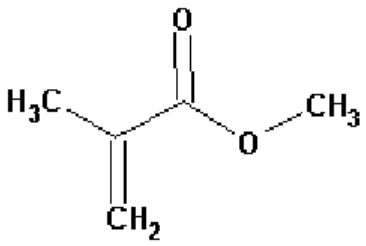
Interim: 10/2008

United States Environmental Protection Agency
Office of Pollution Prevention and Toxics

METHYL METHACRYLATE
(CAS Reg. No. 80-62-6)



INTERIM ACUTE EXPOSURE GUIDELINE LEVELS
(AEGLs)

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PREFACE

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

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

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

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

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

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

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EXECUTIVE SUMMARY

Methyl methacrylate (MMA) is a colorless liquid with an acrid, fruity odor. Odor thresholds are reported as of 0.049 ppm for detection and of 0.34 ppm for recognition.

MMA is miscible with most organic solvents and moderately soluble in water. It is highly volatile with a vapor pressure of 36 - 47 hPa at 20 °C. MMA is used as a basic material for different resins and plastics, either as a monomer or as a polymer (poly-methyl methacrylate). The range of application for methyl methacrylate-based products is broad and includes medical devices, furniture, as well as car, airplane or building components. Exposure results from manufacture, storing or use, mostly by inhalation.

MMA is an irritating and corrosive substance. The nasal olfactory epithelium is the first target tissue and mucosal degeneration and necrosis are reported at low concentrations. Lesions of olfactory epithelium are caused by the MMA metabolite methacrylic acid that is formed enzymatically by carboxylesterase (Mainwaring et al. 2001; Pinto 1997).

Data on acute exposure to humans are limited to a few case reports and epidemiologic studies that often lack a concentration surveillance. Most studies indicate an 8-hour time-weighted average of 50 ppm and short term peak concentrations well above this concentration to be tolerable for workers (Roehm 1994; Coleman 1963; Cromer and Kronoveter 1976; Lindberg et al. 1991) with respiratory irritation being the critical toxicity. The human effect data suggest that the nonlethal toxic response is qualitatively similar to that observed in animal studies. Concerning lethality, no human reports are available. Although some human case studies report asthmatic attacks in workers, no sufficient evidence is available for sensitizing effects of MMA on the respiratory tract. Non-specific asthmatic responses due to respiratory tract irritation cannot be excluded.

MMA shows a low acute toxicity after inhalation with a 4-hour LC_{50} of 7093 ppm in rats (Tansy et al. 1980a). For a 2-hour exposure, LC_{50} values between 10,820 ppm and 16,830 ppm were reported. Death is attributed to respiratory failure. At (sub)lethal concentrations pulmonary lesions are seen including emphysema, edema, and collapsed lungs. High concentrations result in effects on the central nervous system (CNS), liver, kidney, urinary passages, thymus and cardiovascular system (Spealman et al. 1945; Deichmann 1941; Kessler et al. 1977). CNS effects were observed in animal studies at concentrations above 1000 ppm and are expressed by a decrease of reflex activity and result in motor weakness, increased gastrointestinal activity and excretion, effects on respiratory rate and cardiovascular system, and behavioral changes (Tansy et al. 1977; DuPont 1937; Deichmann 1941; DuPont 1993a, b). Respiratory irritation in rats has been reported at concentrations of 110 ppm and above for a 6-hour exposure (Pinto 1997).

Sporadic positive results were observed in in vitro genotoxicity studies, but no evidence of a mutagenic potential arose from in vivo studies with experimental animals or humans. Further, no evidence for carcinogenicity is available from animal studies or from human investigations (IARC, 1994).

AEGL-1 values are based on observations after occupational exposure. In a NIOSH study, medical examinations of workers in poly-MMA-sheet-production plants (n=91 exposed; highest exposure at TWA of 25-50 ppm for 8 hours/day for 24 workers) revealed no significant

acute effects (no cardiovascular changes, no effects on lung function, and no effects in the upper respiratory tract (URT)). Indications of eye and URT effects, and lightheadedness were attributed to occasional spills or chronic exposure (Cromer and Kronoveter, 1976). From this study a no adverse effect concentration (NOAEC) of 50 ppm is derived. An uncertainty factor of 3 is used to extrapolate from workers to the general public including sensitive subpopulations. Slight irritating effects are assumed to be concentration dependent with no relevant increase in severity over time. In accordance to the procedure used for acrylic acid and methacrylic acid, identical AEGL-1 values of 17 ppm are proposed for exposure from 10 minutes to 8 hours. This approach is supported by the result from animal studies. Reversible, slight degenerative effects on the olfactory mucosa were observed in rats after single exposure to 110 ppm (6 hours) (Pinto 1997). The severity of injuries was judged as above AEGL-1 threshold necessitating a modifying factor of 2. Due to the lower susceptibility of humans to MMA-exposure to the nasal tissue, the interspecies uncertainty factor would be reduced to 1. To cover interindividual differences, an intraspecies uncertainty factor of 3 would be chosen, leading to an overall uncertainty/ modifying factor of 6. This approach leads to nearly identical AEGL-1 values based on the human data.

Degeneration and atrophy of olfactory epithelium up to a complete demucosation in rats were observed by Mainwaring et al. (2001) and Jones (2002) and were regarded as key effects for derivation of AEGL-2. These lesions were seen following a 6-hour exposure to 200 ppm as well as 18 hours later with increasing severity (Mainwaring et al., 2001). No major differences in toxicodynamics are expected due to the mode of action of MMA as a local irritant. Toxicokinetic investigations revealed differences between rats and humans, mainly based on a varying enzymatic metabolism. However, enzymatic activity in humans is shown to be generally lower than in rats, thus protecting from effects caused by methacrylic acid. Due to the lower susceptibility of humans to MMA-exposure to the nasal tissue, the interspecies uncertainty factor was reduced to 1. To cover interindividual differences, an intraspecies uncertainty factor of 3 was chosen. There are no suitable studies to derive a substance specific time scaling factor n in the equation $C^n \times t = k$ for local or systemic effects. Thus, the default value of n = 3 in the exponential function was used for extrapolation from the 6-hour exposure to short durations and n = 1 was used for the 8 hour duration. Because extrapolation from 6 hours to short durations of less than 30 minutes leads to a very high uncertainty the value for 10 minutes was set equal to the value for 30 minutes.

The AEGL-3 values are based on a $BMCL_{05}$ of 3613 ppm from a 4-hour exposure to rats showing lethality from the studies of Tansy et al. (1980a) and NTP (1986) analyzed together. Toxic effects other than lethality have not been described in Tansy et al. (1980a). Other authors, including NTP (1986), reported depression, dyspnea, coma, and abnormal gait at high sublethal and lethal exposure concentrations and respiratory failure was the cause of death in lethality studies. No information concerning species differences in toxicokinetics and toxicodynamics in the lower respiratory tractis available. However, lethality concentrations (LC50, 4 hours) differed only marginally between rats, mice, rabbits and guinea pigs. Consequently, no large interspecies differences are expected. Therefore, an interspecies uncertainty factor of 3 was chosen. An uncertainty factor of 3 was used for intraspecies variability, leading to an overall uncertainty factor of 10. There are no suitable studies to derive a substance specific time scaling factor n in the equation $C^n \times t = k$. 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 calculated values are listed in the Table 1 below.

TABLE 1. Summary of AEGL Values for Methyl Methacrylate [ppm (mg/m^3)]*

Classification	10-min	30-min	1-h	4-h	8-h	Endpoint / Species	Reference
AEGL-1 (Nondisabling)	17 (71)	17 (71)	17 (71)	17 (71)	17 (71)	No effect level for notable discomfort; no significant acute effects in workers exposed to 25-50 ppm up to 8 hours/d	Cromer and Kronoveter (1976)
AEGL-2 (Disabling)	150 (620)	150 (620)	120 (500)	76 (320)	50 (210)	No effect level for irreversible health effects; atrophy of olfactory epithelium up to complete demucosation rat	Mainwaring et al. (2001), Jones (2002)
AEGL-3 (Lethal)	720 (3000)	720 (3000)	570 (2400)	360 (1500)	180 (750)	$BMCL_{05}$ for lethality; severe breathing problems up to respiratory failure rat	Tansy et al. (1980a) and NTP (1986) analyzed together

* Skin sensitizing properties of methyl methacrylate can not be excluded.

Based on a study from Hellman and Small (1974) a "level of distinct odor awareness" (LOA) of 0.1 ppm was derived.

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1. INTRODUCTION

Methyl methacrylate (MMA) is a colorless liquid with an acrid, fruity odor. Odor threshold in the range of 0.083 - 0.34 ppm are reported by ECETOC (1995). Maclaine Pont (1991) lists an odor threshold for detection between 0.2 and 0.62 mg/m^3 (0.048 - 0.15 ppm). The lower concentration originates from Hellman and Small (1974) who state a level of odor detection of 0.05 ppm. For recognition values between 0.85 and 1.9 mg/m^3 (0.2 - 0.46 ppm) are listed by Maclaine Pont (1991). The American Industrial Hygiene Association (AIHA 1997) evaluated odor threshold concentrations and reported thresholds of 0.049 ppm for detection and of 0.34 ppm for recognition as most reliable.

TABLE 2. Chemical and Physical Properties

Parameter	Value	Reference
Synonyms	2-Methyl-2-2propenoic acid, methyl ester (CAS name) Methacrylic acid, methyl ester Methyl-α-methacrylate Methyl 2-methylpropeonate Methyl 2-methyl-2-propeonate Methylpropylene-2-carboxylate	ECETOC (1995)
Chemical formula	$C_5H_8O_2$	ECB (2002)
Molecular weight	100.11 100.12 100.13	EPA (1998) ECETOC (1995) ACGIH (2001)
CAS Reg. No.	80-62-6	ECETOC (1995)
Physical state	Colorless liquid	ECETOC (1995)
Solubility in water	16 g/l	ECETOC (1995)
Vapor pressure	36 - 47 hPa at 20 °C	ECETOC (1995)
Vapor density (air =1)	3.5	ECETOC (1995)
Liquid density (water =1)	0.944	ECETOC (1995)
Melting point	- 48 °C - 50 °C	EPA (1998) Patty (1967)
Boiling point	100 - 101 °C	EPA (1998)
Conversion factors	mg/m^3 = 4.16 x ppm 1000 ppm = 4.16 mg/l	ECETOC (1995)

MMA is miscible with most organic solvents (e.g. alcohol, ether, acetone) and moderately soluble in water (ECETOC 1995).

MMA is used in a wide broad of applications, either as monomer or polymer (ECETOC 1995; ECB 2002; EPA 1998). As a monomer it is used to make resins and plastics, or polymerized to poly-methyl methacrylate (poly-MMA) and with other acrylates. The main use of MMA is as an intermediate in the plastics industry. The MMA containing plastics (e.g. "Plexiglas®") are used in the building, automotive, aerospace, and furniture industries. In medicine technics poly-MMA is a component of bone cement which is used for fixation of prosthesis, and artificial teeth. Additionally, hard contact lenses are made of poly-MMA (Scolnick 1992). Medicinal used poly-MMA shows a monomer content of up to 1% (Böhnke et al. 1985). The range of monomeric MMA content in various polymeric products is reported between 0.005 and 1.1%. To prevent polymerization, the MMA monomer is stabilized with

inhibitors, e.g. hydroquinone. In the USA, the commercial production of MMA began in the late 1930s (Collins et al. 1989).

In the environment MMA exclusively results from anthropogenic sources. Detailed measurements of airborne MMA at 5 plants manufacturing poly-MMA sheets revealed mean 8-hour time weighed average concentrations of 3.8 - 86 ppm (16 - 360 mg/m^3) (ECETOC 1995). Workplace concentrations in medical areas are reported as of 0.5 - 100 ppm (2 - 416 mg/m^3). The primary inhalation hazards are manufacture, storing, and use of MMA, either in medicinal or industrial application. Exposure can also occur via dermal contact. Oral uptake is suggested to be rare due to the pungent odor (Tansy and Kendall 1979).

A saturated vapor concentration as of 38 000 ppm (indicated as 3.8%) is reported by Maclaine Pont (1991).

The monomers readily polymerize when exposed to light, heat, oxygen and ionizing radiation (NTP 1986). Below 0 °C no polymerization occurs (ECETOC 1995).

According to Directive 67/548/EEC MMA is classified as highly flammable (risk phrase R11).

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No human case studies concerning lethality following inhalation, oral, and dermal exposure to MMA are available.

Powell et al. (1970) reported a lethal case of an 81-year old woman who died following an operative replacement of a femoral head using MMA based bone cement. 10 to 15 minutes after insertion of the bone cement, the patient became hypotensive and had a cardiac arrest a few seconds later.

2.2. Nonlethal Toxicity

Reports concerning toxic effects following exposure to MMA are mainly restricted to workers and patients during hip replacement surgeries.

2.2.1. Case Reports

A human case study of a 31-year old operating room nurse exposed to MMA at workplace is reported by Scolnick and Collins (1986). During orthopedic surgeries, that usually lasts 30 minutes, she developed a bifrontal headache, slight dizziness, sensation of heaviness in the arms and legs, and a sense of extreme lethargy. Later at the examination she complained of sensation in the chest and breathing difficulties. Blood pressure, pulse, and respiratory rate were elevated. Her conjunctivae were congested and she showed diffuse patchy erythroderma of the chest, back, neck, face, and arms. She suffered from anorexia, nausea, and headache until the day after exposure. Sore throat and chest congestion lasted for additional 2 days. None of the concurrently exposed workers complained of any signs of toxicity. Environmental air samples of

her workplace (collected near the mixing table) revealed 0.4 ppm, 1.0 ppm, and 1.5 ppm MMA over a 15-minute period.

Nayebzadeh and Dufresne (1999) report two cases of occupational asthma among dental technicians. The time-weighted average concentrations of MMA in the 2 investigated dental laboratories were 0.7 ppm and 1.6 ppm with an average peak concentration of 9.3 ppm and 9.7 ppm. The authors mentioned that occupational exposure of dental technicians is not limited to the handling of MMA.

Lozewicz et al. (1985) reported 1 case of asthmatic reaction immediately occurring following provocation by MMA. The worker of a dental laboratory mixed polymethyl methacrylate powder with MMA liquid to produce a paste to be used in a prosthetic. After several years of this work, he developed chest tightness, dyspnea, and cough which persisted for several hours after exposure to even small amounts of MMA.

A further case of an asthmatic reaction was described by Wittczak et al. (1996). A female dental technician suffered from dyspnea, wheezing, coughing, and rhinorrhea following 6-month occupational exposure to MMA. During a provocation test with MMA the patient developed severe stridor and dyspnea with concomitant decrease in respiratory volume and peak respiratory flow. The nasal lavage fluid after a bronchial provocation test revealed increased numbers of leukocytes, eosinophils, basophils, albumin, increased eosinophil cationic protein (ECP) and mast cell tryptase. The authors conclude that MMA may cause asthma (probably non-atopic) in persons occupationally exposed.

Pickering et al. (1986) reported the case of a hospital theater sister who had 11 years experience of preparing bone cement 12 times per week. She developed occupational asthma that was related to the processing of liquid MMA. A peak concentration of MMA of 374 ppm for 45 seconds was reported to result in an asthmatic response. No response was observed by performing the bone cement preparation in a fume cupboard (max. level of 76 ppm MMA). The authors concluded that the appearance of asthmatic symptoms was due to exposure to brief, high levels of MMA vapor.

2.2.2. Epidemiologic Studies and Volunteer Studies

Occupational inhalation exposure

An occupational study conducted by the Connecticut Labor Department reported “very definite irritation” to short term exposure to concentrations of 170 to 240 ppm. The workers stated that 100 ppm could be tolerated without discomfort. In one area with 2300 ppm MMA, this concentration was not tolerable by workers (Coleman 1963). No further data are available.

Roehm (1994) conducted comprehensive examinations of workers exposed in 2 German poly-MMA cast sheet productions. The study included exposure assessment by personal air sampling (as 8-hour average value), a questionnaire and a visual examination of the nasal cavity. The workers spend up to 6 hours per day at MMA processing areas. The medical examination of 211 male chemical workers by rhinoscopy and questionnaire revealed no irritation at current exposure (3-40 ppm, 1-6 h exposure/day). The highest exposed workers (n=56) were exposed to 30-40 ppm for 4-5 h/d. In cases of spills, 100-300 ppm (in one case 680 ppm) MMA were measured; in these cases exposure was limited to 5-15 minutes. Self reported symptoms

(lacrimation, impaired nose breathing, dry nose, reduced sense of smell) occurred at exposures to 10-40 ppm. However, after discussion of confounders (hay fever, sinusitis, smoking, antibiotics, peak exposure) a causal relationship to MMA appears questionable. At or below 40 ppm (6 h) no signs of irritation were evident from rhinoscopy. At short term peak exposures (5-15 minutes) well above 100 ppm transient eye- and URT-irritation were observed. After cessation of exposure the observed effects were quickly reversible. Although the study collective also included 12.8% atopics, no work related case of respiratory or skin sensitization was found.

Cromer and Kronoveter (1976) studied 91 MMA exposed and 43 non-exposed workers in 5 plants manufacturing poly-MMA sheets. The study included occupational history, medical evaluations (including pre- and post-shift examinations), and detailed air sampling. The study was conducted by NIOSH (National Institute for Occupational Safety and Health). Atmospheric samples for the survey were collected by personal samplers that the workers wore for the selected portion of a work shift. The collection devices were clipped on the lapel of the workers' shirt. For each worker shift, 2 organic vapor charcoal tubes with a 10-l volume per tube were used. The samples were analyzed by gas chromatography. The results from the 2 tubes were averaged to determine a specific shift-exposure. No significant acute symptoms, as measured by symptomatology, blood pressure, and pulse rate, were detected during a workday at an 8-hour time-weighted average exposures up to 50 ppm (n=24 with exposures between 25 and 50 ppm). No acute cardiovascular effects, no long term effects on blood pressure, and no significant differences between the exposure and the control groups for a history of allergic problems were noted by exposure of workers to MMA vapor. During the screening survey, questionnaires (n = 350) revealed eye and upper respiratory tract irritation, headache, lightheadedness (a feeling of being high), and skin rash or burn. These effects were attributed to spills. The 8-h TWA at the screening survey were between < 1 to 130 ppm. No significant evidence of acute airway obstruction was found by history and measurement of FVC (forced vital capacity), $FEV_{1.0}$ (forced expiratory volume in 1 second), and $FEV_{1.0}$/FEV ratio.

Lindberg et al. (1991) investigated lung function in 10 floor layers (employed for 0.7 to 12 years) exposed to MMA repeatedly for 20 minutes, followed by 30 to 60 minutes periods (estimated) of no exposure. The concentration measurement was conducted by portable sampling equipment during different stages of work in large and small rooms with different ventilation conditions. Measured MMA concentrations were between 62 and 601 ppm (median 175 ppm) (daily mean values) and were calculated based on concentration measurement and estimated time. The workers were exposed to MMA approximately for one third of the working day. During the no-exposure periods, there was probably additional exposure through contaminated skin. No reduced lung function and no irritability of the airways was observed in any worker. However, 3 workers developed irritation of nose, throat, or eyes as acute response to high concentrations. Five workers reported that they develop frequently some form of problem/symptom in connection with exposure. Three of them reported irritation in the nose or throat. The authors found no evidence that MMA can cause asthma or impair lung function. However it was stated that the sample size is too small to draw definite conclusions. Investigation of chronic effects revealed reddened tonsils and palate in 6 of 10 subjects.

Pickering et al. (1993) investigated the sensitizing effects of MMA in exposed workers by means of a cross sectional questionnaire study. The questionnaire (MRC respiratory questionnaire) intended to identify prevalence of occupational asthma attributable to MMA was distributed at 3 mills where the workers were directly or indirectly exposed to MMA. The study

population was 384 persons (89.1%). Work related respiratory symptoms were persistent cough (2.3%), chronic bronchitis (1%), chest tightness (3.4%), wheeze (2.3%), and breathlessness (1.8%). Nine workers (2.3%) reported 2 or more work related respiratory symptoms of which only 2 suffered from these effects acutely after exposure to high levels of MMA (not further stated). One worker was a smoker, and the other reported the symptoms were worse at the start of the working week. The occupational history from this worker did not support a diagnosis of occupational asthma. No evidence was found that MMA acts as a potent respiratory sensitizer. A possible selection bias can not be excluded by the authors. The data however suggest that MMA does react as a respiratory and mucosal (eye and nasal) irritant.

Mizunuma et al. (1993) studied 49 male factory workers who were exposed to time-weighted average concentration ranged from 0.4 - 112.3 ppm with a geometric mean of 6.1 ppm and a median of 5.3 ppm. The concentrations were measured with personal monitors. Some workers of the high-exposure group (5 - 112 ppm, median 18 ppm) complained of "frequent cough and sputa" and of "throat irritation", however cough and sputa have also been mentioned sporadic in the low-exposure group (< 5 ppm, median 1 ppm). Those with the symptoms were not always the most heavily exposed.

Korczynski (1998) reported irritations of skin, mucous membranes, and eyes following MMA exposure for 20 - 30 minutes of workers in 18 denture clinics. Some workers complained of the acrid, pungent odor. Concentrations measurements in the breathing zone of workers revealed 1 -7.4 ppm (4.09 - 30.64 mg/m^3). Evidences of a dose-response relationship were not given.

Karpov (1954a, b; 1955a,b) investigated respiratory irritation of MMA vapors. Single exposure to 48 - 480 ppm (0.2 - 2 mg/l) for 20 - 90 minutes resulted in irritation of the respiratory tract, weakness, fever, dizziness, nausea, headache, and sleepiness. No further information is available. Due to the broad range of effect concentration and exposure duration, no statement can be made on a dose-response and time-response relationship.

Dobrinskij (1970) reported that 75% of 300 female workers complained of headache, fatigue, and irritability when exposed to MMA concentrations between 24 and 144 ppm. No further information is available. The study is limited due to the broad range of effects concentration and due to the missing control group.

Tansy et al. (1976b) observed that volunteers exhibited a reduction in spontaneous gastric pressure activity when seated next to an open cup of MMA. No further details are reported.

Muttray et al. (1997) investigated the sense of smell in 175 MMA-exposed workers and 88 non-exposed controls from the logistic department with the Rhino-Test®. The mean duration of MMA exposure was 9.6 (±7.1) years. The time-weighted average MMA concentrations were up to 50 ppm for the past 6 years and up to 100 ppm earlier. No higher prevalence of smell disorders has been observed in the test group than in the control group.

Chronic cough was observed in 20% of 40 worker exposed to 77 - 90 mg/m^3 for 5 years (Gezondheidsraad, 1994). In the control group, < 1% revealed a chronic cough (n = 45). Nine ppm (37 mg/m^3) was seen as the upper limit for protection of workers against chronic systemic effects (possible increased heartbeat) and local effects (cough). This effect concentration was

used for the health based recommended occupational exposure limit of the Dutch Expert Committee on Occupational Standards and an exposure limit of 40 mg/m^3 (10 ppm) averaged over an 8 hour working day.

Andrews et al. (1979) investigated 502 dental students by determining the past history and symptoms associated with usual lab activities by a multiple choice questionnaire. Of the exposed students, 6% reported respiratory symptoms and 88% of these had a history of either asthma or allergic rhinitis. Spirometry was performed in normals, asthmatics, and those with allergic rhinitis before and after a controlled exposure to MMA (concentration not stated). There was no significant change in spirometry and symptoms among the test persons.

Savonius et al. (1993) investigated occupational respiratory diseases probably caused by acrylates. The authors report cases of workers exposed to MMA for month or years before onset of symptoms (asthma, sneezing, rhinorrhea, cough). The authors stated that there is no evidence of a specific IgE-mediated reaction at the respiratory tract.

Volunteer Studies with dermal application

Skin sensitization without previous contact was reported by Nyquist (1958). He additionally reported mild erythema and eczematous dermatitis in 18/20 volunteers. No further details are reported.

Cavelier et al. (1981) reported a mild to moderate sensitization rate with undiluted MMA in a 48-hour occlusive patch test in 3 out of 30 volunteers. Two of the 3 persons suffered from allergic dermatitis. No skin reactions were observed in a patch test with 1%, 5%, and 20% MMA in olive oil for 48 to 72 hours at observation after 2, 10, 20, and 30 days, as well as after challenge application after 30 days.

Bäurle (1982) investigated patients with allergic history possibly due to denture materials. A 24-hour occlusive patch test (10% in olive oil; scoring after 24, 48, and 72 h) revealed that 4 of 71 patients developed sensitizing reactions.

Several cases of positive patch test reaction are reported following prosthesis surgery, dental treatment, and use of artificial nail preparations and hearing aids (ECB 2002).

2.3. Genotoxicity and Cytotoxicity

No evidence for a genotoxic potential of MMA in humans are reported from 2 studies that examinated chromosomal aberration and sister chromatid exchange in exposed workers (ECETOC 1995).

Little cytotoxicity as indicated by cell survival has been observed by Fujisawa et al. (2000) in human gingival fibroblasts and in a human submandibular gland adenocarcinoma cell line.

2.4. Carcinogenicity

Collins et al. (1989) observed no significant excesses for specific cancer sites in a cohort study with 1561 persons exposed to MMA occupationally in 2 different plants. Exposure measurements revealed concentration up to 11.5 ppm MMA. The 8-hour time weight average exposure ranged from 0.13 to 1 ppm.

Mortality from colorectal cancer has been reviewed by Walker et al. (1991) using original unpublished reports of three cohorts in two US plants where male workers are exposed to MMA, ethyl acrylate, and volatile by-products of the polymerization process. MMA was the most extensively used chemical (88 - 100%). In the three cohorts, including 13863 white workers employed between 1933 - 86, overall mortality was below that expected on the basis of mortality rates for US white males and the death ratio from all cancers was slightly increased. No consistent increase was observed with increasing exposure duration.

2.5. Summary

The assessment of toxic effects following exposure to MMA in humans is restricted due to the small numbers of valid studies dealing with short-term inhalation exposure. Although several workplace measurements are available, often no information is provided concerning exposure duration, method of concentration surveillance (e.g. personal sampling), and observed acute effects that can be unequivocal assigned to a MMA concentration. However, the NIOSH-study by Cromer and Kronoveter (1976) provides sufficient evidence that no relevant irritation of the URT occurs in workers at exposure to 25-50 ppm. There is no clear lower effect concentration demonstrated in human studies because of insufficient data in the exposure range from 50 to 170 ppm.

TABLE 3. Summary of relevant Nonlethal Inhalation Data in Humans

Concentration	Effects / Remarks	Reference
< 40 ppm (8-h TWA)	No irritation in exposed workers	Roehm (1994)
> 100 - 300 ppm (1 x 680 ppm) (5-15 min)	Transient irritation in exposed workers from concentrations well above 100 ppm onwards	Roehm (1994)
Up to 50 ppm (8-h TWA)	No acute symptoms	Cromer and Kronoveter (1976)
62 - 601 ppm; median 175 ppm (daily mean values)	Irritation of nose, throat or eyes in 10 workers at high concentration	Lindberg et al. (1991)
170 - 240 ppm (duration not explicitly stated; presumably refers to an 8-h TWA)	Marked irritation in exposed workers	Coleman (1963)
374 ppm (45 seconds)	Asthma attacks; developed after 11 years of occupation. No effects at 76 ppm.	Pickering et al. (1986)

Based on Coleman (1963) the ACGIH (2001) derived the TLV-STEL value of 100 ppm. Due to the high vapor pressure of MMA, an 8-hour TWA might not be convincing for the actual exposure that includes high peak concentrations.

Acute effects on the cardiovascular system, reported from patient with surgically inserted poly-MMA (Powell et al. 1070) were not seen in persons exposed to vapor MMA (Cromer and Kronoveter 1976).

As a potential skin sensitizer in humans, MMA was labeled with the risk phrase R43 (May cause sensitization by skin contact) according to the Directive 67/548/EEC. Some case studies indicate that MMA can cause occupational asthma. The affected patients were regularly exposed to MMA at workplace for several month or years (Nayebzadeh and Dufresne 1999; Losewicz et al. 1985; Savonius et al. 1993; Wittczak et al. 1996; Pickering et al. 1986). However, epidemiological studies found no evidence of MMA to act as a potent respiratory sensitizer (Lindberg et al. 1991; Roehm 1994, Cromer and Kronoveter 1976; Andrews et al. 1979; Pickering et al. 1993). According to ECB (2002) sufficient evidence is not available for sensitizing effects of MMA on the respiratory tract. Non-specific asthmatic responses due to respiratory tract irritation cannot be excluded. Pickering et al. (1986) reported the occurrence of an asthma attack following exposure to 374 ppm, which is a concentration that likely causes irritation.

No evidence for genotoxicity or carcinogenicity is available from human data. The IARC (1994) concluded that there is inadequate evidence for carcinogenicity of MMA in humans.

Concentrations of MMA during orthopedic surgery, e.g. hip replacement, are reported as of 280 ppm maximally 0.25 minutes after mixing the cement that decrease quickly due to the high volatility of MMA (McLaughlin et al. 1979). Similar concentrations of 50 - 100 ppm MMA in the breathing zone were reported by Darre et al. (1992) for operating surgeons during 3 knee replacement and 3 hip replacement surgeries. The measurement of concentration was conducted by the use of a Dräger tube and a M21/31 gas detector pump.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1 Non-human Primates

Kessler et al. (1977) reported a lethal case in a rhesus monkey (Macaca mulatta) accidentally exposed to vapors of MMA for 22 hours. The closed-ventilation chamber in which the animal was placed had been cemented with flowing MMA that did not completely polymerize. At time the monkey was found, he was comatose and died shortly afterwards. At necropsy clear yellow fluid was found in each thoracic cavity, the lung was atelectatic (air-free sections) and edematous, and the liver appeared mottled. A centrilobular disintegration and coagulative necrosis of hepatocytes have been observed at histopathology. Microscopic examination of the lung tissue revealed patches of mild pulmonary edema and emphysema. Due to the circumstances of the accident and the pathologic findings, the authors suggest MMA to be responsible. However, the attempt to confirm the diagnosis by gas chromatographic analysis of frozen tissue was unsuccessful. No measurement of chamber MMA concentration was conducted.

3.1.2. Dogs

Lethality after inhalation exposure

Spealman et al. (1945) exposed 2 dogs to MMA concentrations of 41.2 mg/l (approx. 9900 ppm) for 3 hours or 72.1 mg/l (approx. 17 300 ppm) for 90 minutes. The animals were placed in a glass exposure chamber measuring 56 x 61 x 91 cm. MMA containing air was passed at a rate of 500 l/h. MMA concentrations in the chamber were calculated based on the total air volume and amount of material vaporized (nominal concentration). The authors mentioned that

the calculated MMA concentrations were higher than what they were inside the chamber due to the leakage during animal handling. Animals of both sexes were used. After exposure the heart, lungs, spleen, liver, adrenals, kidneys, and gastrointestinal tract were examined. During exposure animals showed excessive salivation, depression, and ataxia, and some vomited. Some temporary conjunctival irritation was observed. All animals died during exposure due to respiratory failure, usually in a depressed condition. Necropsy showed liver degeneration and tubular degeneration in kidney. The liver cells were often swollen and had size- and shape-altered nuclei, as well as changes in cytoplasm (not further characterized). The degree of kidney injuries varied in exposed animals, and could have been observed to a lesser degree in control animals as well.

3.1.3. Rats

Lethality after inhalation exposure

Deichmann (1941) conducted inhalation studies with 6 different MMA concentrations between 5 and 24 mg/l (approx. 1200 - 5750 ppm) for 8 hours. The animals (2 of each group) were exposed in chambers of 47 l volume. Measurement of concentration was conducted by the potassium permanganate method (analytical concentration) and also by computation of the total air volume and vaporized MMA. Some animals were sacrificed immediately after exposure; some after a follow-up observation period of 1 week. Mortality data are presented in Table 3. At toxic or lethal concentrations the animals showed an increased rate of respiration, lacrimation, dyspnea, followed by motor weakness and decreased respiration. Subsequently, respiration became shallow, irregular and labored. Before death in coma increased defecation and urination, as well as loss of reflex activity were reported. At examination, a distinct irritation of the mucous membranes was observed. The pathology showed marked congestion, edema, emphysema, and hemorrhage of different size in lungs, trachea, and bronchi. The thymus gland was congested and swollen. The auricles were dilated and filled with dark clotted blood. Abdominal vessels were dilated and blood was fluid. The urinary bladder was strongly distended and often contained blood. The study is limited due to the small group size of 2 animals.

An additional study was conducted with 6 rats each of different age exposed to 26 mg/l (approx. 6250 ppm) for 4 hours (Deichmann 1941). All adult and 4-week old animals died within a period of 2 to 3 hours, however the 4-day old rats survived 4 hours, but died during extended exposure to 5 hours.

NTP (1986) conducted a study with male and female F344/N rats (age 8 - 10 weeks). Groups of 5 rats of each sex were exposed to MMA vapor concentrations of 1191, 2159, 2220, 4055, 4446, 4632, or 16 000 ppm in a stainless steel and glass chamber. MMA concentrations were monitored twice during each exposure duration either by a photoionization detector or by gas chromatography. All males and 4 of 5 females died within 1 hour of exposure to 16 000 ppm. No lethality was observed following exposure to any of the other concentrations. The animals were held for observation for 14 days and observed daily.

NTP (1986) conducted several inhalation studies with repeated exposure (6 h/day; 5 days/week) in F344/N rats. The animals were exposed in chambers and checked daily. Exposure concentrations were 500, 1000, 2000, 3000, or 5000 ppm. MMA concentrations were monitored twice during each exposure duration either by photoionization detector or by gas chromatography. For every study an unexposed control group was used. In an 11-day inhalation

study with 5 male and 5 female F344/N rats, 2 of 5 females and 1 of 5 males died after the first 6-hour exposure to 5000 ppm (NTP 1986).

Tansy et al. (1980a) determined a LC_{50} of 7093 ppm for a 4-hour exposure in Sprague-Dawley rats (10 animals at each dose group). 5 animals of each sex were exposed to 5 different concentrations (4750, 6146, 8044, 10209, and 13479 ppm) in a 75-liter glass dynamic chamber (see Table 3). Liquid MMA was pumped at a fixed rate into a vaporization chamber where it vaporized almost immediately (described in Tansy et al. 1976a). Measurement of MMA concentration was conducted by gas chromatography. The animals were held for observation for 24 hours. The LC_{50} was calculated based on interpolation of a linear regression with the log of the number of survivors against the vapor concentration. No information on toxic effects other than lethality is given.

A 2-hour exposure LC_{50} - value of 11220 ppm was calculated by Guoshon et al. (1988). At lethal concentrations lacrimation, salivation, nasal irritation (sneezing) were observed. The animals showed a hyperactive behavior, followed by decreased activity, deep and rapid respiration and an abnormal gait. Prior to death they collapsed in a moribund condition. Pathological examinations revealed emphysema, partially collapsed lungs, and a hemorrhagic heart muscle. No further details are available.

Rohm and Haas (1958) conducted an acute inhalation toxicity study in male albino rats. The animals were exposed for 2 hours to different MMA concentrations in an 190 l-chamber in which MMA was continuously injected via a heated tube at a predetermined rate (nominal concentration). LC_{50} values between 10820 ppm and 16830 ppm were determined from 3 different series with animals of different body weight. The data indicated that a lower body weight reduces lethal concentrations of MMA. At all dose groups animals soon became comatose. Prior to death breathing was deep, slow and spasmodic. Recovery took usually a few hours and no animal died later than the night after exposure. Lethality incidences are summarized in Table 3 for all 3 series. No further details are reported.

Rohm and Haas (1958) reported additional studies with an exposure duration of 6 hours. Four animals each were exposed to 6490 ppm, 12981 ppm, or 19231 ppm. After the rats were in the exposure chamber, a definite amount of MMA was placed in a Petri dish from were it evaporated (nominal concentration). Four rats were used as control group. No rat died at 6490 ppm and 12981 ppm, but all rats died within 5 hours at 19231 ppm. During exposure all rats became depressed, but recovered after removal from the chamber at the non-lethal concentrations. At 12981 ppm animals showed a slowed and shallowed breathing. No information concerning a post-exposure observation period is given.

DuPont (1937) conducted a whole-body inhalation study with rats (strain not indicated) exposed to different concentrations of MMA for 8 hours. Determination of MMA concentration was conducted by the potassium permanganate method (analytical concentration). The animals were observed for an unknown duration following exposure. Incidences of lethality are summarized in Table 3. At lethal concentration rats became depressed and died in coma. For non-lethal effects see Section 3.2 (Nonlethal Toxicity). No further details are given.

Nicholas et al. (1979) determined the acute inhalation LT_n values (period of time to cause death in n % of animals at a specific concentration) for female Sprague-Dawley rats. Ten

animals were exposed (head/nose only) to MMA vapor in an 11 l cylindrical chamber. Vapor concentrations were monitored by gas chromatography. Time to death data are summarized in Table 3. Usually the animals died during exposure, however for some animals a delayed death within 24 hours was reported. No details on toxic effects are reported.

3.1.4. Mice

Lethality after inhalation exposure

NTP (1986) conducted a study with male and female $B6C3F_1$ mice (age 8 weeks). For detailed study design see Section 3.1.3 (Rats). Group size and vapor concentrations were identical to the respective rat study. All animals died within 1 hour of exposure to 16000 ppm. One animal each died at 1191 ppm (male), at 4446 ppm (males), and at 4055 ppm (female). Time-to-death was 7 days in the 1191 ppm group, and 1 day for the other 2 concentrations. No lethality was observed following exposure to any of the other concentrations (highest LC_0 concentration 4632 ppm). The animals were held for observation for 14 days and observed daily.

NTP (1986) conducted several inhalation studies with repeated exposure (6 h/day; 5 days/week) in $B6C3F_1$ mice. The animals were exposed in chambers and checked daily. Exposure concentrations were 500, 1000, 2000, 3000, or 5000 ppm. MMA concentrations were monitored twice during each exposure duration either by photoionization detector or by gas chromatography. For every study an unexposed control group was used. In an 11-day inhalation study with 5 male and 5 female $B6C3F_1$ mice, all females and 3 of 5 males died after the first 6-hour exposure to 5000 ppm (NTP 1986).

Spealman et al. (1945) exposed 15 or 20 adult albino mice each to different MMA vapor concentrations. For study details see Section 3.1.2 (Dogs). Depression, ataxia, and excessive salivation were reported as observations during exposure for most animals. Exposure to 26.2 mg/l (approx. 6300 ppm) was lethal for 1 out of 20 animals after 3 hours. At 47.7 mg/l (approx. 11 500 ppm) for 3 or 5 hours (2 separate studies) 2, respectively 9 of 15 animals died after 2 to 3 respectively 5 hours of exposure. All animals died following exposure to 61.8 mg/l (approx. 14 900 ppm) for 3 hours (15 animals) and 96.4 mg/l (approx. 23 200 ppm) for 3 hours (20 animals). At these exposures all animals died within 1 to 3 hours. In a few cases the heart was beating after stoppage of respiration suggesting that death was due to paralysis of respiratory apparatus. At necropsy liver degeneration (swollen liver cells, size- and shape altered nuclei, changes in cytoplasm), hepatitis and focal necrosis were reported for the 2 intermediate concentrations. No details are reported for the other 2 concentrations. Hepatitis and focal necrosis are of questionable relevance for MMA intoxication due to their occurrence in unexposed animals.

Lawrence et al. (1974) determined an acute inhalation LT_{50} (period of time to cause death in 50% of animals at a specific concentration) for male ICR mice. The animals (number not indicated) were exposed in an 8.75 l all glass container, in which air containing MMA was passed. The animals showed depressed activity, lacrimation, and occasional salivation. Lethality incidences for the 8 exposure durations are listed in Table 3.

A 2-hour LC_{50} - value of 7561 ppm was calculated by Guoshon et al. (1988). Identical toxic effects to that observed in rats were described (see Section 3.1.3).

Blagodatin et al. (1976) reported a LC_{50} of 4450 ppm for a 2-hour exposure. No further details are available.

3.1.5 Guinea Pigs

Lethality after inhalation exposure

Deichmann (1941) conducted inhalation studies with 6 different MMA concentrations between 5 and 24 mg/l (approx. 1200 - 5750 ppm). One animal of each dose group was exposed for 8 hours. For study details and observed effects see Section 3.1.3 (Rats). In contrast to rats, urinary bladder revealed no distension. Incidences of lethality are summarized in Table 4.

Spealman et al. (1945) exposed 6 guinea pigs to 72.1 mg/l MMA (approx. 17330 ppm) for 4 ¼ hours. For study details see Section 3.1.2 (Dogs). Depression, ataxia, excessive salivation and conjunctival irritation were reported during exposure for most animals. All animals died after 2 ¾ to 4 ¼ hours due to respiratory failure, usually in a depressed condition. At necropsy liver degeneration, e.g. swollen liver cells, size- and shape altered nuclei, changes in cytoplasm, was observed.

3.1.6 Rabbits

Lethality after inhalation exposure

Deichmann (1941) conducted inhalation studies with 6 different MMA concentrations between 5 and 24 mg/l (approx. 1200 - 5750 ppm). One animal of each dose group was exposed for 8 hours. For study details and observed effects see Section 3.1.3 (Rats). In addition to the congestion and swelling, the thymus gland was spotted with petechial hemorrhages. In contrast to rats, urinary bladder revealed no distension. Incidences of lethality are summarized in Table 3.

Lethality after dermal exposure

Rohm and Haas (1982) reported a dermal LD_{50} of greater than 5 g/kg in New Zealand white rabbits. A LD_{50} from dermal application was reported greater than 9.4 g/kg (> 10 mL/kg) (Autian 1975). At site of application, severe erythema and edema were observed at 5 g/kg.

TABLE 4. Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Conc. (ppm)	Exposure	Result	Number of animals Most important effects	Reference
Dog	17300	1.5 h	LC_{100}	2 Animals; whole-body exposure; nominal concentration; liver degeneration; tubular degeneration in kidney	Spealman et al. (1945)
Dog	9900	3 h	LC_{100}	2 Animals; whole-body exposure; nominal concentration; injuries as above	Spealman et al. (1945)
Rat	16000	1 h	LC_{100}	5 Animals of each sex; whole-body exposure; analytical concentration 5/5 males and 4/5 females died within 1 h	NTP (1986)
Rat	9860	1 h	LC_0	0/10 died Weight loss, irritation of respiratory tract; nose-only exposure; analytical conc.	DuPont (1993a) *see section 3.2.2*

TABLE 4. Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Conc. (ppm)	Exposure	Result	Number of animals Most important effects	Reference
Rat	7930 10580 10820 11780 12020 12980 14420 15870 16830 17550 18510 19230 20430	2 h	LC	0/6 Died 0/6 Died 1/6 Died 8/12 Died 0/6 Died 5/6 Died 2/12 Died 0/6 Died 17/24 Died 3/6 Died 6/6 Died 6/6 Died 4/6 Died	Rohm and Haas (1958)
	16830 10820 - 12020 12020		 LC_{50} LC_{50}	Whole-body exposure; nominal conc. respiratory troubles, coma at all conc. Animal weight of 200 - 300 g Animal weight of 150 - 200 g	
			LC_{50}	Animal weight of about 150 g	
Rat	6250	4 h	LC_{100}	6 Adult and 6 juvenile animals died within 2 - 3 hours Whole-body exposure; analytical conc.; respiratory failure	Deichmann (1941)
Rat	 0 1191 2159 2220 4055 4446 4632 16000	 4 h	 $BMCL_{05}$	5 Animals of each sex; whole-body exposure; analytical concentration 0/10 Died 0/10 Died 0/10 Died 0/10 Died 0/10 Died 0/10 Died 0/10 Died 9/10 Died See Appendix B	NTP (1986)
Rat	 0 4750 6146 8044 10209 13479	 4 h	 $BMCL_{05}$	5 Animals of each sex; whole-body exposure; analytical conc. 0/10 Died 2/10 Died 3/10 Died 8/10 Died 10/10 Died 10/10 Died See Appendix B	Tansy et al. (1980a)
Rat	6250	5 h	LC_{100}	6 Newborn animals died after 5 hours Whole-body exposure; analytical conc.; respiratory failure	Deichmann (1941)
Rat	12981 19231	6 h	LC	0/4 Died (highest non-lethal conc.) 4/4 animal died within 5 h Whole-body exposure; nominal conc. Depression, respiratory troubles	Rohm and Haas (1958)

TABLE 4. Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Conc. (ppm)	Exposure	Result	Number of animals Most important effects	Reference
Rat	5000	6 h	LC	1/5 Males and 2/5 females died after 1st exposure of a repeated exposure study; whole-body exposure; analytical conc.	NTP (1986)
Rat	1200 1700 3750 4200 4550 5750	8 h	LC	0/2 Died 1/2 Died after 5 hours 0/2 Died 1/2 Died after 3.5 hours 2/2 Died after 2.5 hours 2/2 Died after 2 hours Whole-body exposure; analytical conc.; respiratory failure	Deichmann (1941)
Rat	4830 6150 6370 7210 7520 7930 8560 22190	8 h	LC	0/5 Died (highest non-lethal conc.) 3/5 Died ed between 4 and 8 hours 5/10 Died between 5 and 8 hours 6/10 Died between 6 and 30 hours 5/5 Died between 3 and 8 hours 7/10 Died between 4 and 8 hours 5/5 Died between 3 and 8 hours 5/5 Died between 1 - 1.5 hours Whole-body exposure; analytical conc. Depressed condition, coma	DuPont (1937)
Rat	2.6e+09	42.3 min 51.2 min 62 min 75 min 90.8 min 109.8 min 132.9 min 160.8 min 72.2 min	LT LT_{50}	0/10 Died 1/10 Died (death occurred within 24 h) 3/10 Died 7/10 Died (2 death occurred within 24 h) 8/10 Died 9/10 Died (2 death occurred within 24 h) 9/10 Died (1 death occurred within 24 h) 10/10 Died (1 death occurred within 24 h) Nose/head exposure; analytical conc. No further details on toxic effects calculated	Nicholas et al. (1979)
Mouse	16000	1 h	LC_{100}	5 Animals of each sex; whole-body exposure; analytical concentration All animals died within 1 hour of Exposure; no details	NTP (1986)
Mouse	6300	3 h	LC	20 Animals; whole-body exposure; Nominal concentration 1 Animal died within 3 h No details reported	Spealman et al. (1945)
Mouse	11500 14900 23200	3 h	LC	2 of 15 Animals died within 3 h 15 of 15 Animals died between 1 and 3 h 20 of 20 Animals died within 2¼ h whole-body exposure; nominal concentration; same injuries as above;	Spealman et al. (1945)
Mouse	1191 2159 2220 4055 4446 4632	4 h	LC	1 Male died after 7 days 0/10 Died 0/10 Died 1 Male died after 1 day 1 Female died after 1 day 0/10 Died 5 Animals of each sex; whole-body exposure; analytical concentration	NTP (1986)
Mouse	11500	5 h	LC	15 Animals; whole-body; nominal conc.	Spealman et al.

TABLE 4. Summary of Acute Lethal Inhalation Data in Laboratory Animals					
Species	Conc. (ppm)	Exposure	Result	Number of animals Most important effects	Reference
				9 Animals died between 2 - 5 h liver degeneration, hepatitis, necrosis	(1945)
Mouse	5000	6 h	LC	3/5 Males and 5/5 females died after 1th exposure of a repeated exposure study; whole-body exposure; analytical concentration	NTP (1986) see Section 3.3
Mouse	40625	26.95 min	LT_{50}	No number of animals given whole-body exposure; no further details	Lawrence et al. (1974)
Mouse	27650	55.82 min	LT_{50}	No number of animals given whole-body exposure; no further details	Lawrence et al. (1974)
Guinea pig	17330	4 ¼ h	LC_{100}	6 Animals died between 2¾ and 4¼ h whole-body exposure; nominal concentration; liver degeneration	Spealman et al. (1945)
Guinea pig	1200 1700 3750 4200 4550 5750	8 h	LC	0/1 Died 0/1 Died 0/1 Died 0/1 Died 1/1 Died after 5 hours 1/1 Died after 5 hours Whole-body exposure; analytical conc.; respiratory failure	Deichmann (1941)
Rabbit	1200 1700 3750 4200 4550 5750	8 h	LC	0/1 Died 0/1 Died 0/1 Died 1/1 Died after 4.5 hours 1/1 Died after 3.5 hours 1/1 Died after 3.5 hours Whole-body exposure; analytical conc.; respiratory failure	Deichmann (1941)

3.2. Nonlethal Toxicity

3.2.1. Dogs

Nonlethal toxicity after inhalation exposure

Tansy et al. (1977) exposed twelve adult anaesthetized mongrel dogs of both sexes to MMA vapors of 2000 ppm for different durations from 3 minutes up to 12 minutes to examine different motor activities of the gastrointestinal tract. The measurements of gastrointestinal motility were conducted online. A few minutes after exposure onset a slight decline in arterial blood pressure was measured as well as a moderate decrease of contractile activity in stomach and a drastic decrease in duodenum. The authors conclude that the observed decline in spontaneous motor activity was due to an inhibitory effect of MMA upon the smooth muscle of the gastrointestinal tract.

DuPont (1937) investigated the effect of MMA on blood circulation and respiration in 2 anaesthetized dogs exposed to 9620 ppm for 5 hours. Recording of the blood pressure was conducted from the carotid artery and of the respiration from the trachea. During exposure blood pressure remained constant. Respiration was stimulated moderately in the beginning, however decreased from 16 to 7 respirations per minute subsequently.

3.2.2. Rats

Nonlethal toxicity after inhalation exposure

NTP (1986) conducted a study with male and female F344/N rats (age 8 - 10 weeks). Groups of 5 rats of each sex were exposed to the non-lethal MMA vapor concentrations of 1191, 2159, 2220, 4055, 4446, or 4632 ppm for 4 hours (for study details see Section 3.1.3, Rats - Acute Lethality). Hypoactivity, dyspnea, and anesthesia were reported as compound-related effects, however, not assigned to a specific exposure concentration.

Deichmann (1941) exposed 2 rats each to concentrations up to approximately 3440 ppm MMA (indicated as 14.3 mg/l) for 8 hours and revealed no lethality. Study details are reported in Section 3.1.3 (Rats - Acute Lethality). At toxic concentrations the animals showed an increased rate of respiration, lacrimation, dyspnea, followed by motor weakness and decreased respiration. Additionally a loss of reflex activity and increase defecation and urination were described.

DuPont (1993a) investigated the inhalation toxicity of MMA in CrlCDBR rats. Two groups of 5 young adult animals of each sex were exposed (nose-only) for 1 hour to MMA concentrations of 9860 or 17790 ppm in perforated, stainless steel polycarbonate cylinders with conical nose pieces. Vapor concentrations in the 29-l glass exposure cylinder were determined by gravimetric analysis and by gas chromatography. Following exposure the animals were observed for a 14 day-period for clinical signs of toxicity. Exposure to 9860 ppm led to nasal and ocular discharge, irregular respiration, lung noise, and wet fur. The same signs, except wet fur, were also observed at 17790 ppm and irregular respiration and lung noise appeared more frequent at the higher concentration. All signs of toxicity were only observed in some of the exposed animals. Most rats showed a slight to moderate loss of body weight, however gained weight during recovery period.

DuPont (1937) conducted an inhalation study with several concentrations of MMA (for study details see Section 3.1.3, Rats - Acute Lethality). The animals were exposed for 8 hours. Concentrations up to 4830 ppm showed no lethality. At 2690 ppm a slight irritation of the upper respiratory tract was observed. At 3220 ppm a slight depression with a quick recovery was observed. Rats exposed to 3850 ppm revealed an increased bowel movement, increased urination, and a slight dyspnea after 1 hour of exposure. One hour later respiration volume was increased, but respiratory rate remained normal. Moderate depression was observed. At 4830 ppm the same signs of toxicity were recorded, however the depression occurred earlier. Except at the highest non-lethal concentration recovery was rapid. At 4830 ppm 3 of 5 animals remained deeply depressed for several hours.

Rohm and Haas (1958) conducted an acute inhalation toxicity study in male albino rats (3 series with different animal body weight) and reported no mortality following 2-h exposure to 7930 ppm (body weight between 150 and 200 g), 10580 ppm (body weight of about 150 g) and 15870 ppm (body weight between 200 and 300 g) MMA. For study details see Section 3.1.3 (Rats - Acute Lethality). The animals soon became comatose, however recovered within a few hours. Smaller animals seem to be more susceptible to MMA vapors.

Rohm and Haas (1958) reported additional studies with an exposure duration of 6 hours. Four animals each were exposed to 6490 ppm, 12981 ppm, or 19231 ppm. For study details see

Section 3.1.3 (Rats - Acute Lethality). At 6490 ppm all rats became depressed during exposure, but recovered rapidly after removal from the chamber. At 12981 ppm animals showed a slowed and shallowed breathing, and recovery was slow. At 19231 ppm all rats died within 5 hours. No information concerning a post-exposure observation period is given.

Pinto (1997) conducted investigations of the rat nasal epithelium. Parts of this study have been published by Hext et al. (2001). Groups of 5 female F344 rats were exposed to MMA concentrations of 110 or 400 ppm, respectively, for 6 hours in stainless steel cages. Concentration measurement was conducted by gas chromatography. Control animals were exposed to air only and were otherwise treated in a similar manner to the test animals. The day following exposure the animals were sacrificed. Macroscopic and microscopic examinations of lungs, trachea, and nose were conducted. Six standard sections of nose were prepared to include the olfactory and respiratory epithelium, maxillary sinus, olfactory bulbs and accessory structures. During exposure and recovery period no deaths and no symptoms of clinical abnormalities were observed. No gross findings were observed at necropsy at either exposure. Lung and trachea revealed no abnormalities at histopathological examination. Degeneration/necrosis of olfactory epithelium was seen in animals exposed to 110 ppm with minimal severity and with moderate severity at 400 ppm. Degeneration of epithelium included vacuolation with occasional pyknotic nuclei, partly detached cells to complete erosion of the epithelium with only the basal membrane remaining intact. At 400 ppm reduction of bowman glands, an inflammatory exudate within the nasal passages, and an inflammatory infiltrate within the submucosa were observed. Up to 50% of the olfactory epithelium was affected by degeneration and necrosis following exposure to 400 ppm.

Jones (2002) investigated the nasal toxicity of 200 ppm MMA for a 6-h duration. Five male Fischer 344 rats were exposed to MMA (analytical concentrations; gas chromatography) or air (control group) in a chamber. After exposure the animals were immediately sacrificed and processed for the examination of 6 sections of the nasal passages. During exposure the animals behaved normally. Degeneration of olfactory epithelium (central septum and ethmoturbinates) was observed in 3 of the 5 animals with a moderate severity. In 2 animals no abnormalities were observed. The respiratory epithelium as well as the adjacent area was not affected in any animal.

Mainwaring et al. (2001) exposed groups of 5 female F344 rats whole-body to 200 ppm for 3 or 6 hours. No information on concentration surveillance was given. An equivalent number of control rats were exposed to air alone. The animals were sacrificed either immediately after exposure or 18 hours after cessation of exposure. Respiratory and olfactory nasal tissues were examined separately. Nasal passages of the 3 h-group showed no morphological abnormalities compared with control animals. Longer exposure of 6 hours led to degeneration/atrophy of the olfactory epithelium. The lesions included undulating epithelium, tagged and desquamated cells, as well as complete demucosation. These effects were seen at the end of the exposure and 18 h later with increasing severity. The authors suggest that the lack of findings following 3-hour exposure was probably because the lesions hat no time to develop due to the examination immediately after exposure.

Robinson et al. (2003) investigated lesions of the olfactory epithelium. Three male Alpk.AP$_f$SD Wistar rats were exposed (nose-only) to 400 ppm for 4 hours. MMA concentration was sampled regularly by gas chromatography. Three control rats were exposed to clean, dry air. After cessation of exposure, rats were sacrificed and nasal passages were sectioned transversely.

Six levels were selected to represent the lesions, with level 1 being at the front of the nose and level 6 at the back. These levels correspond to levels 5, 7, 10, 17, 23, and 28 described by Mery et al. (1994). The observed lesions have been graded according to severity as follows: vacuolation and pyknosis; undulation and mild stripping; marked/complete stripping. All 3 degrees of severity were observed, however not quantified. From the supplied figures marked stripping and loss of epithelium occurred in 3 of the 6 levels (2, 3, and 5). Undulating and mild stripping was observed in the levels 4, 5, and 6, and the least severe effects (vacuolation and pyknosis) were restricted to the levels 3 and 4. The most severe lesions therefore appeared at level 5, and targeted the medial septum and the medial tips of the 3rd to 5th ethmoturbinates. A further part of the olfactory epithelium at level 5, the Masera´s organ, has also been affected. This structure, a small region of neuroepithelial tissue, is believed to be the first chemosensory structure activated by incoming molecules.

Raje et al. (1985) observed various changes in lung tissue at histopathological examinations following head/nose exposure of male S/D rats (4 animals) to about 95 ppm (395 mg/m^3) for 2, 3 or 4 hours. Exposure concentration analysis was conducted by gas chromatography continuously. The animals were sacrificed immediately after exposure and examination of lung and brain was conducted. The changes observed at exposure durations of 2, 3, and 4 hours were interalveolar congestion and hemorrhage, pulmonary vasodilation and edema. No information on time-response relationship of the observed lesions was given, and no control group was investigated. After 1-hour exposure no changes in lung tissue were observed. Examinations of brain tissue revealed no lesions at any exposure duration. The authors suggest a direct irritant action on pulmonary and alveolar capillaries.

Innes and Tansy (1981) investigated changes in CNS activity in male Sprague-Dawley rats. The anaesthetized animals were exposed to 400 ppm (1.6 mg/l) for 1 hour in a stainless steel chamber. Control animals were used. MMA vapor concentration was controlled by gas chromatography. Before and during exposure as well as after cessation of exposure electroencephalographic and multi-unit activity neuronal recordings were made from 10 different brain areas (2 hours recording time). The animals were exposed individually. Data was obtained from 5 to 19 animals depending on brain section. Exposure resulted in significant alterations in multi-unit neuronal activity in cells located in the lateral hypothalamic (data represent 19 animals) and ventral hippocampal nuclei (data represent 16 animals) within 5 minutes. The neuronal firing rate was slowed down during exposure and turn toward pre-exposure level after cessation of exposure. The authors concluded that the decrease in multi-unit neuronal activity in hypothalamus is related to observations from occupationally MMA exposed persons who frequently reported a loss of appetite.

Tansy et al. (1974) reported a reduced gastric pressure activity and a fall in gastric tonus in anesthetized male Sprague-Dawley rats (number unknown) during exposure to 240 ppm MMA (nominal concentration) for 1 hour.

Morris and Frederick (1995) and Morris (1992) investigated the biochemical responses in surgically isolated upper respiratory tract (URT) of 5 male Fischer-344 rats exposed (nose-only) to 25 ppm, 100 ppm, and 500 ppm MMA (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-(non-protein sulfhydryl) levels would indicate a direct reactivity of toxicants with reduced sulfhydryl compounds. At 500 ppm the NPSH levels decreased significantly by approximately 25%.

3.2.3. Mice

Nonlethal toxicity after inhalation exposure

NTP (1986) conducted a study with male and female $B6C3F_1$ mice (age 8 weeks). Groups of 5 mice of each sex were exposed to the non-lethal MMA vapor concentrations of 1191, 2159, 2220, 4055, 4446, or 4632 ppm for 4 hours (for study details see Sections 3.1.3 and 3.1.4). At 1191 ppm and 4446 ppm, one animal each died within 7, and 1 days, respectively. The cause of death is not stated. There seems to be no dose-response relationship to MMA exposure. Hypoactivity, dyspnea, and anesthesia were reported as compound-related effects, however, not assigned to a specific exposure concentration.

For determination of the inhalation sensory irritation (RD_{50}) male Swiss Webster mice were exposed to 4 different concentrations of MMA (740, 1600, 2900, or 33000 ppm) in groups of 4 animals for 30 minutes (DuPont 1993b). The 2.5-l exposure chamber, in which only the heads were protruding, was supplied with plethysmographs. Respiratory rates were monitored before, during, and after exposure (10 min pre- and postexposure). Vapor concentration was controlled by gas chromatography 3 times during each exposure. Respiratory rates (in breaths/min) were recorded every 15 seconds and compared with baseline respiratory rates during preexposure period. A minimal to moderate decrease in respiratory frequency was observed within all exposure groups (see Table 4). At onset of exposure some signs of a mild sensory irritation was observed, however did not persist. The authors concluded that MMA is not a sensory irritant. No RD_{50} could have been calculated from these results.

3.2.4. Guinea Pigs

Nonlethal toxicity after inhalation exposure

Deichmann (1941) exposed 1 guinea pig each to various concentrations up to approximately 3440 ppm MMA (indicated as 14.3 mg/l) for 8 hours. Study details and observed effects are reported in Sections 3.1.5 (Guinea Pig - Acute Lethality) and 3.2.2 (Rats - Nonlethal Toxicity).

3.2.5. Rabbits

Nonlethal toxicity after inhalation exposure

Deichmann (1941) exposed 1 rabbit each to various concentrations up to approximately 3440 ppm MMA (indicated as 14.3 mg/l) for 8 hours. Study details and observed effects are reported in Sections 3.1.6 (Rabbits - Acute Lethality) and 3.2.2 (Rats - Nonlethal Toxicity).

Nonlethal toxicity after dermal administration

Rohm and Haas (1982b) conducted an acute dermal study in New Zealand White rabbits. Severe erythema and edema were observed at 5 g/kg at site of application. Lower doses of 0.2 and 2 g/kg led to prolonged skin irritation and eschar.

TABLE 5. Summary of Nonlethal Inhalation Data in Laboratory Animals

Species	Conc. (ppm)	Exposure	Number of animals Most important effects	Reference
Dog	2000	3 - 12 min	12 Animals; under anaesthetic decline in spontaneous motor activity	Tansy et al. (1977)
Dog	9620	5 h	2 Animals; under anaesthetic effects on respiration	DuPont (1937)
Rat	22500	15 min	Number of animals unknown anesthetized animals; nominal concentration cessation of gastric pressure activity	Tansy et al. (1974)
Rat	9860 17790	1 h	10 Animals; nose-only exposure nasal and ocular discharge; dose-related respiratory effects	DuPont (1993a)
Rat	95	1 h	4 Animals; head/nose exposure no pulmonary lesions at histopathology	Raje et al. (1985)
Rat	400	1 h	16 / 19 Animals; under anaesthetic changes in neuronal activity	Innes and Tansy (1981)
Rat	240	1 h	Number of animals unknown Anesthetized animals; nominal concentration reduced gastric pressure and gastric tonus	Tansy et al. (1974)
Rat	95	2 h	4 Animals; head/nose exposure pulmonary lesions at histopathology	Raje et al. (1985)
Rat	7930 10580 15870	2 h	6 or 12 Animals, resp.; whole-body exposure; nominal concentration animals became comatose	Rohm and Haas (1958)
Rat	200	3 h	5 Animals; whole-body exposure no morphological abnormalities	Mainwaring et al. (2001)
Rat	1191 2159 2220 4055 4446 4632	4 h	5 Animals of each sex; analytical concentration hypoactivity, dyspnea, anesthesia (not specified to exposure concentration)	NTP (1986)
Rat	400	4 h	3 Animals; nose-only exposure lesions of the olfactory epithelium	Robinson et al. (2003)
Rat	6490 12981	6 h	4 Animals each; whole-body exposure; nominal conc.; dose-dependent depression, respiratory troubles at higher conc.	Rohm and Haas (1958)
Rat	110	6 h	5 Animals; whole-body exposure; analytical concentration degeneration / necrosis of olfactory epithelium	Pinto (1997)
Rat	400	6 h	5 Animals; whole-body exposure; analytical concentration additionally to 110 ppm reduction of bowman glands, inflammatory exsudate and infiltrate	Pinto (1997)
Rat	200	6 h	5 Animals; whole-body exposure; analytical concentration degeneration of olfactory epithelium in 3/5 rats	Jones (2002)
Rat	200	6 h	5 Animals; whole-body exposure degeneration / atrophy of olfactory epithelium	Mainwaring et al. (2001)
Rat	2690 3220 3850 4830	8 h	10 Animals; slight irritation of URT 5 Animals; depression and effects on respiration 5 Animals; same effects; additionally dyspnea 5 Animals; same effects; onset earlier Whole-body exp.; analytical conc.	DuPont (1937)
Rat	3400	8 h	2 Animals; whole-body exposure; nominal conc. effects on respiration, motor activity	Deichmann (1941)
Rat	500	2 d	10 Animals per sex; whole-body exposure;	NTP (1986)

TABLE 5. Summary of Nonlethal Inhalation Data in Laboratory Animals

Species	Conc. (ppm)	Exposure	Number of animals Most important effects	Reference
		(6 h/d)	analytical concentration; repeated exposure; apathy; observed during study duration	see Section 3.3
Rat	2000	2 d (6 h/d)	10 Animals per sex; whole-body exposure; analytical concentration; repeated exposure; Apathy, ocular and nasal discharge, uncoordinated behaviour; observed during study duration	NTP (1986) see Section 3.3
Rat	5000	2 d (6 h/d)	10 Animals per sex; whole-body exposure; analytical concentration; repeated exposure; apathy, ocular and nasal discharge, uncoordinated behaviour, prostration; observed during study duration	NTP (1986) see Section 3.3
Mouse	740 1600 2900 33000	30 min	5.7% Decrease in respiratory rate 9.3% Decrease in respiratory rate 16.5% Decrease in respiratory rate 18.3% Decrease in respiratory rate Whole-body exposure	DuPont (1993b)
Mouse	2159 2220 4055 4632	4 h	5 Animals of each sex; analytical concentration hypoactivity, dyspnea, anesthesia (not specified to exposure concentration)	NTP (1986)
Mouse	500	2 d (6 h/d)	10 Animals per sex; whole-body exposure; analytical concentration; repeated exposure; apathy; observed during study duration	NTP (1986) see Section 3.3
Mouse	2000	2 d (6 h/d)	10 Animals per sex; whole-body exposure; analytical concentration; repeated exposure; apathy, ocular discharge, uncoordinated behaviour; observed during study duration	NTP (1986) see Section 3.3
Mouse	5000	2 d (6 h/d)	10 Animals per sex; whole-body exposure; analytical concentration; repeated exposure; apathy, ocular and nasal discharge, uncoordinated behaviour; observed during study duration	NTP (1986) see Section 3.3
Guinea pig	3400	8 h	2 Animals; whole-body exposure; nominal concentration effects on respiration, motor activity	Deichmann (1941)
Rabbit	3400	8 h	2 Animals; whole-body exposure; nominal concentration effects on respiration, motor activity	Deichmann (1941)

3.3. Repeated Exposure

Only those studies with repeated exposure are described below where relevant (lethal or nonlethal) effects were described after first or second day exposure. Other subacute exposure studies do not contribute relevant data for the assessment of acute toxicity.

NTP (1986) conducted several inhalation studies with repeated exposure (6 h/day; 5 days/wk each) in F344/N rats and $B6C3F_1$ mice. The animals were whole-body exposed in a stainless steel wire cage and checked daily. MMA concentrations were monitored online twice during each exposure duration either by a photoionisation detector or by gas chromatography. For every study section an unexposed control group was used. Necropsy was performed on all

animals that lived to the end of the studies. The exposure durations have been 14 weeks, 10 days, and 11 days. The findings are described in the following.

TABLE 6. Summary of Lethal Inhalation Data following Repeated Exposure (NTP 1986)

Species	Conc. (ppm)	Study	Day of death males / females	Number of animals
Rat	75 - 1000	10-d Study	- / -	0/5 Males died / 0/5 females died
Rat	500 - 2000	11-d Study	- / -	0/5 Males died / 0/5 females died
Rat	3000	11-d Study	- / 4,6	0/5 Males died / 2/5 females died
Rat	5000	11-d Study	1,2,2,2,3 / 1,1,2,3,3	5/5 Males died / 5/5 females died
Mouse	75 - 1000	10-d Study	- / -	0/5 Males died / 0/5 females died
Mouse	500	11-d Study	8,9 / -	2/5 Males died / 0/5 females died
Mouse	1000	11-d Study	8 / -	1/5 Males died / 0/5 females died
Mouse	2000	11-d Study	6,8,10 / -	3/5 Males died / 0/5 females died
Mouse	3000	11-day Study	2,3,6,8 / -	4/5 Males died / 0/5 females died
Mouse	5000	11-day Study	1,1,1,2,2 / 1,1,1,1,1	5/5 Males died / 5/5 females died

14-week study, NTP (1986)

A 14-week study was conducted with 10 animals of each sex and species with exposure concentrations of 500, 1000, 2000, 3000, and 5000 ppm MMA (6 h / d). During the first 2 days rats of all dose groups showed apathy. Serious ocular and nasal discharge, and uncoordinated behaviour from 2000 ppm onwards, and additionally prostration at 5000 ppm have been observed within these first exposures as well. Apathy was reported in mice of all dose groups already after the first or second exposure.

10-day study, NTP (1986)

5 male and female rats and mice exposed to 75, 125, 250, 500, or 1000 ppm in a 10-day study revealed no compound related clinical signs or pathological / histopathological (performed only in mice) alterations. Histological examined tissues were lung, nasal cavity, and kidneys.

11-day study, NTP (1986)

5 rats and 5 mice of each sex were exposed to different concentrations (500, 1000, 2000, 3000, and 5000 ppm) with 10 exposures in 11 days. All of altogether 20 animals (5 of each sex and species) died within the first 2 days of exposure at this 5000 ppm, and lethality occurred at any other concentration in mice with a clear correlation of concentration and time of death (see Table 5). At necropsy no compound-related effects were observed. During exposure mice showed redness and swelling of the nasal region as well as dyspnea, and rats had a ruffled fur. No assignment of effects to a concentration has been reported.

3.4. Skin Sensitization

Cavelier et al. (1981) reported no irritation following application of undiluted MMA to the ears and eyes of 6 rabbits. Only a slight erythema was observed on the skin of all animals.

Parker and Turk (1983) observed no contact sensitivity in guinea pigs (outbred Hardley strain) using 5 different test protocols (split adjuvant, maximization, Polak, 2 different protocols of epicutaneous test).

3.5. Mutagenicity and Genotoxicity

An assessment of mutagenic and genotoxic potential of MMA was conducted by Anderson et al. (1979). Negative results were gained in the Ames test, a mammalian cell transformation assay, in the cytogenetic analysis of rat bone marrow cells, and a dominant lethal test in mice.

Anderson and Hedge (1976) investigated the mutagenic effect of MMA in a dominant lethal test in male CD-1 mice. The animals were exposed to 0, 100, 1000, or 9000 ppm MMA for 6 hours a day for 5 days. No evidence of any mutagenic effect was found, including the number of post-implantational early fetal deaths that was judged as the best indication of mutagenic activity.

NTP (1986) reported no reverse mutations in various strains of Salmonella typhimurium in absence and presence of a metabolic activation up to 10.0 mg/plate. In the mouse lymphoma mutagenicity assay with L5178Y/$TK^{+/-}$ cells mutagenic activity was observed at doses of 0.125 to 1.0 µl/mL or greater in absence and presence of a metabolic activation. A reproducible, dose-related increased frequency of sister-chromatid exchanges has been reported in Chinese hamster ovary cells. An increase of chromosomal aberrations was also seen in Chinese hamster ovary cellsin presence of metabolic activation only at the highest, near-lethal dose of 5 mg/mL.

3.6. Carcinogenicity

NTP (1986) conducted a carcinogenicity study conducted that showed no treatment-related tumors in male and female F344/N rats and male and female B6C3F1 mice following inhalation exposure to 500 or 1000 ppm for 102 weeks (6 h/d, 5 d/wk).

Lomax et al. (1997) reported no treatment-related increases of carcinogenicity in golden hamsters exposed to 25, 100, or 400 ppm MMA vapor for 78 weeks (6 h/d, 5 d/wk).

3.7. Summary

MMA shows a low acute toxicity after inhalation with a 4-hour LC_{50} of 7093 ppm in rats (Tansy et al. 1980a). For a 2-hour exposure LC_{50} values between 10820 ppm and 16830 ppm have been reported by Rohm and Haas (1958) and Guoshon (1988).

As reported from several studies, the olfactory epithelium is the target region for the inhalation toxicity of MMA after acute exposure to low concentrations Degeneration and necrosis were observed at concentration of 110 ppm and above for a 4- or 6-hour exposure duration (Pinto 1997; Mainwaring et al. 2001; Jones 2002; Robinson et al. 2003).

Pulmonary lesions, i.e. congestion, hemorrhage, vasodilation, and edema, following a 2 hour exposure to 95 ppm has been reported by Raje et al. (1985), and at higher concentrations above 1000 ppm by Deichmann (1941). Additional effects on respiratory tract and eyes included nasal and ocular discharge, salivation, irritation of upper respiratory tract, emphysema, and collapsed lung (DuPont 1993a; Deichmann 1941; Guoshon, 1988). The effects observed by Raje at 95 ppm are inconsistent with the rest of the data. Pinto (1997) observed no lung and trachea injuries following a 6-hr exposure to 110 and 400 ppm. The lung injuries were also not seen in

other studies with repeated exposure to MMA at higher concentrations (McLaughlin et al. 1979; NTP 1986).

After high dose exposure, systemic lesions are observed in several tissues. Injuries of liver, kidney, urinary passages, thymus, and cardiovascular system are reported for different species by Spealman et al. (1945), Deichmann (1941), Guoshon et al. (1988), McLaughlin et al. (1973), and Kessler et al. (1977).

Various effects on the central nervous system were observed in animal studies at concentrations above 1000 ppm. They were reported following exposure to various pathways. In animals of different species, central nervous effects are expressed by a decrease of reflex activity and result in motor weakness, increased gastrointestinal activity and excretion, effects on respiratory rate and cardiovascular system (Tansy et al. 1977; DuPont 1937; Deichmann 1941; DuPont 1993a, b). Behavioral effects are expressed by uncoordinated behaviour, motor weakness, abnormal gait (Guoshon et al. 1988; Deichmann 1941).

Some findings on respiration that might be due to a systemic effect of MMA on the central nervous system have been reported. Several authors observed an increase in respiratory rate, followed by a decrease, accompanied by shallow, irregular, labored, spasmodic, or deep breathing (Deichmann 1941; Rohm and Haas 1958; Mir et al. 1974; McLaughlin et al. 1973). Respiratory failure as cause of death was reported several times (Spealman 1945; Deichmann 1941).

Decreased as well as unaffected blood pressure were reported at non-lethal concentrations up to approximately 10000 ppm after i.v. administration (Blanchet et al. 1982; Tansy et al. 1977; DuPont 1937; Mir et al. 1974; McLaughlin et al. 1973). An increase as well as decrease in heart rate complete the manifestation of effects on the cardiovascular system (Blanchet et al. 1982; Mir et al. 1974).

Several authors reported from investigations with dogs, rats, mice, and guinea pigs that death was in coma and usually the terminal event of a depressed state that also has been described as apathy or prostration (DuPont 1037; Deichmann 1941; Spealman et al.1945; Rohm and Haas 1958; Kessler 1977; Guoshon 1988; NTP 1986).

Using biochemical investigations 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 to 500 ppm for 60 minutes. There was a decrease in the NPSH (Non-protein sulfhydryl) level in the nasal lavage. The effect concentration of 500 ppm must be regarded in context with the respective results from methacrylic acid exposure where up to 410 ppm no indications of irritative responses were noticed (see TSD for methacrylic acid). 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.

As demonstrated in Section 3.1 and summarized in Table 3 lethal concentrations differ to a certain degree. Tansy et al. (1980a) remark that the lack of a repeatable, reproducible system of gas generation combined with the lack of an adequate dosimetry are responsible for this discrepancy of values. Their own studies with MMA included a measurement of concentration by gas chromatography (Tansy et al. 1976a). Therefore the authors judge their LC-values based

on analytical MMA concentrations as more reliable. Mode of exposure (whole-body/nose-only) seems to have a certain influence on toxicity. The NTP study (NTP 1986) shows that whole-body exposure to 16000 ppm was lethal to all animals (n = 5 of each sex) within the first hour of exposure. A DuPont (1993a) 1-hr nose-only inhalation study in rats (n = 5 of each sex) revealed no lethality at 17800 ppm. However no exact comparison is possible due to different exposure durations in other studies and due to the small numbers of studies with nose-only or nose/head exposure.

Although various genotoxic test gave positive results (NTP 1986), there is no evidence for carcinogenicity from animal data (Lomax et al. 1997; NTP 1986). The IARC (1994) concluded that there is evidence suggesting lack of carcinogenicity of MMA in experimental animals.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Deposition and Absorption

MMA deposits with a moderate efficiency of 18, 20, and 16% at applied concentrations of 25, 100, and 500 ppm to the surgically isolated upper respiratory tract (URT) of anaesthetized male F344 rats under cyclic flow conditions (Morris and Frederick 1995; Morris 1992). Under unidirectional flow conditions, deposition of MMA was 3% less on the average.

MMA can be absorbed into the blood via the respiratory tract, gastrointestinal tract, and skin. This conclusion is supported by several studies showing lethal and non-lethal effects following exposure from different pathways. Detailed rates of absorption for inhalation and oral exposure have not been reported in various metabolism studies (Bereznowski 1995; Seppäläinen and Rajaniemi 1984; Verkkala et al. 1983).

In a comprehensive metabolism study, Jones (2002) reported that 11% of MMA was absorbed through the whole rat skin in 24 hours. The author remarked that absorption through human skin would be lesser due to the lower lipophilicity. In a human study, the rate of MMA absorption from human skin was determined to be 0.56% under unoccluded conditions; higher absorption occurred under occluded conditions (data not shown) (CEFIC 1993). It is suggested, that evaporation from the skin surface reduces absorption. Seppäläinen and Rajaniemi (1984) reported a decreased sensory conduction velocity due to a mild axonal degeneration in workers exposed dermally to MMA. Verkkala et al. (1983) observed a local neurotoxic reaction due to absorbed MMA in rat tails. Both observations indicate that MMA can penetrate the skin.

Distribution

The mean concentration in blood for a 4-hour exposure was 11.14 mg/ 100 mL blood after head/nose inhalation of approx. 95 ppm (Raje et al. 1985). Measurement of tissue concentrations revealed 20.6 µg MMA/g lung and 25.24 µg/g brain.

Rijke et al. (1977) reported a half-life of 3 hours at 20 °C following addition of 0.185 µl MMA per mL human whole-blood. Disappearance from plasma was very rapid, and concentrations in blood cells were twice as high as plasma concentrations. Further half-life values in human blood of 24 - 40 minutes were determined by Corkill et al. (1976).

Metabolism

Several authors report hydrolysis of MMA to methacrylic acid and methanol (Rijke et al. 1977; Crout et al. 1979; Bereznowski 1995). In combination with results from in vitro investigations (data not shown), Crout et al. (1979) conclude that the initial stage of the metabolism of MMA in vivo is the hydrolysis to methacrylic acid. Rijke et al. (1977) concluded a serum esterase was responsible for the metabolism of MMA to methacrylic acid, which was determined to be 40% of MMA after 90 minutes.

After single administration of 8 mmol/kg MMA (equivalent 800 mg/kg bw) by stomach tube, the appearance of methacrylic acid in rat blood serum was detected 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 concluded that methacrylic acid is removed efficiently from blood serum by liver uptake. Bereznowski (1995) reported that the in vitro rate of MMA hydrolysis in blood serum was approximately threefold higher in rat than in human.

Mainwaring et al. (2001) demonstrated that the toxicity of MMA was reduced by pre-treatment of rats with BNPP (bis-(p-nitrophenyl)phosphate), an inhibitor of carboxylesterase enzymes specific for MMA metabolism. Bereznowski (1995) demonstrated the important role of carboxylesterase in MMA metabolism by inhibiting with physostigmine in rat serum which reduced the formation of methacrylic acid by approximately 50%. Essentially similar results were obtained with human serum (data not shown). The rate of methacrylic acid formation by rat blood serum was approximately 3-fold higher than in the human. The author demonstrated that the carboxylesterase reaction in blood serum shows a typical enzymatic substrate saturation curve. MMA deposition was reduced by approximately one-third by pretreatment with BNPP (Morris and Frederick 1995).

Mainwaring et al. (2001) concluded that lesions of nasal olfactory epithelium are due to methacrylic acid that results from the carboxylesterase mediated metabolism of MMA. Esterases that hydrolyze MMA are present in the nasal epithelium and submucosal compartments (Andersen and Sarangapani 1999 and 2001) as well as in various other tissues, including liver, gastrointestinal tract and blood (Morgan et al. 1994; Mainwaring et al. 2001). In tissue homogenates of nasal sections of different species (e.g. human, rat, mice, hamster) carboxylesterase activity is higher in olfactory than in respiratory epithelium (Mainwaring et al. 2001; Bogdanffy et al. 1987). In rat olfactory tissue, the carboxylesterase activity is mainly restricted to the tips of the sustentacular (or support) cells and on Bowman glands. No activity was found in sensory cells. Lower carboxylesterase activity is found in respiratory and squamous epithelium (Olson et al. 1993). However, there are indications that measurement of esterase activity in tissue homogenate does not reflect the in vivo situation. Bogdanffy et al. (1998) reported similar esterase activity of the olfactory sustentacular cells to that of the respiratory epithelium based on an in vitro gas uptake technique using intact nasal tissue. In human nasal epithelium, the highest carboxylesterase content was found to be in the peripheral areas of cytoplasm of surface epithelial cells (including sensory, sustentacular and basal cells) and the submucosal glands (Jones 2002).

Differences in the metabolic rate constants for metabolism of MMA to methacrylic acid between rat and human in respiratory and olfactory tissue were pointed out by Mainwaring et al. (2001). In vitro studies with S9 fractions showed a V_{max} (nmol/min/mg) in rat nasal tissues of 3.5

(respiratory tissue), and 12 (olfactory tissue). In humans maximum metabolic rates were 0.15 and 0.48 in these tissues, respectively. The microsomal fraction of the respiratory epithelium shows the highest V_{max} in rats (12 nmol/min/mg protein), followed by hamsters (3.6 nmol/min/mg), and humans (2.7 nmol/min/mg). The amount of human olfactory tissue was found to differ between individuals. Mattes and Mattes (1992) observed substantially higher activity of carboxylesterase in the rat nasal extracts than in human nasal polyps. Bereznowski (1995) investigated the methacrylic acid formation from MMA in rat and human serum and found a threefold higher rate of methacrylic acid production in rat serum. Species differences in maximum metabolism rates were also observed in liver microsomes. Humans showed the highest V_{max} of 494 nmol/min/mg protein (rat: 46.5; hamster: 137 nmol/min/mg).

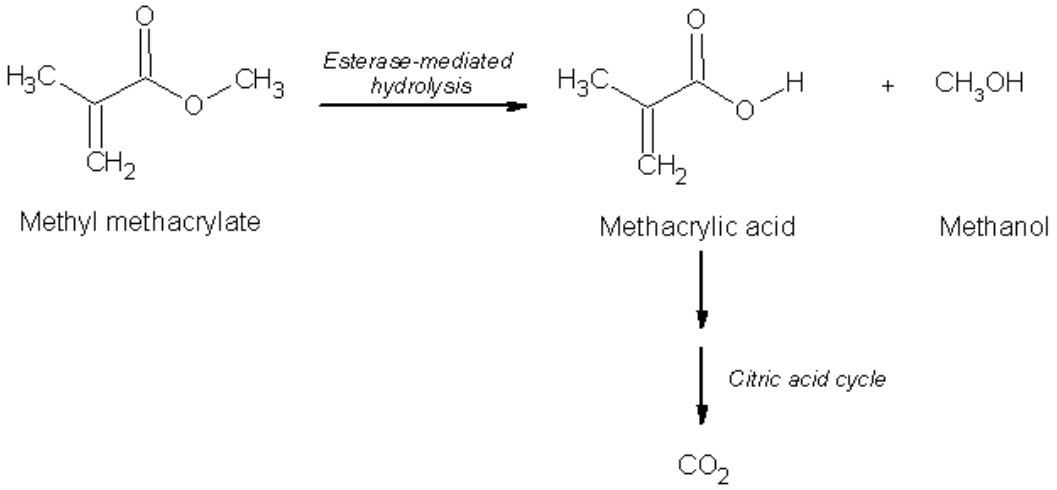

FIGURE 1. Main Pathways for the Metabolism of MMA

The total MMA inhaled is not expected to be metabolized in the upper respiratory tract. The lower respiratory tract also contains carboxylesterase activity. A further site of methacrylic acid production from MMA is probably via enzymatic hydrolysis in saliva as demonstrated by Munksgaard and Freund (1990) for various di- and monomethacrylates.

As reported by Greim et al. (1995) and Lomax et al. (1997), conjugation with glutathion plays only a minor role in metabolism of MMA The conjugation only occurs when the enzymatic route of MMA hydrolysis is saturated (Delbressine et al., 1981). Excretion of MMA as the thioether in rats (11% of an administered dose of 0.14 mmol/kg) only occurs after inhibition of the carboxylase with tri-o-tolyl phosphate (TOTP). Aydin et al. (2002) reported a significant decrease in GSH in rats exposed to 1000 ppm MMA for 4 weeks.

Excretion

Subsequent to hydrolysis methacrylic acid enters a normal catabolic pathway which leads to CO_2 exhalation (Bratt and Hathway,1977; Crout et al., 1982). Methacrylic acid is metabolized through the same pathway as the amino acid valine forming methylacrylyl-CoA, which enters the citric acid cycle (Maclaine Pont 1991). Bratt and Hathway (1977) found 84 - 88% of a single dose of 5.7 mg/kg radiolabeld MMA expired as CO_2 within 10 days in adult male Alderly Park

rats. After 23 hours up to 65% of MMA was measured in respiratory air. Less than 1% of unchanged MMA was expired. Similar ratios of exhaled CO_2 were found by Crout et al. (1982). After injection of 7 mg radiolabeled MMA intraperitoneally to female Wistar rats, 86% was recovered as CO_2.

About half of the single dose of 5.7 mg/kg not exhaled as CO_2 was found to be excreted in the urine (4.7 - 6% of the administered MMA) and the rest was found in body tissues at 240 h (Bratt and Hathway (1977). Comparable urine recovery ratios of 14.5% (of 9 mg MMA administered) and 7.1 (of 7 mg MMA administered) were obtained by Crout et al. (1982). The proportion of urinary excretion seems to increase with increasing dose.

Metabolites found in urine were methacrylic acid (0.8% of the dose), methyl malonic acid (1.4%), and succinic acid (0.2%) (Bratt and Hathway, 1977). Parenteral (i.v.) and enteral administration (stomach tube) as well as higher doses (6.8 and 120 mg/kg) led to similar ratios of excretion. Mizunuma et al. (1993) determined metabolites in urine in workers occupationally exposed to 100 ppm MMA. They found that 1.5% of inhaled MMA was excreted as methanol.

4.2. Mechanism of Toxicity

MMA is irritant to skin and mucosa of respiratory tract. The lung is the major site of injury at high concentrations. Degeneration of the olfactory mucosa in the rat following inhalation of MMA vapors are reported by various authors (Pinto 1997; Mainwaring et al. 2001; Morris and Frederick 1995; Jones 2002; Robinson et al. 2003). The absorption and hydrolysis of MMA to methacrylic acid by local nasal tissue esterases has been considered as the main reason for MMA olfactory toxicity. Several authors reported that injuries to the olfactory epithelium results from effects on sustentacular cells, the major site of MMA metabolism in rats (Muttray et al. 1997; Andersen and Sarangapani 2001). Therefore it can be concluded that the toxicity of MMA results from a high enzyme activity and the formation of methacrylic acid. Formation of methacrylic acid occurs very rapidly and accumulation can cause toxicity (Jones 2002). The lesions are seen in that part of mucosa with the highest level of carboxylesterase activity (Pinto 1997). For humans this would be the whole epithelium including sensory cells, basal cells, and sustentacular cells, as well as the submucosal glands, according to the investigations by Jones (2002).

Mainwaring et al. (2001) proved that pre-treatment of rats with a carboxylesterase-inhibitor reduced severity of nasal lesions following 6-hour MMA exposure to 200 ppm. Reduction of toxicity on olfactory epithelium by esterase inhibitors allows the conclusion that a different enzyme activity influences the toxicity to a high degree. However, based on the findings of Bogdanffy et al. (1998) that carboxylesterase activity is not restricted to the olfactory epithelium, it can also be concluded that the toxic effects of MMA are not only a function of metabolic capacity, but also a function of cellular sensitivity to acid metabolites.

Bereznowski (1994) reported from in vitro examinations that MMA exerts its toxic effects by interacting with the cell membrane. Additionally, mitochondria are intercellular target organelles and interaction of MMA with the mitochondrial membrane leads to structural and functional damage. Following addition of MMA to isolated liver mitochondria, gross changes of their ultrastructure were observed. The outer membrane was ruptured and the matrix structure was disorganized. Cell death was subsequently due to depletion of ATP as a result of the

influence on electron transport and oxidative phosphorylation. Also an effect of MMA on (intra)cellular level is suggested by Borchard (1981). The author concludes that the penetration of the lipophilic MMA leads to a decrease in ionic currents.

At higher exposure not all the MMA will be removed by the upper respiratory tract and MMA reaches the lung. Pulmonary effects (dyspnea, emphysema, edema, and collapsed lungs) have been reported above 1000 ppm (DuPont, 1993a; Deichmann, 1941; NTP, 1986; Guoshon, 1988). Frederick et al. (2002) concluded that the mechanism of toxicity at higher concentration of ethyl acrylate and other esters is related to the depletion of non-protein sulfhydryl (NPSH) in various tissues. In rodent studies it was observed that NPSH depletion is a cause of death at concentrations more than two orders of magnitude above the concentration that induce nasal irritation.

Mainwaring et al. (2001) observed a latency period for the development of nasal lesions following exposure to 200 ppm in rats. Examination of nasal tissue immediately after a 6-hour exposure reveals lower graded lesions than 18 hours later.

Effects on CNS are observed in animals (Tansy et al. 1977; DuPont 1937; Deichmann 1941; DuPont 1993a, b) and humans (Dobrinskij 1970; Scolnick and Collins 1986). As suggested by Innes and Tansy (1981), a reduced appetite reported from human studies is due to effects of MMA on hypothalamus and hippocampus. The authors observed reduced neuronal firing rates after inhalation exposure. Such correlations seem plausible because of the way that the hypothalamus and the superimposed hippocampus control the vegetative nervous system. Therefore all other observed effects related to the central nervous system (decrease of reflex activity, motor weakness, increased gastrointestinal activity and excretion, effects on respiratory rate and cardiovascular system) possibly result from these neuronal changes. This mode of action has also been illustrated by Borchard (1981). Kutzner et al. (1974) also conclude from investigations in guinea pigs that a central nervous system effect causes the observed apnea at high i.v. doses of MMA.

Local nervous effects can result from a stimulation of the receptors or nerve endings in the respiratory tract and lead to a decreased pulmonary function as reported by several authors. It is therefore possible that MMA acts as sensory (pulmonary) irritant. The slight decreased respiratory rate measured in mice is however not classified as sensory irritation by DuPont (1993b) following inhalation exposure to MMA. This seems plausible because a decreased pulmonary function has also been observed following systemic application of MMA injections or during hip replacement surgery.

4.3. Structure Activity Relationships

Olfactory lesions similar to that observed following inhalation exposure of MMA are described for numerous ester vapors, e.g. dibasic esters (DBE), suggesting a common mechanism of toxicity (Morris and Frederick 1995; Bogdanffy and Frame 1994). In accordance with MMA based effects the lesions are seen in mucosa areas with the highest level of carboxylesterase activity and inhibition of carboxylesterase reduces toxicity. Trela and Bogdanffy (1991) demonstrated that DBE induces degeneration of the olfactory, but not the respiratory epithelium of the rat nasal cavity due to the more efficient carboxylesterase-mediated hydrolysis in olfactory epithelium. Morris and Frederick (1995) concluded that the acid

metabolite of various esters is responsible for toxicity as exposure to acid vapors produces similar lesions. Also, for vinyl acetate the carboxylesterase-dependent hydrolysis, which is considerably higher in nasal olfactory epithelium than in any other oral tissue, is thought to be critical for the injuries due to the formation of toxic metabolites (Robinson et al. 2002).

4.4. Other Relevant Information

The toxic effects of MMA are due to the monomer. The polymer appears to be inert (NTP 1986; Maclaine Pont 1991).

MMA reveals a distinct odor threshold that is reported from several studies of 0.083 - 0.46 ppm and has therefore good warning properties (ECETOC 1995; Maclaine Pont 1991). A limit of odor detection of 0.05 ppm has been reported by Hellman and Small (1974) and was accepted by AIHA (1997) to be of sufficient quality. This starting point can be used to derive a "level of distinct odor awareness" (LOA) according to van Doorn et al. (2002) of 0.1 ppm (see Appendix C).

4.4.1. Species Variability

Species differences of carboxylesterase activity in nasal tissue homogenates and blood was reported by several authors (Mainwaring et al. 2001; Bogdanffy et al. 1987; Bereznowski 1995; Andersen et al. 2002). The enzyme activity is several times higher in rats than in humans.

The nasal cavity anatomy differs between rats and humans (Muttray et al. 1997; Lomax et al. 1997; Andersen and Sarangapani 1999). In rats, the nasal cavity has a greater capacity due to the higher ratio of surface area. Additionally, in humans only 8% of the nasal mucous membranes consist of olfactory epithelium compared to 50% in rats. The olfactory epithelium in humans is located in the secondary air flow, whereas the olfactory epithelium is in the primary air flow in rats. Consequently, more of MMA is delivered to target tissues in rats compared to humans.

Andersen et al. (1999) estimated nasal epithelial tissue dosimetric adjustment factors (DAF) for a concentration range from 1 to 400 ppm MMA of 2.4 - 4.76 for rat / human. The DAF is increasing with increasing concentration within this range due to a different clearance in the rat and human. PBPK models with computational fluid dynamics (CFD) predict that equivalent exposure to MMA leads to lower nasal tissue doses in humans than in rats (Andersen et al. 1999; 2002). According to the nomenclature used by U.S.EPA (EPA 1994), the regional gas dosimetric ratio (RGDR) for the RfC calculation based on the PBPK model for MMA would be between 3 and 8. The prediction of human doses included breathing under light and heavy exercise. Frederick et al. (2002) calculated by CFD-PBPK model an olfactory epithelium exposure of acrylic acid from ethyl acrylate of at least 18-fold lower in human tissue than in rat tissue under the same exposure conditions.

Because of these species differences, it is concluded that humans would be less susceptible than rats, or at least show similar susceptibility to the toxic effects of MMA on the olfactory epithelium (Mainwaring et al. 2001; Lomax et al. 1997). Several authors demonstrated the formation of methacrylic acid and subsequent excretion of CO_2 irrespective of the pathway of MMA exposure (Bratt and Hathway 1977; Crout et al. 1982; Bereznowski 1995). This leads

to the conclusion that MMA-metabolizing carboxylesterases are present in several other tissues beside olfactory epithelium. It is not known if the carboxylesterase activity in these other tissues is also higher in rats than in humans. No PBPK models for assessing the dosimetry of the lower respiratory tract are available. This uncertainty must be taken into account at higher concentrations of MMA, where not only the olfactory epithelium, but also the lower respiratory tract might be affected.

No major differences are evident from literature concerning the toxicodynamic properties of MMA. Similar local and systemic effects have been reported in different species.

The concentration causing lethality (LC50, 4 hours) differ only marginally between rats, mice, rabbits and guinea pigs (see Table 3). Consequently, no large interspecies differences are expected.

4.4.2. Susceptible Populations

Considerable differences in the amount of olfactory tissues between human individuals were observed by Mainwaring et al. (2001). Large individual differences of carboxylesterase activity in human liver tissue from 12 individuals have been observed by Hosokawa et al. (1995). At high exposure metabolism of MMA also includes conjugation with glutathione, what also can contribute to intraspecies differences.

An indication of age-related differences in susceptibility is shown by Deichmann (1941) who observed a longer time to death period in newborn rats compared with adult or juvenile rats. This observation is supported by different in vitro studies of carboxylesterase activity in the nasal mucosa that show a clear influence of age (Griem et al., 2002). The enzyme turnover in newborn rats was lower than in adult rats by a factor of 7. Different incidences of lethality from 3 series with animals of different body weight have been reported by Rohm and Haas (1958) indicating that a lower body weight reduces lethal concentrations of MMA. A gender influence of the toxic effects of MMA was not observed from the available data.

4.4.3. Concentration-Exposure Duration Relationship

From several studies a different concentration-exposure duration relationship for low and for high MMA concentrations can be concluded. The slight irritative effects at low exposure depend primarily on concentration and not on exposure duration as shown by occupational studies in which irritation of respiratory tract and eyes show no pronounced increase in severity during the 8 hour workday. At higher concentrations a different mechanism of toxicity has been observed that depends on duration of exposure. However, the data are not adequate to derive a reliable value of n to be used in the C^N x T relationship.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No acute effects were reported by Roehm (1994) below 40 ppm and by Cromer and Kronoveter below 50 ppm in occupationally exposed persons during an 8-hour workday (8-hour TWA). Reversible irritations after short term peak exposures well exceeding 100 ppm in medically examined workers were described by Roehm (1994). Similar effect concentrations

were also reported by Lindberg et al (1991) for floor layers. Definite irritation was observed at concentrations of 170 to 240 ppm for an unknown duration of exposure (Coleman 1963). Long term occupational experience with exposure to 6 ppm (geometric mean) and a maximum concentration of 112 ppm revealed only minor effects such as throat irritation and frequent cough and sputa (Mizunuma et al. 1993). At lower concentrations some studies (Korczynski 1998; Scolnick and Collins 1986; Dobrinskij 1970; Karpov 1954, 1955) indicate respiratory and neurological symptoms in exposed persons. However, due to insufficient reporting these studies cannot be included into quantitative assessments.

5.2. Summary of Animal Data Relevant to AEGL-1

Pinto (1997) reported reversible degeneration and necrosis of the olfactory epithelium of minimal severity at 110 ppm in rats following a 6-hour exposure. At 400 ppm moderate degeneration / necrosis were recorded together with an inflammatory exudate and infiltrate. These effects were also transient and regeneration was seen at both concentrations (110 ppm and 400 ppm). However, the original tissue with its normal physiological functions is not re-established at 400 ppm. During exposure and recovery period no clinical abnormalities have been observed at both concentrations. At macro- and micropathology no alterations at lungs and trachea have been observed following exposure to 110 or 400 ppm.

Raje et al. (1985) observed no pulmonary effects in rats after 1 hour inhalation exposure (head/nose-only) to 95 ppm MMA. Pulmonary effects (interalveolar congestion, hemorrhage, pulmonary vasodilation, edema) were observed after 2 or more hours exposure to the same concentration.

Alterations in neuronal activity, i.e. decreased firing rate in the hypothalamus and hippocampus, have been reported in rats after 5 minutes exposure to 400 ppm (Innes and Tansy 1981).

5.3. Derivation of AEGL-1

AEGL-1 values are based on observations after occupational exposure. In the NIOSH study, medical examinations of workers in poly-MMA-sheet-production plants revealed no significant acute effects (no cardiovascular changes, no effects on lung function and no effects in the URT) (Cromer and Kronoveter, 1976). The measured exposure was 25 -50 ppm for the 8 hour workday. From this study, a no adverse effect concentration for irritation of 50 ppm is derived. An uncertainty factor of 3 is used to extrapolate from workers to the general public including sensitive subpopulations and includes uncertainties about the exact exposure concentration of the examined workers. The value of 17 ppm is used for all time points. This approach is in accordance with the Standing Operating Procedures (NRC 2001) for slight irritating effects.

This approach is supported by the result from animal studies. Reversible degenerative effects on the olfactory mucosa were observed in rats after single exposure to 110 ppm (6 hours) (Pinto 1997). The severity of injuries is judged above AEGL-1 necessitating a modifying factor of 2. Due to the lower susceptibility of humans against MMA-exposure to the nasal tissue the interspecies uncertainty factor would be reduced to 1. To cover interindividual differences, an intraspecies uncertainty factor of 3 would be chosen. Application of the overall uncertainty/

modifying factor of 6 to 110 ppm gives a nearly identical AEGL-1 as derived based on human data. The AEGL-1 of 17 ppm is higher compared to methacrylic acid (6.7 ppm) and acrylic acid (1.5 ppm) . For a more complete comparison of AEGLs on acrylates and their esters see Appendix D.

The lung effects, e.g. edema, reported by Raje et al. (1985) would be considered to be above AEGL-1 level. However, these observations are contradicted by the findings reported by Pinto (1997). At 110 and 400 ppm, only dose-dependent effects on the olfactory epithelium were reported and no injuries of lung and trachea have been observed. Likewise, effects on the lung were not seen in much higher concentrations in mice (1500 ppm, 2 hrs per day for 10 days) (McLaughlin et al. 1979). The findings described by Raje et al. (1985) are quoted by Cary et al. (1995) as of doubtful significance due to the contradiction with several well-conducted and well-reported repeated exposure studies that lacks of similar observations.

The slight alterations in neuronal activity in the rat brain at a 5- minute exposure to 400 ppm, reported by Innes and Tansy (1981) were judged as below AEGL-1 level.

TABLE 7. AEGL-1 Values for Methyl Methacrylate*)

10-min	30-min	1-h	4-h	8-h
17 ppm (71 mg/m^3)	17 ppm (71 mg/m^3)	17 ppm (71 mg/m^3)	17 ppm (71 mg/m^3)	17 ppm (71 mg/m^3)

*) Sensitizing properties of methyl methacrylate can not be excluded.

The derived level of distinct odor awareness of 0.1 ppm (LOA) demonstrates that MMA will probably be recognized by odor well below AEGL-1 level.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Coleman (1963) reported that a concentration of 170 to 240 ppm causes definite irritations in exposed workers based on an industry study. Although not explicitly stated, this concentration is presumably an 8-hour TWA. Medical examination at workplace indicate that concentrations below 40 ppm to 50 ppm result in no effects (Roehm 1994; Cromer and Kronoveter 1976). Lindberg et al. (1991) reported slight irritative effects in some floor layers exposed to concentrations between 62 ppm and 601 ppm as daily mean values with a median of 175 ppm. It is further reported that MMA exposure to 2300 ppm is not tolerable by workers (Coleman 1963).

Some human case studies described the occurrence of occupational asthma in workers that had contact to MMA for several month or years. Pickering et al. (1986) reported an asthmatic attack after 45 seconds of exposure to 374 ppm MMA.

6.2. Summary of Animal Data Relevant to AEGL-2

In animal studies Mainwaring et al. (2001) reported that exposure to 200 ppm for 6 hours led to degeneration and atrophy of the olfactory epithelium up to complete demucosation in rats. The lesions were seen both at the end of the exposure and 18 h later with increasing severity.

Although the study conducted by Mainwaring et al. (2001) lacks analytic surveillance of exposure concentration, the reported histopathological findings have been supported by Pinto (1997) who demonstrated that single 400 ppm inhalation exposure for 6 hours leads to a moderate degeneration and necrosis of the olfactory epithelium with up to 50% of the tissue affected.

Relevant effects (lesions of the olfactory epithelium up to marked or complete stripping of epithelium) were also seen by Robinson et al. (2003) at 400 ppm and by Jones (2002) at 200 ppm both following a 6-hour exposure.

NTP (1986) reported that a single exposure of mice to 500 ppm for 6 hours resulted in apathy of the animals. Similar effects were seen in rats after two exposures at the same concentration. The extent of apathy is not further specified. The observed effect is considered as possibly restricting the ability to escape. The next higher concentration of 2000 ppm in this study led to ocular discharge and uncoordinated behaviour.

6.3. Derivation of AEGL-2

Irritating effects on the respiratory tract and degeneration, atrophy and necrosis of olfactory epithelium are considered as most relevant endpoints for AEGL-2 derivation. The target tissue at lower exposure is the olfactory epithelium and injuries have been observed in various studies from 200 ppm and above for a 6-hour exposure (Mainwaring et al. 2001; Pinto 1997; Robinson et al. 2003; Jones 2002).

Effects observed at 200 ppm in female rats by Mainwaring et al. (2001) and in male rats by Jones (2002) after a 6 hour exposure are judged as appropriate for the derivation of AEGL-2 values. The threshold for irreversible effects is 200 ppm for a 6-hour exposure.

As discussed in Section 4.4.1 differences in the toxicokinetics exist between rats and humans. Several studies dealing with the toxic effects of MMA as well as its metabolism suggest that humans are less susceptible than rats regarding effects on the nasal cavity. Additionally, no indications for a higher susceptibility are given from human examinations. Due to the mode of action of MMA as an irritant, no major differences in toxicodynamics are expected. For these reasons the interspecies factor is reduced to 1. An uncertainty factor of 10 would reflect the toxicokinetic mechanisms, however AEGL-values based on such factor would contradict to human data. Therefore, an uncertainty factor of 3 to account for susceptible populations was chosen.

There are no appropriate studies to be used for the derivation of a time scaling factor n. The exposure of 200 ppm was scaled to AEGL time frames using the default equation $C^n \times t = k$ (ten Berge et al. 1986). A 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 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.

TABLE 8. AEGL-2 Values for Methyl Methacrylate*)

10-min	30-min	1-h	4-h	8-h
150 ppm	150 ppm	120 ppm	76 ppm	50 ppm

(620 mg/m^3)	(620 mg/m^3)	(500 mg/m^3)	(320 mg/m^3)	(210 mg/m^3)

* Skin sensitizing properties of methyl methacrylate can not be excluded.

The established AEGL-2 (50 ppm, 8 hours) is higher than methacrylic acid (25 ppm) and acrylic acid (14 ppm). For a more complete comparison of AEGLs on acrylates and their esters see Appendix D.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human data with MMA concentrations that cause serious long-lasting or irreversible effects following inhalation exposure are available.

7.2. Summary of Animal Data Relevant to AEGL-3

From animal studies, lethality data for guinea pigs, rabbits, dogs and monkeys are insufficient to derive a lethality threshold. Very similar effect concentrations for lethality are shown for rats and mice (NTP 1986).

At lethal concentrations animals of different species developed severe breathing problems of local and systemic cause that led to respiratory failure. Usually the animals show motor weakness, prostration and died in a depressed condition. Below lethal concentrations animals also developed breathing problems, including shallow, labored or / and irregular respiration, and dyspnea. Additionally, pathological alterations of lung and liver were reported at high or lethal exposure concentrations.

Tansy et al. (1980a) and NTP (1986) reported a clear dose-response relationship for lethal effects. These data are summarized in Table 3. Although post-exposure observation of only 24 hours in Tansy et al. (1980a) could lead to less conservative LC-values, observed lethality incidences from this study are in accordance with those reported in the NTP study with 14-day observation (NTP 1986).

The BMDS software from EPA (version 1.4.1) (U.S. EPA, 2007) was applied to the data of Tansy et al. (1980a) and NTP (1986) and shown in Appendix B. The protocol of each study has limitations. Tansy et al. (1980a) had no exposures to MMA without lethality and NTP (1986) has no exposures with lethality between 0 and 90%. Although these studies were conducted in different laboratories with different strains of rats (Sprague-Dawley in Tansy et al., 1980a, and F344 in NTP, 1986) an analysis of these studies together overcomes some of the limitations in the protocols and results in a $BMCL_{05}$ of 3613 ppm and a BMC_{01} of 3486. Although the lower value of the $BMCL_{05}$ or BMC_{01} is often used to derive AEGL-3 values (NRC, 2001), in this case the higher value, the $BMCL_{05}$, is used as it is considered more representative based on the entire data for lethality. Accordingly, the $BMCL_{05}$ of 3613 for a 4 hour exposure from the analysis of the combined studies is used as the point of departure for further AEGL-3 assessment.

7.3. Derivation of AEGL-3

As discussed in Section 4.4.1 differences in the toxicokinetics exist between rats and humans. Several studies dealing with the toxic effects of MMA as well as its metabolism suggest that humans are less susceptible than rats regarding effects on the nasal cavity. This conclusion is probably not valid for other parts of the respiratory tract. To cover uncertainties of toxicokinetics in the lower respiratory tract, an interspecies factor of 3 was chosen. Due to the mode of action of MMA as a local acting corrosive substance, no major differences in toxicodynamics are expected. As demonstrated in Section 4.4.2 indications for different susceptibility between individuals are available. An uncertainty factor of 10 would reflect the toxicokinetic mechanisms, however AEGL-values based on such factor would contradict to human data. Therefore, an uncertainty factor of 3 to account for susceptible populations was chosen. The resulting overall uncertainty factor is 10.

There are no appropriate studies to be used for the derivation of a time scaling factor n The derived exposure by benchmark calculation of 3613 ppm ($BMCL_{05}$) (4 h) was scaled to AEGL time frames using the default equation $C^n \times t = k$ (ten Berge et al. 1986): a value of n = 3 in the exponential function was used for extrapolation from the 4-hour exposure to short durations and n = 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.

TABLE 9. AEGL-3 Values for Methyl Methacrylate*)

10-min	30-min	1-h	4-h	8-h
720 ppm (3000 mg/m^3)	720 ppm (3000 mg/m^3)	570 ppm (2400 mg/m^3)	360 ppm (1500 mg/m^3)	180 ppm (750 mg/m^3)

*Skin sensitizing properties of methyl methacrylate can not be excluded.

The AEGL-3 (180 ppm, 8 hours) is higher than methacrylic acid (71 ppm) and acrylic acid (58 ppm). For a more complete comparison of AEGLs on acrylates and their esters see Appendix D.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

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

The AEGL-1 values are based on human experience showing no effects at workplace exposure to 25-50 ppm; (Cromer and Kronoveter, 1976) with an uncertainty factor of 3. No increase in severity of effect with time was assumed.

The AEGL-2 values are based on degeneration and atrophy of olfactory epithelium of rats at 200 ppm for 6 hours (Mainwaring et al. 2001; Jones 2002) with an uncertainty factor of 3. The proposed derivation was supported by several human workplace studies (Coleman 1963; Roehm 1994; Cromer and Kronoveter 1976; Lindberg et al. 1991). The time scaling was conducted according to the default approach.

The AEGL-3 values are based on a $BMCL_{05}$ of 3613 ppm for mortality from a 4 hour exposure from rat studies by Tansy et al. (1980a) and NTP (1986) analyzed together) with an uncertainty factor of 10. The time scaling was conducted according to the default approach.

The odor threshold of MMA is reported from several studies of 0.083 - 0.46 ppm (ECETOC 1995; Maclaine Pont 1991). The derived level of distinct odor awareness of 0.1 ppm (LOA) demonstrates that MMA will probably be recognized by odor well below AEGL-1 level.

TABLE 10. Summary of AEGL Values*)

Classification	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	17 ppm (71 mg/m^3)	17 ppm (71 mg/m^3)	17 ppm (71 mg/m^3)	17 ppm (71 mg/m^3)	17 ppm (71 mg/m^3)
AEGL-2 (Disabling)	150 ppm (620 mg/m^3)	150 ppm (620 mg/m^3)	120 ppm (500 mg/m^3)	76 ppm (320 mg/m^3)	50 ppm (210 mg/m^3)
AEGL-3 (Lethal)	720 ppm (3000 mg/m^3)	720 ppm (3000 mg/m^3)	570 ppm (2400 mg/m^3)	360 ppm (1500 mg/m^3)	180 ppm (750 mg/m^3)

* Skin sensitizing properties of methyl methacrylate can not be excluded.

A category plot is presented in Figure 2.

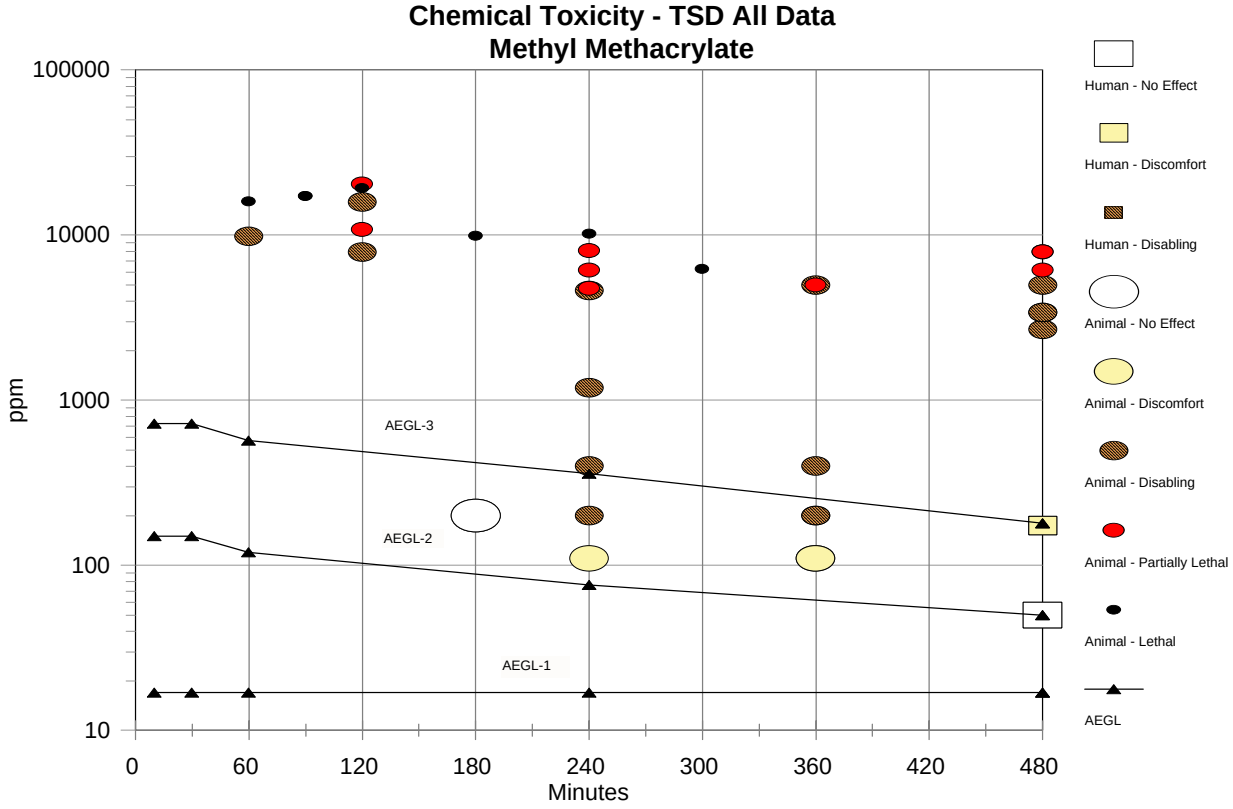

FIGURE 2. Category Plot of Toxicity Data compared to AEGL Values

8.2. Comparison with Other Standards and Guidelines

Cary et al. (1995) proposed an OES (Occupational Exposure Standard) of 50 ppm (8-hour TWA) with a short-term exposure limit of 100 ppm for a 15-minute period for the UK

Health and Safety Executive (HSE). These values are based on the observation that no significant human health effects have been reported up to 50 ppm. The short-term limit of 100 ppm is justified by the observations of eye and respiratory tract irritation, and occupational asthma.

9 ppm (37 mg/m^3) was seen as the upper limit for protection of workers against systemic effects (possible increased heartbeat) and local effects (cough) by the Dutch Expert Committee on Occupational Standards (DECOS) (Gezondheidsraad 1994). This concentration was used for the health based recommended occupational exposure limit of 40 mg/m^3 (10 ppm) (8 h TWA) was recommended.

The Concise International Chemical Assessment Document (CICAD) for MMA established a tolerable concentration (TC) of 0.2 mg/m^3 (0.048 ppm) based on a 2-year study in rats with a NOEL of 25 ppm (102 mg/m^3) (International Program on Chemical Safety, IPCS 1998).

TABLE 11. Existent Standards and Guidelines for Methyl Methacrylate

Guideline	Exposure Duration				
	10 min	**30 min**	**1 h**	**4 h**	**8 h**
AEGL-1	17 ppm	17 ppm	17 ppm	17 ppm	17 ppm
AEGL-2	150 ppm	150 ppm	120 ppm	76 ppm	50 ppm
AEGL-3	720 ppm	720 ppm	570 ppm	360 ppm	180 ppm
ERPG-1 (AIHA)[a]					
ERPG-2 (AIHA)					
ERPG-3 (AIHA)					
EEGL (NRC)[b]					
PEL-TWA (OSHA)[c]					100 ppm
PEL-STEL (OSHA)[d]					
IDLH (NIOSH)[e]		1000 ppm			
REL-TWA (NIOSH)[f]					100 ppm
REL-STEL (NIOSH)[g]					
TLV-TWA (ACGIH)[h]					50 ppm
TLV-STEL (ACGIH)[i]					100 ppm
MAK (Germany)[j]					50 ppm
MAK Peak Limit (Germany)[k]					100 ppm
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. For MMA no ERPG-1 was derived.

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. For MMA no ERPG-2 was derived. 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. For MMA no ERPG-3 was derived.

[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. For MMA no EEGL was derived.

[c]**OSHA PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits - Time Weighted Average)** (OSHA 1992) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[d]**OSHA PEL-STEL (Permissible Exposure Limits - Short Term Exposure Limit)** (OSHA 1992)
is defined analogous to the ACGIH-TLV-STEL.

[e]**IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** (NIOSH 1996) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects. The IDLH for MMA of 1000 ppm i based on acute inhalation toxicity data in humans (Coleman 1963) and animals (Blagodatin et al. 1976; Deichmann 1941).

[f]**NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** (NIOSH 1988)
is defined analogous to the ACGIH-TLV-TWA.

[g]**NIOSH REL-STEL (Recommended Exposure Limits - Short Term Exposure Limit)** (NIOSH 1988)
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 2001)
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.

[i]**ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit)** (ACGIH 2001)
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])** (DFG, Deutsche Forschungsgemeinschaft [German Research Association] 2003)
is defined analogous to the ACGIH-TLV-TWA.

[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 15 minutes with no more than 8 exposure periods per work shift; total exposure may not exceed 8-hour MAK.

[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:	Cromer and Kronoveter (1976)
Toxicity endpoint:	No acute adverse effects in workers exposed to 25-50 ppm (8h); et higher levels irritation in the URT
Supporting Studies:	Pinto (1997), animal study with rats, 110 ppm (6h) necrosis and degeneration of the olfactory epithelium
Time scaling:	No time scaling was conducted. Same concentrations for 8 hours, 4 hours, 1 hour, 30 minutes and 10 minutes
Uncertainty factors:	No interspecies extrapolation (human data) 3 for intraspecies variability (ltd. variability for local effects) Combined uncertainty factor of 3
Modifying factor:	None
Overall factor:	3
Calculations:	
10-minute AEGL-1	C = 17 ppm (50 ppm / 3)
30-minute AEGL-1	C = 17 ppm (50 ppm / 3)
1-hour AEGL-1	C = 17 ppm (50 ppm / 3)
4-hour AEGL-1	C = 17 ppm (50 ppm / 3)
8-hour AEGL-1	C = 17 ppm (50 ppm / 3)

Derivation of AEGL-2

Key Studies:	Mainwaring et al. (2001) Jones (2002)
Toxicity endpoint:	Degeneration and atrophy of olfactory epithelium up to complete demucosation in rats following a 6-hour exposure to 200 ppm.
Supporting Studies:	Roehm (1994); Coleman (1963); Lindberg et al. (1991) These human workplace studies support the AEGL-values based on Mainwaring et al. (2001): Marked irritations of upper respiratory tract are expectable in workers exposed to above 150 ppm, but not below 100 ppm
Time scaling:	$C^3 \times t$ for extrapolation to 4 hours,1 hour, 30 minutes $k = 200^3$ ppm^3 x 6 h = 48000000 ppm^3 x h $C^1 \times t$ for extrapolation to 8 hours k = 200 ppm x 6 h = 1200 ppm x h The 10-min AEGL-2 was set at the same concentration as the 30-min AEGL-2
Uncertainty factors:	1 for interspecies variability 3 for intraspecies variability Combined uncertainty factor of 3
Modifying factor:	None
Overall factor:	3
Calculations:	
<u>10-minute AEGL-2</u>	10-min AEGL-2 = 30-min AEGL-2 = 150 ppm (620 mg/m^3)
<u>30-minute AEGL-2</u>	$C^3 \times 0.5$ h = 48000000 ppm^3 x h C = 458 ppm 30-min AEGL-2 = 458 ppm/3 = 150 ppm (620 mg/m^3)
<u>1-hour AEGL-2</u>	$C^3 \times 1$ h = 48000000 ppm^3 x h C = 363 ppm 1-hour AEGL-2 = 363 ppm/3 = 120 ppm (500 mg/m^3)
<u>4-hour AEGL-2</u>	$C^3 \times 4$ h = 48000000 ppm^3 x h C = 229 ppm 4-hour AEGL-2 = 229 ppm/3 = 76 ppm (320 mg/m^3)
<u>8-hour AEGL-2</u>	$C^1 \times 8$ h = 1200 ppm x h C = 150 8-hour AEGL-2 = 150 ppm/3 = 50 ppm (210 mg/m^3)

Derivation of AEGL-3

Key Study:	Tansy et al. (1980a) and NTP (1986) analyzed together
Toxicity endpoint:	Calculated $BMCL_{05}$ for lethality of 3613 ppm for a 4 hour exposure
Time scaling	$C^3 \times t$ for extrapolation to 1 hour, 30 minutes $k = 3613^3$ ppm^3 x 4 h = 188653069588 ppm^3 x h $C^1 \times t$ for extrapolation to 8 hours k = 3613 ppm x 4 h = 14452 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
Overall factor:	10
10-minute AEGL-3	10-min AEGL-3 = 30-min AEGL-3 = 720 ppm (3000 mg/m^3)
30-minute AEGL-3	$C^3 \times 0.5$ h = 188653069588 ppm^3 h C = 7230 ppm 30-min AEGL-3 = 7230 ppm/10 = 720 ppm (3000 mg/m^3)
1-hour AEGL-3	$C^3 \times 1$ h = 188653069588 ppm^3 h C = 5735 ppm 1-hour AEGL-3 = 5735 ppm/10 = 570 ppm (2400 mg/m^3)
4-hour AEGL-3	C = 3613 ppm 4-hour AEGL-3 = 3613 ppm/10 = 360 ppm (1500 mg/m^3)
8-hour AEGL-3	$C^1 \times 8$ h = 14452 ppm h C = 1807 ppm 8-hour AEGL-3 = 1807 ppm/10 = 180 ppm (750 mg/m^3)

APPENDIX B: Benchmark Calculations

```
1
2
3   ================================================================
4           Probit Model. (Version: 2.8;  Date: 02/20/2007)
5           Input Data File: C:\BMDS\DATA\TANSY_PLUS_NTP.(d)
6           Gnuplot Plotting File:  C:\BMDS\DATA\TANSY_PLUS_NTP.plt
7                                           Thu Nov 15 12:18:18 2007
8    ================================================================
9
10   BMDS MODEL RUN
11  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
12     The form of the probability function is:
13
14        P[response] = Background + (1-Background)*
15        CumNorm(Intercept+Slope*Log(Dose)),
16     where CumNorm(.) is the cumulative normal distribution function
17
18     Dependent variable = COLUMN3
19     Independent variable = COLUMN1
20     Slope parameter is not restricted
21
22     Total number of observations = 13
23     Total number of records with missing values = 0
24     Maximum number of iterations = 250
25     Relative Function Convergence has been set to: 1e-008
26     Parameter Convergence has been set to: 1e-008
27
28     User has chosen the log transformed model
29
30                   Default Initial (and Specified) Parameter Values
31                      background =           0
32                       intercept =     -14.1915
33                           slope =      1.60731
34
35     Asymptotic Correlation Matrix of Parameter Estimates
36   ( *** The model parameter(s)-background have been estimated at a boundary
37    point, or have been specified by the user, and do not appear in the
38   correlation matrix )
39                intercept        slope
40    intercept            1           -1
41        slope           -1            1
42
43   Parameter Estimates
44
45                                          95.0% Wald Confidence Interval
46   Variable     Estimate     Std. Err.     Lower Conf. Limit   Upper Conf. Limit
47   background   0            NA
48   intercept    -29.0871     4.56397       -38.0323            -20.1419
49   slope          3.28088    0.518465        2.26471             4.29706
50
51   NA - Indicates that this parameter has hit a bound implied by some inequality
52   constraint and thus has no standard error.
53
54   Analysis of Deviance Table
55   Model           Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
56   Full model      -19.3675        13
57   Fitted model    -25.9641         2           13.1932   11         0.2809
58   Reduced model   -81.7917         1          124.848    12         <.0001
59             AIC:  55.9283
60   Goodness  of  Fit
61                                                                    Scaled
62        Dose     Est._Prob.    Expected    Observed     Size       Residual
63     ---------------------------------------------------------------------
```

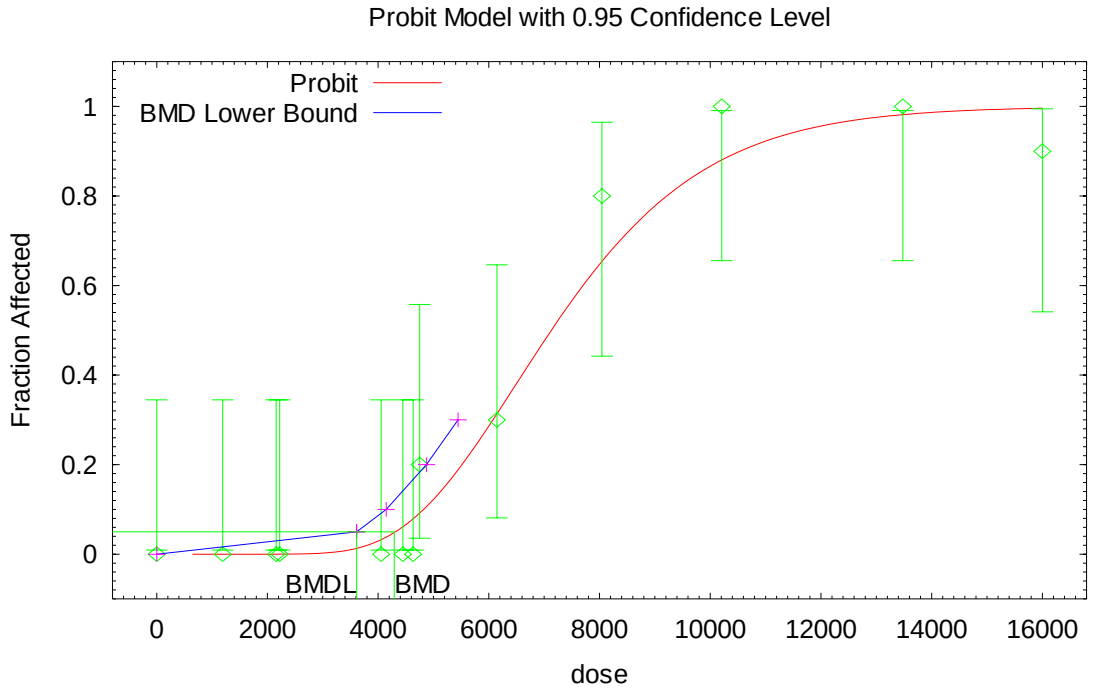
0.0000	0.0000	0.000	0	10	0.000
1191.0000	0.0000	0.000	0	10	-0.000
2159.0000	0.0000	0.000	0	10	-0.022
2220.0000	0.0001	0.001	0	10	-0.027
4055.0000	0.0336	0.336	0	10	-0.590
4446.0000	0.0632	0.632	0	10	-0.821
4632.0000	0.0817	0.817	0	10	-0.943
4750.0000	0.0949	0.949	2	10	1.135
6146.0000	0.3206	3.206	3	10	-0.139
8044.0000	0.6616	6.616	8	10	0.925
10209.0000	0.8847	8.847	10	10	1.142
13479.0000	0.9826	9.826	10	10	0.421
16000.0000	0.9962	9.962	9	10	-4.973

Chi^2 = 30.29 d.f. = 11 P-value = 0.0014

Benchmark Dose Computation

Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMD = 4291.02
BMDL = 3613.03

Specified effect = 0.01
Risk Type = Extra risk
Confidence level = 0.95
BMD = 3486.19
BMDL = 2773.89



12:18 11/15 2007

APPENDIX C: Derivation of a level of distinct odor awareness (LOA)

Derivation of the Level of Distinct Odor Awareness (LOA)

The level of distinct odor awareness (LOA) represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, about 10 % of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception. The LOA derivation follows the guidance given by van Doorn et al. (2002). For derivation of the odor detection threshold (OT_{50}), a study is available in which the odor threshold for the reference chemical n-butanol (odor detection threshold 0.04 ppm) has also been determined:

Hellman and Small (1974):
odor detection threshold for MMA: 0.05 ppm
odor detection threshold for n-butanol: 0.3 ppm
corrected odor detection threshold (OT) for MMA: OT_{50} : OT (MMA) x 0.04 ppm/OT (n-Butanol)= 0.007 ppm

0.05 ppm * 0.04 ppm / 0.3 ppm = 0.007 ppm

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

$$I = k_w * \log (C / OT_{50}) + 0.5$$

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

$3 = 2.33 * \log (C / 0.007) + 0.5$ which can be rearranged to
$\log (C / 0.007) = (3 - 0.5) / 2.33 = 1.07$ and results in
$C = (10^{1.07}) * 0.007 = 11.8 * 0.007 = 0.08$ ppm

The resulting concentration is multiplied by an empirical field correction factor. It takes into account that in every day life factors, such as sex, age, sleep, smoking, upper airway infections and allergy as well as distraction, increase the odor detection threshold by a factor of 4. In addition, it takes into account that odor perception is very fast (about 5 seconds) which leads to the perception of concentration peaks. Based on the current knowledge, a factor of 1/3 is applied to adjust for peak exposure. Adjustment for distraction and peak exposure lead to a correction factor of 4 / 3 = 1.33

$$LOA = C * 1.33 = 0.08 \text{ ppm} * 1.33 = 0.1 \text{ ppm}$$

The LOA for MAA is 0.1 ppm.

APPENDIX D: 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**	720	720	570	360	180
MAA	3;3;1;**10**	280	280	220	140	71
Acrylic acid	3;3;1;**10**	480	260	180	85	58

APPENDIX E: Derivation Summary for Acute Exposure Guideline Levels for Methyl Methacrylate (CAS Reg. No. 80-62-6)

1

AEGL-1 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
17 ppm	**17 ppm**	**17 ppm**	**17 ppm**	**17 ppm**
Reference: Cromer and Kronoveter (1976)				
Test Species/Strain/Number: Human workplace exposure				
Exposure Route/Concentrations/Durations: 50 ppm, no adverse effect level (8h), n=24				
Effects: 170/175 ppm: definite irritation after occupational exposur, especially in cases of spills (Lindberg et al. 1991; Coleman 1963) 25-50 ppm: no effects: lung, cardiovascular, upper respiratory tract				
Endpoint/Concentration/Rationale: irritation, 50 ppm, no effects				
Uncertainty Factors/Rationale: Total uncertainty factor: 3 Interspecies: 1 :human data Intraspecies: 3: sensitive subpopulations, local effects, limited variability				
Modifying Factor:: no modifying factor				
Animal to Human Dosimetric Adjustment: not relevant (human 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 assumed Data Adequacy: The key study was well conducted and comprehensively reported. The NOAEL is supported by a similar study from Roehm (1994) with lower exposures (30-40 ppm, 4-5h/d). The effect concentrations were further supported by animal studies (Pinto 1997). After application of an total uncertainty factor of 6 on animal data (110 ppm, 6h single exposure; degeneration and necrosis of olfactory epithelium; Interspecies:1; Intraspecies:3; Modifying:2 because of effect size) very similar values would be derived. AEGL-1 is well above level of odor awareness of 0.1 ppm				

2

1

AEGL-2 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
150 ppm	**150 ppm**	**120 ppm**	**76 ppm**	**50 ppm**

Reference: Mainwaring et al. (2001); Jones (2002)

Test Species/Strain/Number:
Mainwaring et al (2001): Groups of 5 female F344 rats were exposed.
Jones (2002): Groups of 5 male F344 rats were exposed

Exposure Route/Concentrations/Durations: Whole-body exposure to 200 ppm for 3 or 6 hours. No information on concentration surveillance (Mainwaring et al. 2001) resp. gaschromatographic measurements (Jones 2002). Rats were sacrificed either immediately after exposure or 18 hours later (only 6-hour exposure) (Mainwaring et al. 2001). In Jones (2002) study animals were sacrificed immediately after exposure.

Effects: Degeneration and athrophy of olfactory epithelium up to complete demucosation at 6-hour exposure (Mainwaring et al. 2001; Jones 2002). 3-hour exposure did not result in morphological abnormities. Investigation after 18 hour postexposure showed effects with increased severity.

Endpoint/Concentration/Rationale: Atrophy and demucosation of olfactory epithelium after 6-hour exposure to 200 ppm, observed in both studies (Mainwaring et al. 2001; Jones 2002).

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 toxikodynamics, no significant species differences are to be expected.
Intraspecies: 3 : There exist individual differences in susceptibility, that would justify a factor 10. However, AEGL-2 values based on such factor would contradict human effect concentrations.

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-2 was set at the same concentration as the 30-min AEGL-2.

Data Adequacy: The effect concentrations were supported by further studies with similar outcomes (Pinto 1997; Robinson et al. 2003). The derived AEGL-values were further supported by human effect concentrations reported by Coleman (1963): 170 ppm - 240 ppm (8-h TWA) caused marked irritation in exposed workers.

2

1

AEGL-3 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
720 ppm	**720 ppm**	**570 ppm**	**360 ppm**	**180 ppm**

Reference: Tansy et al. (1980a) and NTP (1986) analyzed together

Test Species/Strain/Number: Groups of 5 Sprague-Dawley rats of each sex were exposed (Tansy et al., 1980a) or groups of 5 F344 rats of each sex were exposed (NTP, 1986).

Exposure Route/Concentrations/Durations: Whole-body exposure to 5 different concentrations (4750, 6146, 8044, 10209, or 13479 ppm) in Tansy et al. (1980a) or 0, 1191, 2159, 2220, 4055, 4446, or 4632 (NTP, 1986) for 4 hours. Analytical concentration. The animals were held for observation for 24 hours (Tansy et al., 1980a) or 14 days (NTP, 1986).

Effects:

Tansy et al. (1980a)		NTP (1986)	
		0 ppm	0/10 died
4750 ppm	2/10 animals died	1191 ppm	0/10 died
6146 ppm	3/10 animals died	2159 ppm	0/10 died
8044 ppm	8/10 animals died	2220 ppm	0/10 died
10209 ppm	10/10 animals died	4055 ppm	0/10 died
13479 ppm	10/10 animals died	4446 ppm	0/10 died
16000 ppm	9/10 animals died	4632 ppm	0/10 died

No information on toxic effects other than lethality was given in Tansy et al. (1980a). In other studies, including NYP (1986) local effects on the lower respiratory tract, e.g. lung, have been reported (Deichmann 1941; DuPont 1993a; Guoshon et al. 1988). Respiratory failure was cause of death in most of these studies.

Endpoint/Concentration/Rationale: Calculated $BMCL_{05}$ of 3613 ppm was used as starting point. The lethality incidences reported in these studies revealed a clear dose-response relationship.

Uncertainty Factors/Rationale:

Total uncertainty factor: 10

Interspecies: 3 : Regarding toxicokinetics, no information on species susceptibilities at the lower respiratory tract are available. Regarding toxicodynamics, no significant species differences are to be expected.

Intraspecies: 3 : There exist individual differences in susceptibility, that would justify a factor 10. However, AEGL-3 values based on such factor would contradict human effect concentrations.

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: Tansy et al. (1980a) was published with limited reporting on toxic effects and post-exposure observation period was only 24 hours. NTP (1986) included additional reporting of toxic effects and a post-exposure observation period of 14 days.

2