Social Europe

Recommendation from the Scientific Committee on Occupational Exposure Limits for methyl methacrylate

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Table of Contents

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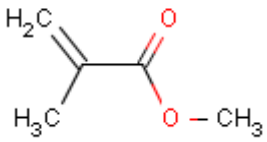
8 hour TWA:	50 ppm
STEL:	100 ppm
Additional classification:	none

Substance Identification

Substance:	Methyl methacrylate
Synonyms:	Methacrylic acid methyl ester Methyl 2-methyl-2-propenoate 2-methyl-2-propenoic acid methyl ester
CAS Registry No.:	80-62-6
EINECS No.:	201-297-1
IUPAC Name:	2-Methyl-2-propenoic acid, methyl ester
Molecular formula:	$CH_2=C(CH_3)COOCH_3$
Molecular weight:	100.13
Classification:	F;R11, Xi;R37/38,R43
Structural Formula:	



Parameter	Value	Comments
Physical state at normal temperature and pressure	A colourless liquid with a characteristic fruity odour.	It is slightly soluble in water and miscible with most organic solvents.
Melting point	-48°C	
Boiling point	100°C (at 760 mmHg)	Polymerisation is also likely
Specific Gravity	0.9836 at 20°C	
Vapour pressure	40 mmHg at 25.5°C	
Vapour density	1.09 (air=1)	
Solubility in water	16 g/l at 20°C approx	
Partition coefficient (Octanol:water)	Log Pow 1.38	
Flash point	10°C (closed cup)	
Autoflammability	430°C	
Flammability	Highly flammable	
Explosive limits (in air)	not explosive	
Oxidising properties	no oxidising properties	
Conversion factor	1 ppm = 4.10 mg.m-3 at 25°C	

1. Occurrence and Use

Hundreds of thousands of tonnes of MMA monomer are produced annually in the EU (ESR, 2002). The principal end use of MMA monomer is in the manufacture of clear and coloured cast acrylic (polyMMA) sheet with a wide range of consumer applications. Other major uses include the manufacture of resins and surface coatings, and the production of moulded and extruded products, multifunctional methacrylates and adhesives. It also has medical uses in the manufacture of prosthetic devices, artificial eyes, hearing aids, dentures and as a cement in arthroplastic surgery; and appears in beauty products.

2. Health Effects

2.1 Toxicokinetics

There are many studies addressing the toxicokinetics of MMA in both experimental animals and humans. The toxicokinetics profile is qualitatively very similar between species.

Experimental animal studies have shown that MMA is rapidly and almost completely (~97%) absorbed into the bloodstream following oral administration (Bratt and Hathway, 1977; Bereznowsky, 1995). A study with rats has shown that 10-20% of inhaled MMA vapor is deposited in the upper respiratory tract; available study results and prediction would suggest that following inhalation, much of the dose of MMA passes quickly into the epithelial lining along the length of the respiratory tract (Morris, 1992; Raje *et al*, 1985). An *in vitro* skin absorption study, conducted with human epidermis, has shown that there is relatively low absorption of MMA through the skin although the extent of absorption became significant under extended periods of occlusion (Ward & Heylings, 1993).

In experimental rodents, the nasal epithelium (particularly the olfactory region) is a primary site of expression of MMA toxicity following airborne exposure (see below). It has been demonstrated that toxicity at this site is dependent on local metabolism of MMA by carboxylesterases, producing methacrylic acid (Mainwaring *et al*, 2001). *In vitro* studies have shown that carboxylesterase activity (V_{max}) in samples of morphologically normal human nasal epithelium, obtained from 5 individuals undergoing craniofacial surgery, was much lower than in rat nasal epithelium. For the olfactory region, the carboxylesterase activity was 13-fold lower in human samples than in rat; and for the respiratory region it was 6-fold lower in the human samples than in rat. Another difference is in the distribution of carboxylesterases, which in human nasal epithelium are widely dispersed, whereas in the rat carboxylesterases are concentrated in the olfactory submucosa and Bowman's glands (Mainwaring *et al*, 2001). This is a significant observation in relation to interpreting the toxicity profile of MMA (see below).

Andersen *et al* (2002) used data from Mainwaring *et al* (2001) to create a physiologically-based pharmacokinetic (PBPK) model to determine the nasal tissue dosimetry of methacrylic acid following MMA exposure. It was predicted that, for a given airborne exposure to MMA, nasal olfactory epithelium tissue concentrations of methacrylic acid would be 3-fold lower in humans compared with rats if the esterase distribution in humans was similar to rats, or 8-fold lower in human tissues if it is taken that, in contrast to rats, human esterases are distributed evenly throughout the epithelial layer. Previous modelling attempts estimated a similar dosimetric adjustment of between 2.4 and 4.76, operating in the direction of a lower nasal epithelium concentration of methacrylic acid in humans than in rats, for a MMA concentration range of 1-400 ppm (Andersen & Sarapagani, 1999, 2001; Bogdanffy *et al*, 1998).

Further metabolism of absorbed MMA within body tissues results in entry of its metabolites into normal biochemical pathways (the tricarboxylic acid cycle). In radiolabel studies it was found that 65% of orally administered MMA was exhaled as CO_2 within 2 hours, and 76-88% within 10 days. The remaining radiolabel was excreted in the urine, with a small proportion in the faeces (Bratt & Hathway, 1977).

Due to the rapid metabolism and excretion, MMA is unlikely to accumulate within tissues.

2.2. Acute Toxicity

There are no useful human data. Experimental studies in animals have shown that MMA has low lethality following single exposure by all three exposure routes with oral and dermal LD_{50} value in excess of 5000 mg/kg and 2-4 hour inhalation LC_{50} values of approximately 5000-16 000 ppm (Spealman *et al*, 1945; Deichman, 1941; Lawrence *et al*, 1974; Schwach & Hofer, 1978; Röhm & Haas, 1982; NTP 1986; Tansy *et al,* 1980).

However, toxicity of the airborne substance towards the nasal epithelium is a major focus of attention for MMA and in this respect, nasal lesions (characterized by degeneration or atrophy specifically in the olfactory region of the nasal epithelium) were observed in rats acutely exposed to 200 ppm for 6 hours (Mainwaring *et al*, 2001).

2.3. Irritation

Based on both experimental animal and human data, liquid methyl methacrylate can produce a degreee of irritation of both the skin and the eyes on direct contact (ESR, 2002). Some eye irritation has been reported in humans with exposure to airborne MMA vapour; a clear dose-response curve for this effect has not been reliably established, although the threshold concentration would appear to be above 100 ppm. Similarly, symptoms of sensory irritation of the upper respiratory tract have been reported in workers exposed to airborne MMA; as with eye irritation, the threshold for sensory irritation of the respiratory tract has not been reliably established but would appear to be above 100 ppm (Pausch *et al*, 1994; ESR, 2002).

2.4. Sensitisation

MMA is clearly a skin sensitizer. There are numerous case reports of skin sensitisation to MMA in certain occupational situations, where frequent and prolonged unprotected skin contact with monomer-containing preparations was common practice. Single cases of skin sensitization were also reported in some medical and cosmetic applications (ESR, 2002). The available animal data also indicate that MMA is a skin sensitiser with positive results seen in well-conducted guinea pig maximisation tests (ESR, 2002).

There have been a small number of cases reported of asthmatic reactions associated with occupational exposure to MMA (eg Andrews *et al* 1979; Lozewicz *et al,* 1985; Pickering *et al,* 1986; Reynaud-Gaubert *et al,* 1986; Savonius *et al,* 1993; Pickering *et al*, 1993). However, MMA is clearly a sensory irritant towards the respiratory tract and in the majority of these cases "asthmatic" respiratory responses have been attributed to exposure to transiently high concentrations of MMA that may have resulted in respiratory irritation in individuals with normal airway responsiveness, or perhaps in some cases with pre-existing, generally hyperreactive airways. There are also other features that confound the interpretation of the experiences reported in some of these cases. Overall, there is no convincing evidence that methyl methacrylate is a significant inducer of asthma in humans (ESR, 2002; HSE, 1997; Pickering *et al*, 1993; Pausch *et al*, 1994)

2.5. Repeated Dose Toxicity

In experimental repeated dose inhalation studies in rats and mice, the predominant target organ is the respiratory tract, primarily the olfactory epithelium of the nasal passages.

In a 2-year inhalation study in rats, a clear NOAEL was evident at 25 ppm (Rohm and Haas, 1979; Lomax, 1992). At 100 ppm there were "minimal to slight" changes in the nasal olfactory epithelium (epithelial cell degeneration/atrophy and replacement of damaged cells with ciliated cells, basal cell hyperplasia, and olfactory mucosa/submucosa inflammation); and at 400 ppm these changes were somewhat more pronounced in the olfactory region, and also evident in the respiratory region of the nasal epithelium.

Other repeated inhalation exposure studies in rats and mice, with exposure periods of between 11 days and 2 years, have produced nasal olfactory epithelial damage at MMA concentrations of several hundreds of ppm and above (NTP, 1986; ESR, 2002).

No convincing evidence for any systemic toxicity arising from repeated inhalation of MMA has arisen in these studies. No toxicologically significant effects were seen in hamsters and dogs exposed repeatedly to 100 or 400 ppm (in the case of hamsters) MMA, although the extent of examination of the nasal epithelium is unclear (Smith *et al,* 1979).

No significant effects have been seen in repeated oral dosing studies in rats and dogs (see ESR, 2002).

In terms of the effects of repeated inhalation exposure in humans, a number of studies have attempted to characterise the effects of repeated workplace exposure to MMA; the more informative studies are summarised briefly here. The main focus of these studies was on respiratory health.

In a cross-sectional study conducted in the UK, workers at three factory sites producing poly-MMA sheets were assessed (Pickering *et al*, 1993). Based on workplace station measurements the workers were distributed into three exposure level groups: low (<1ppm 8-hr TWA), medium (5ppm 8-hr TWA) and high (20ppm 8-hr TWA). However, it was also predicted that the distribution of personal exposures at this factory would be similar to that of the study of Pausch *et al*, 1994 (see below), indicating that a significant proportion of workers would have been exposed to an average concentration of 50 ppm (8h TWA). In addition, a significant proportion of the workers self-reported daily exposure to transiently high levels of MMA as a result of 'cell bursts' or spills; such events have been shown to create transient peaks of several hundreds of ppm (up to 500 ppm).

The results showed a low prevalence of respiratory symptoms among the workforce with no indication of an exposure-response relationship. The results of spirometry tests showed no exposure-related changes and any differences from expected values were so small as to be of no functional significance. Overall, there were no significant respiratory health effects in this worker population, a significant proportion of whom were thought to have had average exposures of approximately 50 ppm (8h TWA).

In another worker survey, a questionnaire study and visual examination of the nasal cavity was performed over a 2-year period on 211 workers at a poly-MMA sheet production factory in Germany (Pausch *et al*, 1994). Working areas were classified into the following 8h TWA exposure ranges (as geometric means) of 3-10 ppm (7 people), 10-20 ppm (128 people), 20-30 ppm (20 people) and 30-40 ppm MMA (56 people). However, about one-third of the measurements in the higher exposure category exceeded 40 ppm (up to 50 ppm; and were beyond 50 ppm in 15% of cases).

Small numbers of workers reported respiratory symptoms of "mild" to "moderate" severity; these included impaired nose breathing (6/211), dry nose (6/211), rhinitis (1/211), reduced sense of smell (2/211), eye irritation and lacrimation (3/211) and chronic bronchitis (2/211). The only findings that showed any clear evidence of an association with MMA exposure were those indicative of transient eye and nose irritation, which correlated with short-term peaks of peak exposure (airborne concentrations somewhere between 100 and 680 ppm for periods of 5-15 minutes duration). There were no abnormalities of the nasal cavity in this workforce.

Marez *et al,* (1993) reported workplace exposure data and health status for workers at two cast acrylic sheet factories in France. A shift-related decrease in the ratio of MEF_{50}/MEF, described as an airways obstruction, was reported for workers exposed to an 8h TWA of 18.5 – 21.6 ppm MMA, with a range of 11.9 – 38.5 ppm. However, there was no significant change in the FEV_1/FVC ratio, which is a more reliable measure of airways obstruction than MEF_{50}/MEF. Furthermore, the robustness of the association with quoted levels of exposure is doubtful. In a previous paper that examined chromosomal aberrations in the same population, exposure concentrations of 114-400 ppm MMA, averaged over 1 hour, were reported but these were not mentioned when assessing the respiratory effects (Marez *et al*, 1991). It is concluded that this study does not offer convincing evidence of an effect of MMA on respiratory health, and particularly not in relation to the 8h TWA exposure level cited.

Overall, the available studies provide considerable reassurance that workers exposed to MMA levels of up to approximately 50 ppm (8-hr TWA) have not suffered any ill-health consequences resulting from such long-term exposures. Acute, transient symptoms indicative of sensory irritancy towards the respiratory tract have occasionally been experienced, probably resulting from short-term peak exposures.

2.6. Mutagenicity

Methyl methacrylate was negative in bacterial gene mutation tests (Zeiger *et al*, 1987; Waegemaekers & Benskin, 1984; Lijinsky & Andrews, 1980; Hachiya *et al*, 1982; Poss *et al*, 1979). From mammalian cell culture assays it may be concluded that MMA has some clastogenic potential *in vitro,* but only at high doses producing strong cytotoxic effects (Anderson *et al*, 1990; Moore *et al*, 1988; Myhr *et al*, 1990; Röhm & Haas, 1985). A negative *in vivo* micronucleus test and a negative dominant lethal assay indicate that this potential is probably not expressed *in vivo* (Hachiya *et al*, 1982; Rohm & Haas, 1989). Overall, it is considered that MMA has no significant genotoxicity.

2.7. Carcinogenicity

Long-term studies with rats and mice have shown that MMA exhibits no carcinogenic potential, under conditions producing chronic nasal epithelium toxicity (Röhm & Haas, 1979; NTP 1986, Smith et al, 1979). The mortality of three cohorts of MMA-exposed workers (two in the US and one in the UK) has been studied (Collins *et al,* 1989; Walker *et al*, 1991; Tomenson *et al*, 2000). Although some excesses of colorectal or colon cancer were initially apparent, closer examination of these findings indicated no consistent relationship with exposure duration, intensity of exposure or cumulative exposure levels. Overall, the evidence suggests that MMA has no carcinogenic potential.

2.8. Reproductive Toxicity

There are no fertility studies on MMA; however, the absence of significant systemic toxicity with MMA suggests that there are no concerns in this respect. The developmental toxicity of MMA has been examined following inhalation exposure in rats and mice. There were

no signs of developmental toxicity in rats at exposure levels up to 2028 ppm for 6 hours/day during days 6-15 of the gestation period. There were also no significant developmental effects in mice following repeated 2-hour exposures of mice to 1330 ppm during the gestation period (see ESR, 2002). Overall, there is no indication that MMA can exhibit reproductive toxicity.

Recommendation

In relation to the establishment of an occupational exposure limit for airborne MMA, the toxicity profile for this substance is straightforward. The key observation made in experimental animal studies is that repeated inhalation of MMA produces a focal lesion of the olfactory region of the nasal epithelium in both rats and mice. Mechanistically, this lesion arises as a consequence of local metabolism of MMA to methacrylic acid by carboxylesterases in the nasal epithelial cells.

A reliable NOAEL of 25 ppm has been established in a 2-year inhalation study in rats, with slight effects on the nasal olfactory epithelium being evident at the next higher dose of 100 ppm. Extensive PBPK modelling work has predicted that on kinetic grounds, for a given level of exposure to MMA, human nasal olfactory epithelium will be at least 3 times less sensitive than that of rats to the toxicity of MMA.

Studies of workforces have provided reassuring evidence that workers exposed to MMA levels of up to approximately 50 ppm (8-hr TWA) have not suffered any respiratory ill-health consequences related to their long-term exposure; the occasional respiratory symptoms reported seem to be clearly connected with short-term peak exposures and the sensory irritant potential of MMA which starts to be expressed at concentrations somewhere in excess of 100 ppm. The few reports in the literature of asthmatic reactions arising from MMA exposure also seem most likely to be (in the majority of cases at least) as a consequence of this sensory irritancy.

Overall, SCOEL recommends an occupational exposure limit of 50 ppm (8h TWA) as being the highest level of exposure at which one can be confident of avoiding any ill-health consequences.

Control of short-term peak exposures is also needed, in view of the sensory irritancy of MMA. There are no data to clearly indicate the threshold concentration above which such irritancy begins to be expressed in humans. However, irritant concentrations clearly lie above 100 ppm. Hence a STEL of 100 ppm is recommended.

A "Sk" notation is not appropriate; absorption through the skin is relatively low and there is no concern for systemic toxicity arising as a consequence. Although a skin sensitiser, there is no convincing evidence that methyl methacrylate is a significant inducer of asthma in humans and therefore the "Sen" notation is not appropriate. There are no grounds for recommending a biological monitoring limit value for methyl methacrylate

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