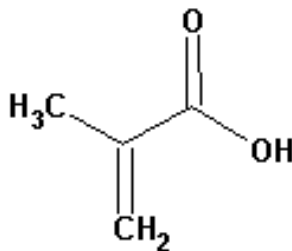# INTERIM ACUTE EXPOSURE GUIDELINE LEVELS
(AEGLs)

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

for NAS/COT-Subcommittee on AEGLs

December, 2006

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INTERIM ACUTE EXPOSURE GUIDELINE LEVELS
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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 acts irritating and corrosive to eyes, skin and the respiratory tract. No metabolites were identified that contribute to the toxic effects. MAA enters the citric acid cycle in form of it´s coenzyme A ester, to which it is converted by the enoyl-CoA-hydratase.

Data on acute effects in humans are largely missing, and none of the available 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 high-toxic and lethal 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).

One negative mutagenicity test, and no carcinogenicity studies are available for MAA. However, the ester of methacrylic acid, methyl methacrylate, from which MAA is a metabolite (hydrolysis) does not express a genotoxic potential in vivo, and 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.

In a range finding study with repeated (10 day) exposure with 2 strains of rat and 1 strain of mice (6 hours/day, 5 animals/sex/strain/exposure level) no obvious effects have been observed after first day exposure to 100 or 500 ppm, but were seen after 1000 ppm (CIIT 1983). However, no sufficient examinations (e.g., no histopathology) were performed. The AEGL-1 values are based on effects in a more detailed study: rhinitis, hyperkeratosis, inflammation and slight degeneration of olfactory epithelium were observed in rats (Fischer-344 and Sprague-Dawley), that have been exposed to 20 ppm for 6 hours at 4 consecutive days, with increasing effect size at 100 ppm and 300 ppm (CIIT 1984).
Even though this effect is above AEGL-1- effect size it is used as starting point without further reductions because of its occurrence after repeated exposure and because no obvious effects were seen at higher exposure levels in the range finding study after first exposure (CIIT 1983). Slight irritating effects usually show only little aggravation over time, therefore it was considered to use the same exposure concentration for all exposure durations between 10 minutes and 8 hours. Evidences of a lower susceptibility of humans than of rats against MAA vapors are available by comparing with methyl methacrylate and acrylic acid, therefore an

interspecies factor of 1 was chosen. For direct and locally acting substances limited interindividual variability is expected, leading to an intraspecies factor of 3. The overall uncertainty factor is 3 with an AEGL-1 of 6.7 ppm for durations from 10 minutes to 8 hours. A very similar AEGL-1 of 10 ppm would result by using 100 ppm as a starting point (no obvious effects seen the range finding study after first exposure, CIIT 1983) and applying an additional modifying factor of 3 (overall uncertainty factor of 10) because of insufficient study design to detect respiratory irritational effects in that study. It would not be appropriate to use 500 ppm from this range finding study as a starting point as severe effects have been found at 300 ppm after only 4 exposures in the detailed study (CIIT 1984). The established AEGL-1 (6.7 ppm) is located between those of acrylic acid (1.5 ppm) and methyl methacrylate (17 ppm) and is, thus, supported by plausibility considerations on irritating potency.

The AEGL-2 values are based on inflammation, exudate and ulceration of olfactory epithelium reported in a study by CIIT (1984). These effects were seen with dose-relationship after repeated exposure at 300 ppm (4 times; 6 hours each) in 2 different rat strain (Fischer-344 and Sprague-Dawley) as well as in a mouse strain (B6C3F1) with no irreversible effects at 100 ppm. This study is used as starting point without further reductions because of its occurrence after repeated exposure and because no obvious effects were seen at higher exposure levels in the range finding study after first exposure (CIIT 1983). The pronounced effects observed at or above AEGL-2 level are presumed to aggravate with increasing exposure duration, as also observed with acrylic acid. No suitable data to derive a substance specific exponent n in the equation for time scaling $C^n \times t = k$ are available. Therefore, the default value of $n = 3$ was used for extrapolation from the 6-hour exposure to short durations and $n = 1$ was used for extrapolation to 8 hours. 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. Evidences of a lower susceptibility of humans than of rats against MAA vapors at the upper respiratory tract are available by comparing with methyl methacrylate and acrylic acid, therefore an interspecies factor of 1 was chosen. For direct and locally acting substances limited interindividual variability is expected, leading to an intraspecies factor of 3. The overall uncertainty factor is 3. The established AEGL-2 (25 ppm at 8 hours) is located between those of acrylic acid (14 ppm) and methyl methacrylate (50 ppm) and is, thus, supported by plausibility considerations on irritating potency.

The AEGL-3 values are based on a study by DuPont (1993a), in which rats have been exposed to 4 different MAA-concentrations (vapor/aerosol mixture) for 4 hours each. A LC_{50} of 1980 ppm was established in this study. At the LC_0 of 1200 ppm exposure irregular respiration, lethargy, lung noise and colored discharge have been observed in CrlCD®BR rats, and the next higher experimental exposure concentration of 1650 ppm in this study led to lethal effects in 1 out of 10 animals. Applying BMDS-software from EPA (1999), version 1.3.2, a $BMCL_{05}$ of 1414 ppm was calculated (log probit) and used as starting point for AEGL-3 derivation. No suitable data to derive a substance specific exponent n in the equation for time scaling $C^n \times t = k$ are available. Therefore, the default value of $n = 3$ was used for extrapolation from the 4-hour exposure to short durations and $n = 1$ was used for extrapolation to 8 hours. 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. Some species differences may be assumed for respiratory effects and gross toxicity to the pulmonary reagion of the respiratory tract. However, for a direct acting substance these differences are expected to be limited in size. Therefore an interspecies factor of 3 was chosen. To cover intraspecies differences in susceptibility a factor of 3 was selected, leading to an overall uncertainty factor of 10. The established AEGL-3 (71 ppm at 8 hours) is located between those of acrylic acid (58 ppm) and methyl methacrylate (160 ppm) and is, thus, supported by plausibility considerations on relative effect potency of these substances.

The calculated values are listed in the table below.

Summary of AEGL Interim Values for Methacrylic Acid [ppm (mg/m^3)]							
Classification	10-min	30-min	1-hour	4-hour	8-hour	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 concentrations are not sufficiently qualified to derive a level of odor awareness (LOA) according to qualified criteria. However, a provisional (and highly uncertain) „level of distinct odor awareness" (provisional LOA) of 1.5 ppm is estimated, based on a detection limit 0.17 ppm and based on a comparison to other acrylates by Grudzinskii (1988).

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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 of by Grudzinskii (1988).

TABLE 1. 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 t/a 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).

To prevent polymerization, MAA is stabilized, e.g. with hydroquinone (< 100 ppm) or hydroquinone monomethyl ether (< 250 ppm) (ECETOC 1996). At temperatures exceeding storage instructions significantly as well as at light exposure MAA polymerize readily and spontaneously.

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).

Medical reports of acute workplace exposures to 113 ppm at the highest revealed 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 own investigations in a MAA manufacture, 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, and none of the available effects can be related to a specific exposure duration. However it can be assumed, that local effects of MAA exposure are in the foreground of intoxication and that eyes and skin are first target tissues following inhalation exposure. MAA reacts 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.   Dogs

Lethality after i.v. administration

Mir et al. (1974) administered 96 mg/kg MAA via i.v. injection to anesthetized male mongrel dogs. This dose was rapidly fatal. The number of animals was not documented.

3.1.2.   Rats

Lethality after inhalation exposure

6 adult albino rats died within 19 minutes following inhalation exposure to approx. 57000 ppm MAA (indicated as 204 mg/l) (Food and Drug Research Laboratory 1973). 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.

Inhalation toxicity of MAA was investigated in CrlCD®BR rats by DuPont (1993a). 4 groups of 5 young adult animals of each sex were nose-only exposed 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, and the particle size distribution was determined once. The percentage of aerosol/vapor was 21/79 at 1200 ppm, 37/63 at 1650 ppm, 50/50 at 2040 ppm, and 57/43 at 2290 ppm, respectively. 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 already during exposure. Lethality incidences are summarized in Table 2. 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 the days after exposure. A LC_{50} of 1980 ppm (7.1 mg/l) for a 4-hour exposure was calculated.

An acute inhalation toxicity study was conducted by Mastri (1973) where 6 albino rats each have been whole-body exposed to 1120, 1540, or 1840 ppm (vapor; nominal concentration; 4, 5.5, or 6.6 mg/l) for 1 hour in a 325-l inhalation chamber. The inhaled MAA had a stabilizer content (hydroquinone monomethyl ether) of 250 ppm (at 1540 ppm MAA) and of 100 ppm (at 1840 ppm MAA). Exposure to 1120 ppm MAA included the inhalation of 1000 ppm hydroquinone as a stabilizer. Following exposure the rats have been observed for 14 days. No death occurred at any concentration. Nonlethal effects are reported in Section 3.2.2. Due to the combined exposure to relevant concentrations of the stabilizer, these data are not qualified for the assessment of MAA.

In a range-finding inhalation study at saturated vapor concentration of 2000 ppm (as calculated by the authors) with 3 female rats, whole-body exposed for 7 hours, no lethality was observed (Dow Chemicals 1956). No information on a post-exposure observation period is given. For further effects see Section 3.2.2 (Rats, Nonlethal Toxicity).

No Fischer-344 or Sprague-Dawley rats (5 animals of each sex) died after first 6-h exposure of a repeated whole-body exposure study at 1000 ppm (CIIT 1983), but all Fischer-344 rats and 1 Sprague-Dawley rat died after repeated exposure (2 weeks of study duration). For study details see Section 3.3 (Repeated Exposure).

Lethality after oral exposure

For male albino rats, Rohm and Haas (1957) reported an oral LD_{50} of approx. 2210 mg/kg. A similar LD_{50} of 2260 mg/kg has been given by Eastman Kodak (1979). Elf Atochem (1977) derived a LD_{50} of 1320 mg/kg for male Wistar rats.

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

3.1.3.   Mice

Lethality after inhalation exposure

3 of 10 B6C3F1 mice (1 male and 2 females) died after first 6-h exposure of a repeated (2 weeks) whole-body exposure study at 1000 ppm (CIIT 1983). All of the surviving mice died within 4 days of the 2-week-study. For study details see Section 3.3 (Repeated Exposure).

Lethality after oral exposure

A LD_{50} of 1600 mg/kg has been reported by Eastman Kodak (1979). Clinical signs included weakness and rough haircoat.

3.1.4.   Guinea Pigs

Lethality after dermal exposure

A dermal LD_{50} between approx. 1000 - 5000 mg/kg (indicated as 1 - 5 mL/kg) is reported by ECB (Eastman Kodak 1979).

3.1.5.   Rabbits

Lethality after oral exposure

A LD_{50} value of 1200 mg/kg bw (15 animals) is given by ECB (2000).

Lethality after dermal exposure

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

Dosage of 2000 mg/kg on intact skin for a 24-hour contact was lethal for 2 of 3 animals, and 2000 mg/kg on abraded skin resulted in 100% lethality (3/3 animals) (Food and Drug Research Laboratory 1973). Examinations revealed severe erythema and edema at application site, however no abnormalities were observed at gross necropsy.

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

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

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

TABLE 2. 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 minutes severe pulmonary edema, hemorrhage; corneal opacity	Food & Drug Research Laboratory (1973)
rat	1200 1650 2040 2290	4 h	LC	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	DuPont (1993a)
	1980 1414		LC_{50} $BMCL_{05}$	calculated calculated	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)
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.   Dogs

Nonlethal toxicity after i.v. administration

Mir et al. (1974) investigated the respiratory and cardiovascular effects of MAA in dogs. Doses of 9.6, 19, and 48 mg/kg MAA were administered to 3 male mongrel dogs each by i.v. injection (suspended in saline with 0.1% gum acacia). A dose-dependent decrease in blood pressure (as initial response 2 minutes after injection) (-79% at high dose), and heart rate (- 22% at high dose), as well as an increase in respiratory rate (+ 158% at high dose) were observed. As secondary response the blood pressure rose up to + 15% of control

animals a few minutes later. The authors suggested, that the observed effects were due to an intrinsic action of MAA, and not to a physical blockage of small vessels by the suspension.

3.2.2. Rats

Nonlethal toxicity after inhalation exposure

An acute inhalation toxicity study was conducted by Mastri (1973) where 6 albino rats each have been whole-body exposed to 1120, 1540, or 1840 ppm (nominal concentration; 4, 5.5, or 6.6 mg/l) for 1 hour in a 325-l inhalation chamber. The inhaled MAA had a stabilizer content (hydroquinone monomethyl ether) of 250 ppm (at 1540 ppm MAA) and of 100 ppm (at 1840 ppm MAA). Exposure to 1120 ppm MAA included the inhalation of 1000 ppm hydroquinone. Following exposure the rats have been observed for 14 days. Exposure to 1540 ppm and 1840 ppm were reported to cause no death or untoward behavioral reactions. At necropsy no gross pathologic alterations have been detected. Exposure to 1120 ppm were reported to cause a bloody nasal discharge during exposure, that subsided within 3 hours after cessation of exposure. At necropsy 4 animals revealed mild focal discoloration of lung and slight discoloration was observed in a further animal. Due to the combined exposure to relevant concentrations of a per se irritative acting stabilizer, these data are not qualified for the assessment of MAA.

Dow Chemicals (1956) conducted a range-finding inhalation study at saturated vapor concentration of 2000 ppm (as calculated by the authors). 3 female rats, whole-body exposed for 7 hours (single exposure) revealed definite eye irritation and slight to moderate weight loss. At pathology no essential alterations have been observed. 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 3.1.2 - 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, 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 developed increased activity at 1000 ppm. Sprague-Dawley rats casually revealed 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 to nasal albumin, protein and NPSH (Non-protein sulfhydryl) levels in the surgically isolated upper respiratory tract (URT) of 5 male Fischer-344 rats nose-only exposed 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 NPSH-levels point to a direct reactivity of toxicants with reduced sulfhydryl compounds. Up to 410 ppm no significant biochemical effects have been observed that would indicate an irritation of the upper respiratory tract.

3.2.3.   Mice

Nonlethal toxicity after inhalation exposure

For determination of the inhalation sensory irritation (RD_{50}) male Swiss Webster mice were exposed to 5 different concentrations of MAA (4900, 9400, 18000, 27000, and 42000 ppm) in groups of 4 animals for 30 minutes (DuPont 1993b). The exposure chamber, in which only the heads were protruding, was supplied with plethysmographs. Respiratory rates were monitored before, during and after exposure (10 minutes pre- and postexposure). Vapor concentration was controlled 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 3). 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, starting almost immediately after onset of exposure, were recorded. 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. Although it was not clearly stated, it can be assumed, that no extended post exposure follow-up observation had been included.

CIIT (1983) conducted a repeated exposure study in 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 developed increased activity at 1000 ppm, and in male mice hypoactivity and prostration in 1 animal were reported. Severe necrosis of the nasal mucosa and submucosa have been observed after first exposure. No treatment-related clinical signs were noticed at 100 and 500 ppm after the first exposure.

TABLE 3. 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

TABLE 3. Summary of Nonlethal Inhalation Data in Laboratory Animals				
Species	**Conc. (ppm)**	**Exposure**	**Number of animals Most important effects**	**Reference**
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 3. 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 information on concentration measurement, e.g. analytics, vapor / aerosol exposure, or whole body / nose-only exposure, was given.

A range-finding probe investigation for a 90-day inhalation study (see below) was conducted in rats (Fischer-344 and Sprague-Dawley) and in mice (B6C3F1) (CIIT 1983). 5 animals of each sex were whole-body exposed to concentrations of 100, 500, or 1000 ppm for 2 weeks (6 h/d, 5 d/wk). Measurement of concentration was conducted by HPLC. Every exposure day, the animals have been thoroughly evaluated before and after exposure, and periodically observed during the exposure period.

During the first day of exposure, animals of all strains developed increased activity at 1000 ppm, for male mice hypoactivity and prostration in 1 animal were reported. Sprague-Dawley rats casually revealed 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.

Histopathology after 10 exposures included nasal turbinates (4 sections), trachea, lungs, and gross lesions. No mortality was observed at 100 ppm and 500 ppm, but at 1000 ppm all mice (day 1 - 4), all Fischer-344 (days 4 and 5) and 1 Sprague-Dawley rat (following 11th exposure) died. 1 male and 2 female mice died already after first exposure. 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. Mild necrosis of the nasal mucosa accompanied by acute inflammation, metaplasia of the respiratory epithelium and mild hyperkeratosis of the eyelid have been noticed in Fischer-344 rats. In the Sprague-Dawley rats hyperplasia and metaplasia of the nasal mucosa, as well as small focal areas of necrosis were reported.

At 1000 ppm, severe necrosis of the nasal mucosa and submucosa has been observed after first exposure in mice. Fischer-344 rats showed acute necrosis of the nasal mucosa and submucosa and mild keratitis of cornea. Similar effects on nose and eyes have also been reported for Sprague-Dawley rats.

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

A 90-day inhalation study with B6C3F1 mice, Sprague-Dawley rats and Fischer-344 rats was conducted by CIIT (1984). 20 animals each were whole-body exposed to 20, 100, or 300 ppm for 6 hr/d, 5 days/wk. Additional, a control group of 20 animals of each 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 with 10 of 20 animals on day 5. At all concentrations, minimal to mild dose-related rhinitis, inflammation of respiratory epithelium, and degeneration of the olfactory epithelium in both, male and female rats were observed within both strains after 4 exposures, that aggravated to a moderate degeneration after 90 days. Eosinophilic globules have been 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 4. On account of the lower relevance for acute exposure risk assessment, pathological and histopathological findings after 90-day exposure are not described below.

A 4-month study in rats and mice, exposed to 0.12, 2.5, or 61.7 ppm, is reported by Lobanova et al. (1979). The animals revealed reversible, dose-dependent „dystrophic and destructive changes" in the lungs. No further data are available. As remarked by ECETOC (1996), the results are of questionable validity.

TABLE 4. 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	

TABLE 4. 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	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

The developmental toxicity of MAA following inhalation exposure was investigated by Saillenfait et al. (1999) in Sprague-Dawley rats. Groups of 19 - 25 pregnant females were exposed to 50, 100, 200, and 300 ppm for 6 hours per day from day 6 to day 20 of gestation. The whole-body exposure was conducted in a 200l-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 have been observed within the other dose groups, however acute effects might not have been reported. No signs of toxicity related to embryolethality or teratogenicity have been observed.

3.5. Sensitization

No contact sensitivity in guinea pigs (outbred Hardley strain) was observed by Parker and Turk (1983) 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). Doses from 4000 mg/plate were cytotoxic.

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

3.8.   Summary

The local effects are in the foreground of MAA toxicity and result in irritation and corrosion to respiratory tract, eyes and skin (Food and Drug Research Laboratories 1973; Greim et al. 1995).

At high-toxic and lethal inhalation concentrations of MAA increased motor activity, lethargy, respiratory distress, lung noises, nasal, ocular and vaginal discharge, and corrosive effects to the eyes have been reported during exposure (Food and Drug Research Laboratory 1973; DuPont 1993a; Gage 1970; CIIT 1983). These kinds of effects were seen at 1000 ppm and above for an acute exposure up to 6 hours. The pathological examination revealed severe pulmonary edema, hemorrhage, and discoloration. A LC_{50} of 1980 ppm for a 4-hour exposure was reported by DuPont (1993a).

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, e.g. closed eyes, sores, weakness, and body-weight loss, can develop during recovery period. Delayed effects were also reported by CIIT (1984), where an aggravation of olfactory epithelium ulceration following 4 exposures was observed.

Using biochemical investigations, no indications of irritation of the upper respiratory tract were observed by Morris and Frederick (1995) and Morris (1992) by exposure of the isolated respiratory tract of rats up to 410 ppm for 60 minutes. The measured biochemical parameter have been 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 approx. 25% (see TSD for methyl methacrylate). Moreover, cyclic flow studies do no 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.

One negative mutagenicity test, and no carcinogenicity studies are available for MAA. However, the ester of MAA, methyl methacrylate, from which MAA is hydrolized 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 it is stated, that most of the MAA does not reach the lung (Morris and Frederick 1995; Morris 1992). A deposition efficiency of 95% was measured in the URT of rats following exposure to 133 ppm. However at high exposure concentrations above 1000 ppm lung effects, e.g. 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 concentration 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 the appearance of MAA in rat blood serum was measured already after 5 minutes with 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.

For the entering of MAA to a normal catabolic pathway, which leads to CO_2 exhalation, evidence was delivered by Bratt and Hathway (1977) and Crout et al. (1982). MAA, in form of it´s coenzyme A ester, is a normal intermediate in the catabolism of valine (Crout et al. 1979). The enzyme enoyl-CoA-hydratase, that converts MAA into the coenzyme An ester (ECB 2002), would permit MAA to enter a normal catabolic pathway, leading to CO_2. Bratt and Hathway (1977) found out, 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 entry. The toxicity of MAA is presumably completely due to the intact molecule, and no metabolites were identified that contribute to the toxic effects. Inhalation of MAA results in the deposition at the upper respiratory tract, where it is capable of inducing 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 high exposure concentrations above 1000 ppm additionally 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 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 initiated 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 ester 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, in case the acid metabolite is responsible for the toxicity, 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 concentration additionally the lower respiratory tract is affected. Equally to MAA, no metabolite of acrylic acid was identified to contribute to the toxic effects. Therefore toxicodynamic and toxikokinetic 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). These concentrations are presumably below toxic effect concentrations. From an English translation of the original article in Russian language, Klimkina et al. (1973) tested MAA, as stabilized with 0.1% hydroquinone the odor detection limit is said to be 116 ± 10 mg/l. in water. We did not locate any air concentration nor details how this odor detection limit in water had been derived. Hence, the reported odor threshold of 0.032 ppm is not confirmed from the original literature.
Grudzinskii (1988) report some odor detection limits on other acrylates, e.g., methyl methacrylate (0.2 to 1.2 mg/m³) and describe the current testing on MAA: 6 concentrations were used: 0.4, 0.6, 1.0, 1.5, 2.0, 3.0 mg/m³. 21 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/m³, the lowest concentration was only detected by few persons. 0.4 mg/m³ was not detected as odor. An EC_{16} of 1.8 mg/m³ was calculated and a limit value of 0.25 mg/m³ was derived. (For comparison, acrylic acid was assigned an EC_{16} of 0.24 mg/m³ and a limit value of 0.08 mg/m³) [personal translation of Russian original article]. The data are not sufficiently detailed to derive a level of odor awareness (LOA) of similar quality as demanded by Doorn et al. (2002). However, the EC_{16} of 0.24 mg/m³ (0.08 ppm) for acrylic acid is still below the LOA for this substance, which was derived from other data to be 0.2 ppm (see TSD on acrylic acid). For a preliminary assessment, we use the ratio from $EC_{16, \text{Acrylic acid}}$ / $EC_{16, \text{Methacrylic acid}} = 7.5$ from the study of Grudzinski (1998) to estimate a LOA of 0.2 x 7.5 = 1.5 ppm for MAA. This estimate suggests a) that the reported odor detection thresholds are quite low and even lower than the assumed LOA for this substance, b) that MAA will be smelled by most exposed persones well below AEGL-1, c) that methyl metacrylate and acrylic acid will probably perceived in much lower concentrations in air by most persons compared to MAA. A provisional LOA of 1.5 ppm is selected.

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% in rats. The olfactory epithelium in humans is located in the secondary air flow, whereas in the primary air flow in rats. Consequently, in rats more of MAA is delivered to target tissues. 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, too. 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 of reactions against MAA within a population are available. Regarding toxikokinetic properties, MAA is a local acting substance and no metabolic component contributes to the toxic effect. Regarding toxicodynamics, certain individual differences, may exist: for example, the amount of the olfactory epithelium as first target tissue may differ interindividually. Summarizing, there is, presumably, 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 aggravated with increasing exposure duration by comparing a repeated short-term exposure of 4 consecutive days with a 90-day exposure duration. During single exposures to low, non cytotoxic concentrations of MAA, no marked aggravation of effects with time is expected since very slight irritative effects relevant for AEGL-1 level primarily depend on the actual exposure concentration and not much on exposure time, as was elucidated for acrylic acid (o.V. 2003). At higher concentrations relevant for AEGL- 3 it can be assumed, that an increasing proportion of MAA is not efficiently removed by the nose respectively upper respiratory tract but reaches the lung. Effects as lung noises and edema have been observed in rats above 1000 ppm by Food

& Drug Research (1973) and DuPont (1993a). For such effects on the lower respiratory tract, but also for pronounced effects on the nasal passages (AEGL-2-level) a clear concentration - exposure duration relationship can be assumed for MAA, as also observed 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 reveals no effect on the respiratory tract, however, severe effects on the eye (corneal burn). Such effects must be judged as above AEGL-1. Due to insufficient reporting , these findings can only be used as supporting evidence.

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.

In a range finding study with repeated (10 day) exposure (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 1000 ppm (CIIT 1983). After repeated exposure (10 consecutive days), necrosis, acute inflammation, hyperplasia and metaplasia of the olfactory epithelium were reported at exposures to 100 ppm in rats, but not in mice in this range-finding study. Additionally, necrosis of nasal mucosa as well as hyperkeratosis were reported at 500 ppm (CIIT 1983).
A comprehensively reported study with repeated exposure, revealed rhinitis, discharge, inflammation and slight degeneration of olfactory epithelium after repeated exposure to 20 ppm for 4 days with 6 hours daily 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 4). At 300 ppm also mice were affected.

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 slight degeneration of olfactory epithelium observed following exposure to 20 ppm for a duration of 6 hours for 4 times (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. Moreover, effect size was described only as „minimal to slight“. In a previous range finding study (CIIT 1983) no apparent clinical effects were seen after the first day of exposure to 100 or 500 ppm. The AEGL-1 values are based on effects in the more detailed study (CIIT 1984).
Alternatively, the no observed effect concentration of 100 or 500 ppm after first 6 hour exposure in the range finding study (CIIT 1983) could be used as a starting point. Because relevant effects were seen after only 4 exposures to 300 ppm in the more detailed study (CIIT 1984) the lower concentration (100 ppm) would then be more appropriate and an additional modifying factor of 3 has to be used because of the lack of appropriate histopathology in the range finding study. This would result in a very similar starting point and very similar AEGL-1 values for the two approaches.

Sometimes, a screening comparison supports an AEGL-1 based on the RD_{50} divided by 100. However, the RD_{50} of 22000 ppm would result in a starting point of 220 ppm (30 min) which would be clearly above AEGL-1 level based on the CIIT-study (CIIT 1984).

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, that are caused by the parent compound. 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 factor of 1 was applied. Regarding individual differences, 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 aggravation of slight irritative effects on the upper respiratory tract with increasing exposure duration is limited. Therefore, the experimental derived exposure value of 20 ppm (6 hours), derived by CIIT (1984), was used for all time points. This approach is in accordance with the Standing Operating Procedures (NRC 2001) for slight irritating effects.

The established AEGL-1 (6.7 ppm) is located between those of 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), from which a provisional „level of distinct odor awareness" of 1.5 ppm is derived. These concentrations are very likely below any toxic effects.

TABLE 5. AEGL-1 Values for Methacrylic Acid				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
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. The observed effects would be judged as relevant for AEGL-2 levels.

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) reported by DuPont (1993a) effects, that are clearly above AEGL-2, i.e. irregular respiration, lung noises, gasping and lethargy, have been observed. This concentration is there seen as to close to the $BMCL_{05}$ of 1414 ppm (4 hours).

A study, conducted by CIIT (1984) with four times 6-hour exposures to 100 and 300 ppm, revealed 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. These effects were dose-related, less pronounced and reversible at 100 ppm. Corrosion and irritative effects on the respiratory tract and eyes aggravate with increasing exposure duration. 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). Additionally hyperkeratosis has been reported. 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 has been observed at this concentration.

At 300 ppm MAA (whole-body exposure for 6 hours/day, 15 exposures), but not at 200 ppm, pregnant Sprague-Dawley rats revealed significant decreases in weight gain and food consumption (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, e.g. rhinitis, and inflammation of the respiratory epithelium, are reversible. At 300 ppm, but not at 100 ppm more severe effects, i.e. ulceration of olfactory epithelium, have been observed additionally, which would be not reversible. Therefore, the 100 ppm concentration was chosen for the AEGL-derivation. At 500 ppm for repeated 6-hour exposure (10 times) more severe effects, most of them irreversible, e.g. necrosis and metaplasia, were seen (CIIT 1983). This effect concentration is further supported by the observation, that repeated exposure to 300 ppm had significant effects on body weight and food consumption in pregnant rats. These effects are seen as above AEGL-2 level.

Sometimes, if better data are lacking, AEGL-2 is based on the RD_{50} divided 30. However, the RD_{50} of 22000 ppm would result in a starting point of approx. 730 ppm (30 min) which would be clearly above AEGL-2 level based on the CIIT-study (CIIT 1984).

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 that are caused by the parent compound. By comparing MAA with the similar acting acrylic acid, it can be assumed that humans are comparable susceptible to MAA vapors to rats regarding effects at the upper respiratory tract. Therefore, an interspecies factor of 1 was applied. With respect to certain intraspecies differences in susceptibility an uncertainty factor of 3 was applied. This factor is used to cover the toxicodynamic and toxicodynamic differences between individuals.

The experimental derived exposure value of 100 ppm, reported by CIIT (1984), 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 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 established AEGL-2 (25 ppm, 8 hours exposure) is located between those of 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 6. AEGL-2 Values for Methacrylic Acid				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
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 longlasting 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 nose-only 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 as 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 of 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 has been 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. Dow Chemicals (1956) revealed a higher LC_0 of 2000 ppm (7-hour) for rats, however no measurement of concentration was conducted in this study (nominal concentration; whole-body). Regarding the effects observed by DuPont (1993a) at lower exposure concentration and duration, calculation of exposure by Dow Chemicals might be an underestimation. This study was also not considered in derivation of AEGL-3 values because of the small group size of 3 animals.

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} (max. likelihood estimate) 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. Regarding the inhalation exposure conditions in the DuPont study (DuPont 1993a), some uncertainties exist concerning the increasing aerosol ration 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.

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, that are caused by the

parent compound. Indications are available, that mice are more susceptible against MAA inhalation than rats at lethal concentration. 3 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. Usually no high interspecies differences occur with local irritative and corrosive acting substances. Moreover, this factor is justified by the observation, that for the similar acting acrylic acid also a factor of 3 was chosen, based on a more comprehensive database. To cover certain toxicodynamic and toxicokinetic intraspecies differences in susceptibility an uncertainty factor of 3 was applied. 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 established AEGL-3 (71 ppm at 8 hours) is located between those of 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 7. AEGL-3 Values for Methacrylic Acid				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
280 ppm (1000 mg/m³)	280 ppm (1000 mg/m³)	220 ppm (790 mg/m³)	140 ppm (500 mg/m³)	71 ppm (250 mg/m³)

*) 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 8.

For all effect levels an uncertainty factor of 3 was used to cover certain intraspecies variabilities, resulting from certain individual differences. 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 not higher 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 additionally 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 aggravation 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 have been observed in CrlCD®BR rats, and the next higher experimental exposure concentration 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.

An useful presentation to evaluate the derived AEGL values in context of the existing empirical effect concentration is presented in Figure 1. For this plot, the toxic responses are placed into severity categories according to the AEGL levels: no or minimal effect, disabling, some lethality, lethality (100%). No human data are suitable to show in the category plot, because for none of the available effect concentration an exposure duration is given.

TABLE 8. Summary of AEGL Values					
Classification	**Exposure Duration**				
	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
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.
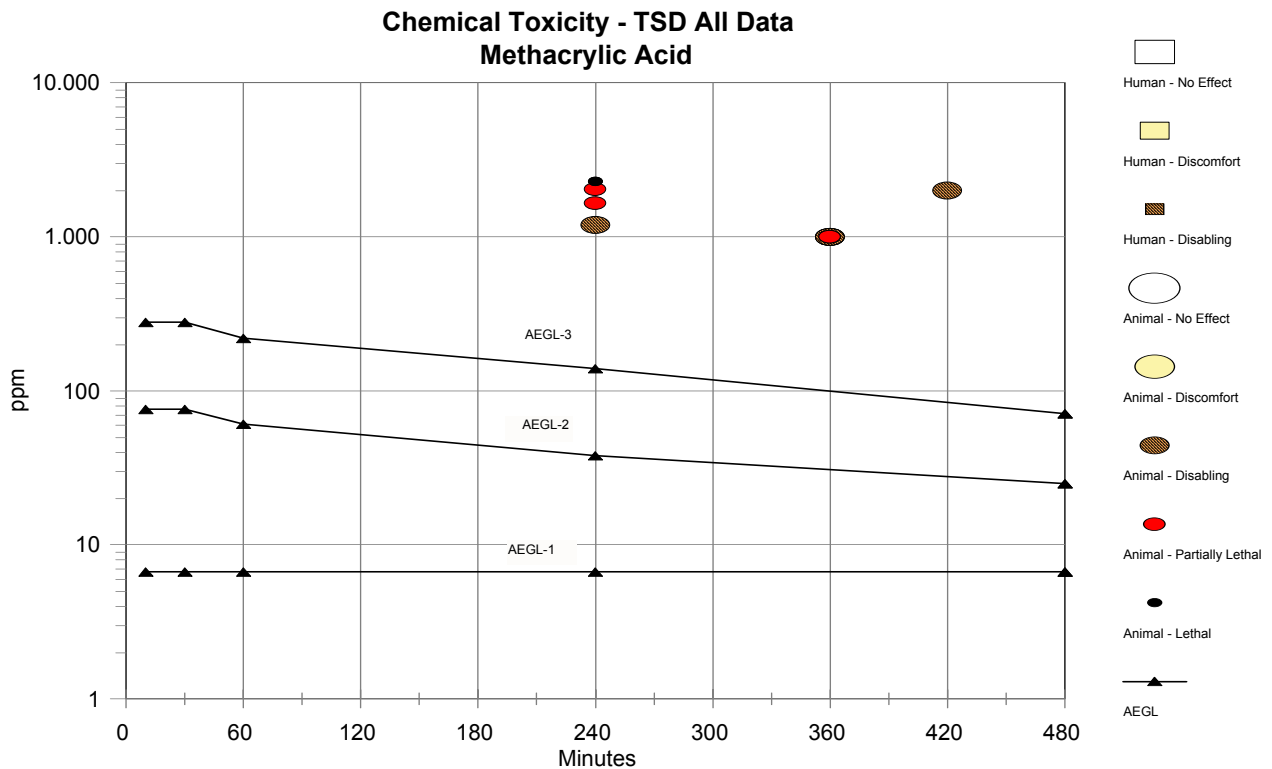

FIGURE 1. Category Plot of Toxicity Data compared to AEGL Values

8.2.   Comparison with Other Standards and Guidelines

TABLE 9. Existent Standards and Guidelines for Methacrylic Acid					
Guideline	**Exposure Duration**				
	10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
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 hours
(4 exposures).

Time scaling: No time scaling was conducted. Same concentrations for 8 hours, 4 hours, 1
hour, 30 minutes and 10 minutes

Uncertainty factors: 1 for interspecies variability
3 for intraspecies variability
Combined uncertainty factor of 3

Modifying factor: None

Calculations:

10-minute AEGL-1   C = 20 ppm
10-minute AEGL-1 = 20 ppm/3 = 6.7 ppm (24 mg/m³)

30-minute AEGL-1   C = 20 ppm
30-minute AEGL-1 = 20 ppm/3 = 6.7 ppm (24 mg/m³)

1-hour AEGL-1   C = 20 ppm
1-hour AEGL-1 = 20 ppm/3 = 6.7 ppm (24 mg/m³)

4-hour AEGL-1   C = 20 ppm
4-hour AEGL-1 = 20 ppm/3 = 6.7 ppm (24 mg/m³)

8-hour AEGL-1   C = 20 ppm
8-hour AEGL-1 = 20 ppm/3 = 6.7 ppm (24 mg/m³)

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 hours (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 x t for extrapolation to 1 hour, 30 minutes
                            $k = 100^3$ ppm^3 x 6 h = 6000000 ppm^3 x h
                            C^1 x t for extrapolation to 8 hours
                            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-minute AEGL-3   10-min AEGL-2 = 30-min AEGL-2 = 76 ppm (270 mg/m^3)

30-minute AEGL-3 C^3 x 0.5 h = 6000000 ppm^3 h
                            C = 228 ppm
                            30-min AEGL-2 = 228 ppm/3 = 76 ppm (270 mg/m^3)

1-hour AEGL-3 C^3 x 1 h = 6000000 ppm^3 h
                            C = 183 ppm
                            1-hour AEGL-2 = 183 ppm/3 = 61 ppm (220 mg/m^3)

4-hour AEGL-3 C^3 x 1 h = 6000000 ppm^3 h
                            C = 114 ppm
                            4-hour AEGL-2 = 114 ppm/3 = 38 ppm (140 mg/m^3)

8-hour AEGL-3 C^1 x 8 h = 600 ppm h
                            C = 75 ppm
                            8-hour AEGL-2 = 75 ppm/3 = 25 ppm (90 mg/m^3)

Derivation of AEGL-3

Key Studies:	DuPont (1993a)
Toxicity endpoint: 1414 ppm	LC_{50} of 1980 ppm for a 4-hour exposure. Calculation of $BMCL_{05}$ with
Time scaling	C^3 x t for extrapolation to 1 hour, 30 minutes k = 1414^3 ppm^3 x 4 h = 11308583776 ppm^3 x h C^1 x t for extrapolation to 8 hours 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
<u>10-minute AEGL-3</u>	10-min AEGL-3 = 30-min AEGL-3 = 280 ppm (1000 mg/m^3)
<u>30-minute AEGL-3</u>	C^3 x 0.5 h = 11308583776 ppm^3 h C = 2828 ppm 30-min AEGL-3 = 2828 ppm/10 = 280 ppm (1000 mg/m^3)
<u>1-hour AEGL-3</u>	C^3 x 1 h = 11308583776 ppm^3 h C = 2245 ppm 1-hour AEGL-3 = 2245 ppm/10 = 220 ppm (790 mg/m^3)
<u>4-hour AEGL-3</u>	C = 1414 ppm 4-hour AEGL-3 = 1414 ppm/10 = 140 ppm (500 mg/m^3)
<u>8-hour AEGL-3</u>	C^1 x 8 h = 5656 ppm h C = 707 ppm 8-hour 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}.

Probit Model with 0.95 Confidence Level

10:27 10/15 2003
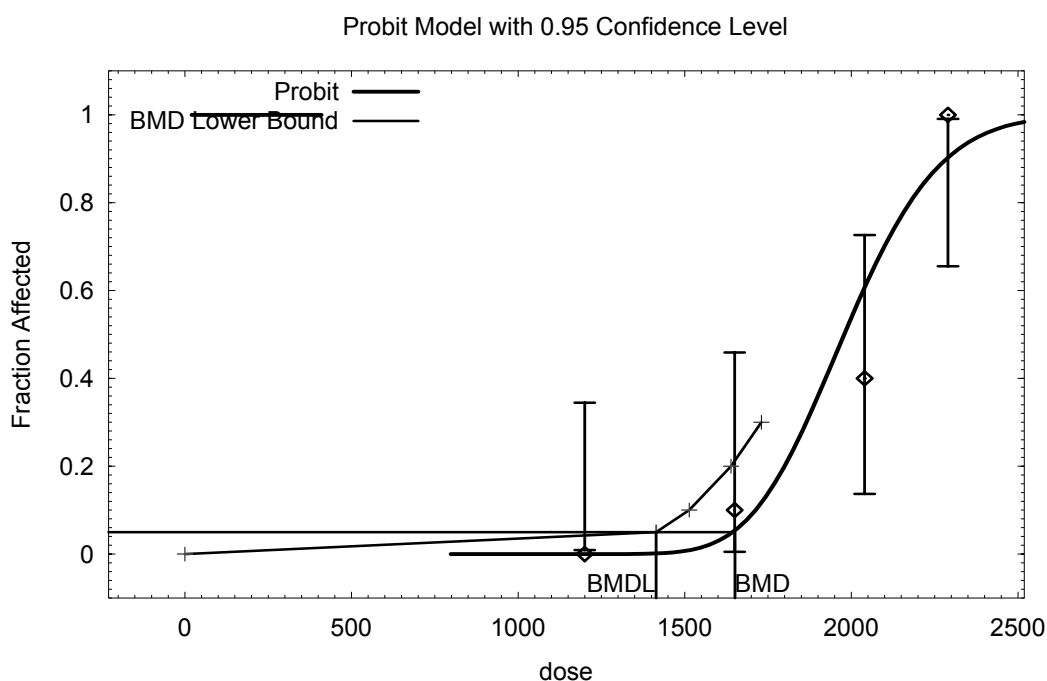
Model Parameter
The form of the probability function is: P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)), where CumNorm(.) is the cumulative normal distribution function.
  Dependent variable = n_lethal
  Independent variable = concentration
  Background parameter is set 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

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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.	Expected	Observed	Size	Scaled 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	8h
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**	630	630	500	310	160
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-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
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

AEGL-2 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
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

AEGL-3 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
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