive a substance specific exponent n for time extrapolation were available. Thus, the default value of n = 3 in the exponential function was used for extrapolation from the 6-hour exposure to short durations and n = 1 was used for the 8 hour duration. Because extrapolation from 6 hours to short durations of less than 30 minutes leads to a very high uncertainty the value for 10 minutes was set equal to the value for 30 minutes.

The AEGL-2 (25 ppm, 8 hours exposure) for MAA is between those for acrylic acid (14 ppm) and methyl methacrylate (50 ppm) and is, thus, supported by plausibility considerations on irritating potency (see Appendix C for a more complete comparison of acrylates and acrylate esters).

TABLE 7. AEGL-2 Values for Methacrylic Acid *

10-min	30-min	1-h	4-h	8-h
76 ppm (270 mg/m^3)	76 ppm (270 mg/m^3)	61 ppm (220 mg/m^3)	38 ppm (140 mg/m^3)	25 ppm (90 mg/m^3)

* Relevant skin uptake of methacrylic acid can not be excluded.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human experiences with MAA concentrations that cause serious long lasting or irreversible effects following inhalation exposure are available.

7.2. Summary of Animal Data Relevant to AEGL-3

Irregular respiration, lethargy, lung noise and colored discharge have been observed in rats exposed to 1200 ppm for 4 hours (DuPont 1993a). At the next higher concentration of 1650 ppm, 1 animal out of 10 died and similar typical clinical observations have been made at 1200 ppm, however with higher incidence of affected animals. Additionally corneal opacity was reported for 1 animal. From this study a LC_{50} of 1980 ppm was derived.

In contrast to the observation by DuPont (1993a), Dow Chemicals (1956) observed no lethality and no essential alterations at necropsy in 3 rats exposed for 7 hours to the saturated vapor concentration, which was calculated as 2000 ppm by the authors (nominal concentration). Only a definite eye irritation and slight to moderate weight losses were reported.

6-hour exposure to 1000 ppm was lethal for 3 of 10 mice, but no lethality was observed in rats (CIIT 1983). During exposure to this concentration, animals of two rat and one mouse strains developed increased activity and in male mice hypoactivity and prostration in 1 animal were reported. Occasionally, respiratory problems, lacrimation, crusty eyes, and a clear nasal discharge were observed in Sprague-Dawley rats. Mice revealed severe necrosis of the nasal mucosa and submucosa.

Necropsy of animals that died within 19 minutes of exposure to approx. 57000 ppm revealed severe pulmonary edema and hemorrhage (Food and Drug Research Laboratory 1973).

7.3. Derivation of AEGL-3

The most reliable data to derive AEGL-3 values are from DuPont (1993a). The LC_0 from this study was 1200 ppm for a 4-hour exposure in rats. In this study some uncertainties exist concerning the increasing aerosol ratio with increasing exposure concentration. However, because the study is with nose-only exposure and a relevant amount is vaporized, these uncertainties are considered to be tolerable.

The given analytical concentrations and effect sizes by DuPont (1993a) allow for derivation of a benchmark concentration, using the software BMDS from EPA (1999), version 1.3.2. This dose-response analysis results in a $BMCL_{05}$ of 1414 ppm (log probit) and a BMC_{01} of 1528 ppm. A graphical presentation of this benchmark derivation is given in Appendix B. As BMC_{01} is identical to an observed lethal effect concentration of 1650 ppm (4 hours) in the same study (DuPont 1993a) it was not regarded to be the appropriate starting point for the AEGL-3 derivation. Therefore, the $BMCL_{05}$ was used.

As demonstrated in Sections 4.4.1 and 4.4.2, no major differences in interspecies and intraspecies variability are to be expected due to the local acting irritative and corrosive properties of MAA. There is some suggestion that mice are more susceptible to MAA than rats. Three of 10 mice, but no rat died following single 6-hour exposure to 1000 ppm (CIIT 1983). For the derivation of AEGL-3 values, the rat study by DuPont (1993) was however seen as more appropriate due to the higher quality of a nose-only study. No nose-only study with mice is available. Therefore, the data derived from exposure in rats were used to derive AEGL-3 values and an interspecies factor of 3 was applied. This factor covers the uncertainty regarding species differences occurring at the lower respiratory tract. Moreover this factor is justified by the observation that for acrylic acid a factor of 3 was chosen based on a more comprehensive database. An uncertainty factor of 3 was applied for intraspecies toxicodynamic and toxicokinetic variability. This results in a total uncertainty factor of 10.

The calculated $BMCL_{05}$ of 1414 ppm was scaled to AEGL time frames using the equation $C^n \times t = k$ (ten Berge et al. 1986). No suitable data to derive a substance specific exponent n for time extrapolation were available. Thus, the default value of n = 3 in the exponential function was used for extrapolation from the 4-hour exposure to short durations and n = 1 was used for the 8 hour duration. Because extrapolation from 4 hours to short durations of less than 30 minutes leads to a very high uncertainty the value for 10 minutes was set equal to the value for 30 minutes.

The AEGL-3 for MAA (71 ppm at 8 hours) is between those for acrylic acid (58 ppm) and methyl methacrylate (160 ppm) and is, thus, supported by plausibility considerations on relative effect potency of these substances (see Appendix C for a more complete comparison of acrylates and acrylate esters).

TABLE 8. AEGL-3 Values for Methacrylic Acid*

10-min	30-min	1-h	4-h	8-h
280 ppm (1000 mg/m^3)	280 ppm (1000 mg/m^3)	220 ppm (790 mg/m^3)	140 ppm (500 mg/m^3)	71 ppm (250 mg/m^3)

*Relevant skin uptake of methacrylic acid can not be excluded.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

The derived AEGL values for various levels of effects and duration of exposure are summarized in Table 9.

For all effect levels, an uncertainty factor of 3 was used for intraspecies variability. The effects reported following exposure to lower levels of MAA in experimental animals, i.e. AEGL-1 and AEGL-2 levels, were mainly restricted to the nasal cavity. For such effects evidence is available that humans are less susceptible than rats. Therefore, an interspecies factor of 1 was used in AEGL-1 and AEGL-2 derivation. At (sub)lethal concentrations, the lower respiratory tract is affected to an increasing degree. Because no information is available concerning species susceptibilities at the lower respiratory tract, an interspecies uncertainty factor of 3 was used for the AEGL-3.

The AEGL-1 values are based on rhinitis, inflammation, and slight degeneration of olfactory epithelium observed in rats (Fischer-344 and Sprague-Dawley), that have been exposed to 20 ppm for 6 hours at 4 consecutive days (CIIT 1984). Because no major increase in severity of effects over time is expected, the derived value of 6.7 ppm was used for all time points.

The AEGL-2 values are based on inflammation, exudate and ulceration of olfactory epithelium reported in the study by CIIT (1984). These effects were described after repeated exposure to 300 ppm (4 times) in 2 different rat strain (Fischer-344 and Sprague-Dawley) and in mice, but were not seen at 100 ppm. The time scaling was conducted according to the default approach.

The AEGL-3 values are based on a $BMCL_{05}$ of 1414 ppm calculated from a study by DuPont (1993a). At the LC_0 of 1200 ppm for a 4-hour exposure irregular respiration, lethargy, lung noise and colored discharge were observed in CrlCD®BR rats, and the next higher experimental exposure of 1650 ppm in this study led to lethal effects in 1 out of 10 animals. The time scaling was conducted according to the default approach.

A category plot is presented in Figure 1. No human data are suitable to show in the category plot.

TABLE 9. Summary of AEGL Values*					
Classification	**Exposure Duration**				
	10-min	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1 (Nondisabling)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)	6.7 ppm (24 mg/m^3)
AEGL-2 (Disabling)	76 ppm (270 mg/m^3)	76 ppm (270 mg/m^3)	61 ppm (220 mg/m^3)	38 ppm (140 mg/m^3)	25 ppm (90 mg/m^3)
AEGL-3 (Lethal)	280 ppm (1000 mg/m^3)	280 ppm (1000 mg/m^3)	220 ppm (790 mg/m^3)	140 ppm (500 mg/m^3)	71 ppm (250 mg/m^3)

*Relevant skin uptake of methacrylic acid can not be excluded.

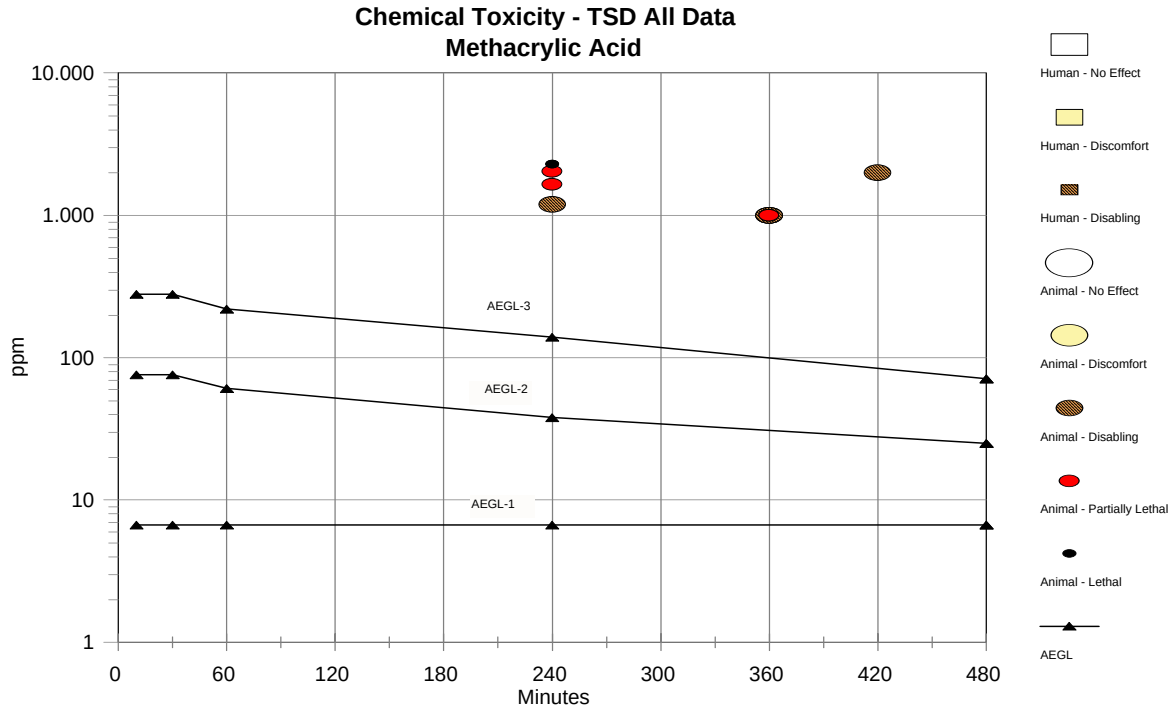

FIGURE 1. Category Plot of Toxicity Data compared to AEGL Values

8.2. Comparison with Other Standards and Guidelines

TABLE 10. Existent Standards and Guidelines for Methacrylic Acid

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	6.7 ppm	6.7 ppm	6.7 ppm	6.7 ppm	6.7 ppm
AEGL-2	76 ppm	76 ppm	61 ppm	38 ppm	25 ppm
AEGL-3	280 ppm	280 ppm	220 ppm	140 ppm	71 ppm
ERPG-1 (AIHA)[a]					
ERPG-2 (AIHA)					
ERPG-3 (AIHA)					
EEGL (NRC)[b]					
PEL-TWA (OSHA)[c]					
PEL-STEL (OSHA)[d]					
IDLH (NIOSH)[e]					
REL-TWA (NIOSH)[f]					20 ppm "skin"
REL-STEL (NIOSH)[g]					-
TLV-TWA (ACGIH)[h]					20 ppm
TLV-STEL (ACGIH)[i]					---
MAK (Germany)[j]					
MAK Peak Limit (Germany)[k]					
MAC (The Netherlands)[l]					

[a]**ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association** (AIHA 1994)
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]**EEGL (Emergency Exposure Guidance Levels, National Research Council** (NRC 1985)
The EEGL is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace, but avoids death, other severe acute effects and long-term or chronic injury.

[c]**OSHA PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits - Time Weighted Average)** is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.
The OSHA does not currently regulate MAA.

[d]**OSHA PEL-STEL (Permissible Exposure Limits - Short Term Exposure Limit)**
is defined analogous to the ACGIH-TLV-STEL. The OSHA does not currently regulate MAA.

[e]**IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects. No IDLH for MAA was derived.

[f]**NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** (NIOSH 1992) is defined analogous to the ACGIH-TLV-TWA.

[g]**NIOSH REL-STEL (Recommended Exposure Limits - Short Term Exposure Limit)** (NIOSH 1992) is defined analogous to the ACGIH TLV-STEL.

[h]**ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH 1993)
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. Although MAA was judged as less irritating than acrylic acid, the TLV-TWA was set the same, based on the limited animal and human data.

[i]**ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit)** (ACGIH 1993)
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.

[j]**MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration])** (Deutsche Forschungsgemeinschaft [German Research Association] 2003) is defined analogous to the ACGIH-TLV-TWA. For MAA, no MAK values were derived due to the insufficient data base.

[k]**MAK Spitzenbegrenzung (Peak Limit [give category])** (German Research Association 2003)
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. For MAA, no MAK peak limit was derived due to the insufficient data base.

[l]**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.

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APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1

Key Study:	CIIT (1984)
Toxicity endpoint:	Rhinitis, discharge, inflammation and slight degeneration of olfactory epithelium in rats and mice following repeated exposure to 20 ppm for 6 h (4 exposures).
Time scaling:	No time scaling was conducted. Same concentrations for 8 h, 4 h, 1 h, 30 min and 10 min
Uncertainty factors:	1 for interspecies variability 3 for intraspecies variability Combined uncertainty factor of 3
Modifying factor:	None
Calculations:	
10-min AEGL-1	C = 20 ppm 10-min AEGL-1 = 20 ppm/3 = 6.7 ppm (24 mg/m^3)
30-min AEGL-1	C = 20 ppm 30-min AEGL-1 = 20 ppm/3 = 6.7 ppm (24 mg/m^3)
1-h AEGL-1	C = 20 ppm 1-h AEGL-1 = 20 ppm/3 = 6.7 ppm (24 mg/m^3)
4-h AEGL-1	C = 20 ppm 4-h AEGL-1 = 20 ppm/3 = 6.7 ppm (24 mg/m^3)
8-h AEGL-1	C = 20 ppm 8-h AEGL-1 = 20 ppm/3 = 6.7 ppm (24 mg/m^3)

Derivation of AEGL-2

Key Studies:	CIIT (1984)
Toxicity endpoints:	Mild rhinitis, and inflammation of respiratory epithelium following repeated exposure to 100 ppm for 6 h (4 exposures) with additional exudate, ulceration of the olfactory epithelium (rats) and additional necrosis of the respiratory epithelium (mice) at 300 ppm.
Time scaling:	$C^3 \times t$ for extrapolation to 1 h, 30 min $k = 100^3$ ppm$^3 \times 6$ h = 6000000 ppm$^3 \times$ h $C^1 \times t$ for extrapolation to 8 h k = 100 ppm x 6 h = 600 ppm x h The 10-min AEGL-3 was set at the same concentration as the 30-min AEGL-3
Uncertainty factors:	1 for interspecies variability 3 for intraspecies variability Combined uncertainty factor of 3
Modifying factor:	None
Calculations:	
10-min AEGL-3	10-min AEGL-2 = 30-min AEGL-2 = 76 ppm (270 mg/m^3)
30-min AEGL-3	$C^3 \times 0.5$ h = 6000000 ppm^3 h C = 228 ppm 30-min AEGL-2 = 228 ppm/3 = 76 ppm (270 mg/m^3)
1-h AEGL-3	$C^3 \times 1$ h = 6000000 ppm^3 h C = 183 ppm 1-h AEGL-2 = 183 ppm/3 = 61 ppm (220 mg/m^3)
4-h AEGL-3	$C^3 \times 1$ h = 6000000 ppm^3 h C = 114 ppm 4-h AEGL-2 = 114 ppm/3 = 38 ppm (140 mg/m^3)
8-h AEGL-3	$C^1 \times 8$ h = 600 ppm h C = 75 ppm 8-h AEGL-2 = 75 ppm/3 = 25 ppm (90 mg/m^3)

Derivation of AEGL-3

Key Studies:	DuPont (1993a)
Toxicity endpoint:	LC_{50} of 1980 ppm for a 4-h exposure. Calculation of $BMCL_{05}$ with 1414 ppm
Time scaling	$C^3 \times t$ for extrapolation to 1 h, 30 min $k = 1414^3$ ppm^3 x 4 h = 11308583776 ppm^3 x h $C^1 \times t$ for extrapolation to 8 h k = 1414 ppm x 4 h = 5656 ppm x h The 10-min AEGL-3 was set at the same concentration as the 30-min AEGL-3
Uncertainty factors:	3 for interspecies variability 3 for intraspecies variability Combined uncertainty factor of 10
Modifying factor:	None
10-min AEGL-3	10-min AEGL-3 = 30-min AEGL-3 = 280 ppm (1000 mg/m^3)
30-min AEGL-3	$C^3 \times 0.5$ h = 11308583776 ppm^3 h C = 2828 ppm 30-min AEGL-3 = 2828 ppm/10 = 280 ppm (1000 mg/m^3)
1-h AEGL-3	$C^3 \times 1$ h = 11308583776 ppm^3 h C = 2245 ppm 1-h AEGL-3 = 2245 ppm/10 = 220 ppm (790 mg/m^3)
4-h AEGL-3	C = 1414 ppm 4-h AEGL-3 = 1414 ppm/10 = 140 ppm (500 mg/m^3)
8-h AEGL-3	$C^1 \times 8$ h = 5656 ppm h C = 707 ppm 8-h AEGL-3 = 707 ppm/10 = 71 ppm (250 mg/m^3)

APPENDIX B: Benchmark Calculations

Benchmark Calculations

For the AEGL-3, the derived benchmark value of 1414 ppm ($BMCL_{05}$, Log Probit Model) based on a study with rats was used (DuPont 1993a).

$BMCL_{05}$ = 1414.4 ppm

BMC_{01} = 1650.65 ppm

We assume, that no mortality would occur at background concentration (mortality 0 at dose 0). According to default assumptions (SOP) the log probit-model was employed for calculation of $BMCL_{05}$ and BMC_{01}.

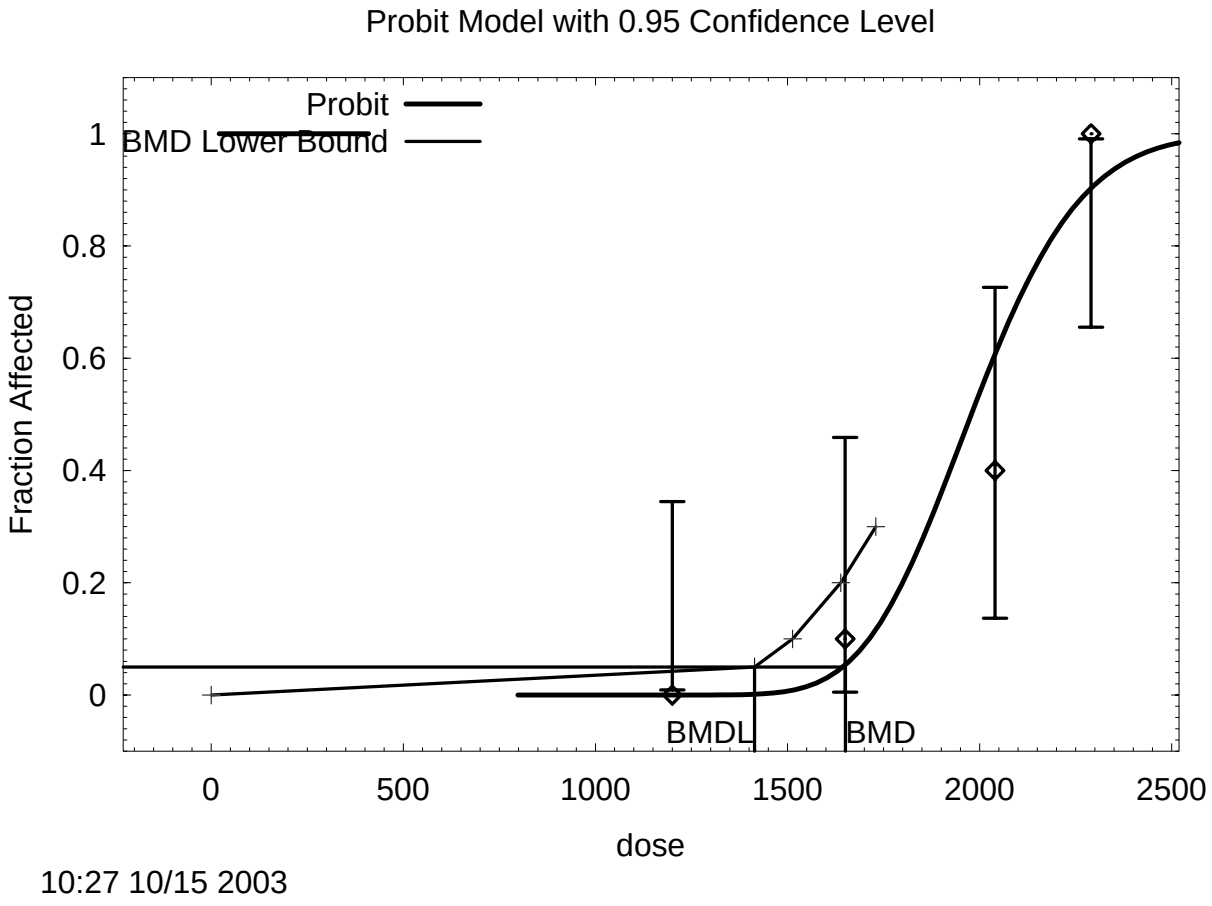

FIGURE 2. Benchmark Calculations

Model Parameter

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 = n_lethal

Independent variable = concentration

Background parameter is set to zero

Slope parameter is restricted as slope >= 1

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 Specified

Intercept = -35.1007

Slope = 4.65131

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.
Intercept	-67.4181	19.5356
Slope	8.87757	2.56902

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-9.98095			
Fitted model	-12.0383	4.11473	2	0.1278
Reduced model	-26.4625	32.9632	3	<.0001

AIC: 28.0766

Goodness of Fit

Dose	Est._Prob.	Scaled Expected	Observed	Size	Residual
1200.0000	0.0000	0.000	0	10	-0.006174
1650.0000	0.0496	0.496	1	10	0.7332
2040.0000	0.5930	5.930	4	10	-1.242
2290.0000	0.8964	8.964	10	10	1.075

Chi-square = 3.24 DF = 2 P-value = 0.1983

Benchmark Dose Computation

Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95

APPENDIX C: Comparative list of AEGL-values as proposed for different acrylates or acrylate esters

CONSISTENCY WITH RELATED SUBSTANCES

[ppm]

AEGL-1	**UF (Inter; Intra; Modify) Total)**	**10 min**	**30 min**	**60 min**	**4 h**	**8 h**
MMA	1 (hum);3;1;**3**	17	17	17	17	17
MAA	1;3;1;**3**	6.7	6.7	6.7	6.7	6.7
Acrylic acid	1 (hum);3;1;**3**	1.5	1.5	1.5	1.5	1.5

AEGL-2						
MMA	1;3;1;**3**	150	150	120	76	50
MAA	1;3;1;**3**	76	76	61	38	25
Acrylic acid	1;3;1;**3**	68	68	46	21	14

AEGL-3						
MMA	3;3;1;**10**	720	720	570	360	180
MAA	3;3;1;**10**	280	280	220	140	71
Acrylic acid	3;3;1;**10**	480	260	180	85	58

July, 20, 2004

APPENDIX D: Derivation Summary for Acute Exposure Guideline Levels for Methacrylic Acid (CAS Reg. No. 79-41-4)

AEGL-1 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
6.7 ppm	6.7 ppm	6.7 ppm	6.7 ppm	6.7 ppm

Key Reference: CIIT (1984), CIIT (1983)

Test Species/Strain/Number: Groups of 20 animals of each sex; Sprague-Dawley rats, Fischer-344 rats, B6C3F1 mice

Exposure Route/Concentrations/Durations: Repeated whole-body exposure to 20, 100, or 300 ppm for 6 hours / 5 d/wk for 90 days. Control groups exposed to air. Analytical concentration. After the 4th exposure 10 animals each were sacrificed (scheduled interim sacrifice).

Effects: After the 4th exposure, dose-related minimal to slight dose-related rhinitis, hyperkeratosis, lymphocyte infiltrate, inflammation of respiratory epithelium, degeneration were observed at all concentrations in both male and female rat at and above 20 ppm

Endpoint/Concentration/Rationale: Rhinitis, inflammation and slight degeneration of the olfactory epithelium observed after 4 exposures to 20 ppm in rats. Although degeneration of olfactory epithelium would be above AEGL-1 level, this effect was seen after 4 exposures. No obvious clinical effects in a range-finding study at higher concentrations

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1: Regarding toxicokinetics, humans are expected to be of lower susceptibility than rats regarding effects on the nasal cavity. Regarding toxicodynamics, no significant species differences are to be expected.
Intraspecies: 3: Interindividual differences are expected to be small regarding the only local effects of MAA.

Modifying Factor: none

Animal to Human Dosimetric Adjustment: not applied (insufficient data)

Time Scaling: The experimental derived exposure value was used for all time points, because no relevant aggravation of effects with increasing exposure duration was observed.

Data Adequacy: No other study was conducted at exposure concentrations relevant for AEGL-1 effects and no human data are available. Therefore, no data are appropriate to support the derived AEGL-1 values. However, a) the CIIT (1984) study is comprehensively conducted and reported and the observed effect concentrations seem reliable; b) supported by alternative extrapolation from range-finding study (CIIT 1983) after inclusion of a modifying factor, c) further supported by comparison to AEGL of other acrylates, acrylate esters

1

1

AEGL-2 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
76 ppm	76 ppm	61 ppm	38 ppm	25 ppm

Key Reference: CIIT (1984), CIIT (1983)

Test Species/Strain/Number: Groups of 20 animals of each sex; Sprague-Dawley rats, Fischer-344 rats, B6C3F1 mice

Exposure Route/Concentrations/Durations: Repeated whole-body exposure to 20, 100, or 300 ppm for 6 hours / 5 d/wk for 90 days; Control groups exposed to air. After the 4th exposure 10 animals each were sacrificed (scheduled interim sacrifice). Analytical concentration.

Effects: After the 4th exposure, dose-related minimal to mild dose-related rhinitis, exudate, inflammation of respiratory epithelium, and ulceration of olfactory epithelium were observed at 300 ppm in both males and females (all species/strains)

Endpoint/Concentration/Rationale: Irritative and corrosive effects on the respiratory and olfactory epithelium. 100 ppm are seen as threshold between reversible effects observed (e.g. inflammation of the respiratory epithelium) and serious, presumable not reversible health effects observed at 300 ppm (e.g. ulceration of olfactory epithelium in rats, necrosis of the respiratory epithelium in mice)

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1: Regarding toxicokinetics, humans are expected to be of lower susceptibility than rats regarding effects on the nasal cavity. Regarding toxicodynamics, no significant species differences are to be expected.
Intraspecies: 3: Interindividual differences are expected to be small regarding the only local effects of direct acting MAA.

Modifying Factor: none

Animal to Human Dosimetric Adjustment: not applied (insufficient data)

Time Scaling: $C^3 \times t$ for extrapolation to 4 , 1, and 0.5 hours. $C^1 \times t$ for extrapolation to 8 hours. The 10-min AEGL-2 was set at the same concentration as the 30-min AEGL-2, starting from data to 6 hours exposure (default)

Data Adequacy: The CIIT (1984) study is comprehensively conducted and reported and the observed effect concentrations seem reliable. The plausibility of the derived AEGL-2 is supported by the range finding study (CIIT 1983), where 500 ppm for a repeated 6-hour exposure (10 times) resulted in more severe, mostly irreversible effects, that are judged as above AEGL-2 level. No human data are appropriate to support the derived AEGL-2 values, except the observation that 113 ppm for an unknown exposure duration resulted in corrosive effects on eyes and skin in exposed workers. Further supported by comparison to AEGL of other acrylates, acrylate esters

2

1

AEGL-3 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
280 ppm	280 ppm	220 ppm	140 ppm	71 ppm

Key Reference: DuPont (1993a)

Test Species/Strain/Number: Groups of 5 CrlCD®BR of each sex were exposed

Exposure Route/Concentrations/Durations: Nose-only exposure to 4 different concentrations (1200, 1650, 2040, and 2290 ppm) for 4 hours. Analytical concentration. The animals were held for observation for 14 days.

Effects:

1200 ppm 0/10 Animals died
1650 ppm 1/10 Animals died
2040 ppm 4/10 Animals died
2290 ppm 10/10 Animals died

At lethal concentrations, dose-related signs of toxicity included corneal opacity, gasping, irregular respiration, lethargy, lung noises, stained and wet fur, and nasal, ocular and vaginal discharge.

Endpoint/Concentration/Rationale: LC_{50} of 1980 ppm. Calculation of a $BMCL_{05}$ of 1414 ppm was used as starting point. The lethality incidences reported in this study revealed a clear dose-response relationship.

Uncertainty Factors/Rationale:

Total uncertainty factor: 10

Interspecies: 3: Regarding toxicokinetics, humans are expected to be of lower susceptibility than rats regarding effects on the nasal cavity. No such indications are available concerning the lower respiratory tract. Regarding toxicodynamics, no significant species differences are to be expected.

Intraspecies: 3: Interindividual differences are expected to be small regarding the only local effects of MAA.

Modifying Factor: None

Animal to Human Dosimetric Adjustment: not applied (insufficient data)

Time Scaling: $C^3 \times t$ for extrapolation to 1 hour, 30 minutes. $C^1 \times t$ for extrapolation to 8 hours. The 10-min AEGL-3 was set at the same concentration as the 30-min AEGL-3.

Data Adequacy: Qualified key study. Some uncertainty because of vapor and aerosol mixture. No human data are appropriate to support the derived AEGL-3 values. Supported by comparison to AEGL of other acrylates, acrylate esters

2