Recommendation from the Scientific Committee on Occupational Exposure Limits for Methylacrylate

8 hour TWA:	5 ppm (18 mg/m^3)
STEL (15 mins):	10 ppm (36 mg/m^3)
Additional classification:	Skin sensitizer -

Substance:

Methylacrylate $H_2C=CH-COOCH_3$

Synonyms : Acrylic acid, methyl ester; methyl propenoate, 2-propenoic acid, methyl ester; Curithane 103; methoxycarbonylethylene
EINECS Nº : 202-500-6
EEC Nº : 607-034-00-0
CAS Nº : 96-33-3
MWt : 86.10

Conversion factor (20º, 101kPa) : 3.58 mg/m^3 = 1 ppm

EU Classification :	F; R11	Highly flammable
	Xn; R20/21/22	Harmful by inhalation, in contact with skin and if swallowed
	Xi; R36/37/38	Irritating to eyes, respiratory system and skin
	R43	May cause sensitization by skin contact.

Occurrence/use:

Methylacrylate is a colourless volatile, flammable liquid with an acrid odour. It has a MPt of -75°C, a BPt of 80.5°C and a flash point of -3°C. It has a vapour pressure of about 9 kPa at 20°C, a vapour density of 3 times that of air and it is explosive in the range 2.8 - 25 % in air. The odour threshold is about 0.005 - 0.01 ppm (0.02 - 0.05 mg/m^3). It polymerises easily on standing, accelerated by heat, light and peroxides, and can react vigorously with oxidising material.

Methylacrylate is used primarily as a co-monomer with acrylonitrile in the preparation of acrylic and methacrylic fibres, which are used in clothing and furnishings. The production rate in the EU is in excess of 10,000 tonnes per annum.

Health Significance:

Single oral, dermal or inhaled doses of methylacrylate are of moderate toxicity; oral LD_{50} of 300 mg/kg bw for rats, dermal LD_{50} for rabbits of 1250 mg/kg bw, and 4h LC_{50} for rats of 1000 and 1350 ml/m^3 are given. Methylacrylate is irritating to the skin, eyes, and mucous membranes (ACGIH, 2000; DFG, 1993).

After occlusive application of radioactive labelled methylacrylate to the skin of guinea pigs the substance is absorbed only slowly preceded by a strong edema (Seutter and Rijntjes, 1981).

Methylacrylate is metabolised rapidly by unspecific carboxylases to acrylic acid and it was shown to bind with nonprotein sulfhydryl groups (DFG, 1993).

In a well-conducted 2 year study Sprague-Dawley rats (86 rats per sex and group) developed no systemic effects at concentrations of 15, 45 and 135 ppm Methylacrylate (54, 161 or 483 mg/m^3) (Reininghaus *et al.*, 1991). In the cornea a dose-related increase in neovascularization and parenchymal cloudiness was observed in male and female animals (Table 1). However, little importance can be attached to this finding because it is a result of anatomical and geriatric features of the rat which are not found in man. The rat eye is spherical and the cornea highly domed so that external factors have more effect on the rat than on the human eye. The lacrimal glands of some strains including the Sprague-Dawley rat, are often subject to age-related changes. This is also to be seen in the author's own historical data for the Wistar rat. The changes lead to inadequate lacrimation which means that the cornea of such animals is no longer adequately protected. Any additional adverse external influences, such as the irritation caused by methyl acrylate, can then result in (dose-dependent) corneal changes. Furthermore, the neovascularization of the cornea in rats exposed to methyl acrylate is known to be a reversible non-specific reaction to chronic irritation. Thus the alterations in the lacrimal glands and cornea which developed in rats under the conditions described above are not to be expected in man. Corneal damage has not been reported in workers in factories producing methyl acrylate (DFG 1993). The critical effect was irritation of the nasal mucosa. Dose-related changes occurred in the nasal mucosa at the level of the dorsal lamella of the second endoturbinate. At the lowest concentration tested (15 ppm, 54 mg/m^3) slight atrophy of the neurogenic part of the olfactory epithelium was observed in a few male rats. At 45 and 135 ppm, almost all exposed rats developed a partial loss of the columnar cell layer, with an accompanying stratified reserve-cell hyperplasia (Table 1). No treatment-related changes were detected in the posterior nasal cavity, which is mainly lined with olfactory epithelium. No irritative changes were observed in the larynx, trachea or lungs of the exposed rats. The LOAEL of this study for basal-cell hyperplasia is 15 ppm with a very steep concentration-response-curve at higher concentrations (Reininghaus *et al*., 1991). Calculation of a benchmark dose (BenchMark dose Software from US EPA, Version 1.3.2, dichotomous logistic model with 0.95 confidence level) gave a BMDL of 14 ppm. In contrast to methylacrylate, the concentration-response-curve for butylacrylate was flat, resulting in a BMDL of 6 ppm, which is in accordance with the 8-h TWA of 2 ppm.

Table 1: Frequency (%) of methylacrylate induced changes in Sprague-Dawley rats (male plus females) (Reininghaus *et al.*, 1991)

Organ	Exposure duration (month)	Concentration of methylacrylate (ppm)			
		0	15	45	135
Eye:	12[1)]	0	4	8	33
corneal neovascularization or parenchymal cloudiness	18[2)]	0	10	17	63
	24[3)]	1	10	30	59
absolute number of rats[4)]		1	14*	37*	87*
Nose:	12[1)]	0	0	65	91
basal-cell hyperplasia in level 2 of the nasal mucosa	18[2)]	0	0	88	100
	24[3)]	1	6	96	99

absolute number of rats[5)]	1	9	154*	168*

*p < 0.05
[1)] 10 male and 10 female animals examined per group
[2)] 15 male and 15 female animals examined per group
[3)] 46--53 male and 46--49 female animals examined per group
[4)] 150 - 157 rats were examined per group, excluding rats re-examined after 6 months post-exposure
[5)] 167 - 171 rats were examined per group

Methylacrylate did not induce mutations in bacteria *in vitro* (IARC, 1999). In mammalian cells methylacrylate was tested only in the absence of exogenous metabolic activation. Methylacrylate induced small colony mutations in L5178Y mouse lymphoma cells at the *tk* locus (Amtower et al., 1986, Moore *et al.,* 1988), but no mutations in Chinese Hamster ovary cells at the *hprt* (Moore *et al.,* 1989, 1991) or *xprt* locus (Oberly *et al.,* 1993). Chromosomal aberrations were detected in L5178Y mouse lymphoma cells (Moore et al. 1988) and in Chinese hamster lung (Ishidate *et al.,* 1981, Sofuni *et al.,* 1984a) and ovary cells (Moore *et al.,* 1989). The results indicate a clastogenic activity of methylacrylate. In vivo, micronuclei formation was observed in bone marrow cells of mice following intraperitoneal injection (37,5-300 mg/kg bw) at high doses which caused toxicity (Przybojewska *et al.*, 1984) but not after inhalation (2100 ppm for 3 h; Sofuni *et al.,* 1984b) or oral application of methylacrylate (250 mg/kg bw; Hachiya *et al.,* 1981).

No carcinogenic effects were observed in the 2 year study with Sprague-Dawley rats (Reininghaus *et al.,* 1991).

In a developmental toxicity study Sprague-Dawley rats were exposed during days 6 to 20 of gestation to 25, 50, or 100 ppm methylacrylate for 6 h/day. No treatment-related increases in embryo/fetal mortality or fetal malformations were observed. Fetal toxicity, indicated by reduced fetal body weight, was observed after exposure to 100 ppm methylacrylate in the presence of overt signs of maternal toxicity (Saillenfait *et al.,* 1999).

A concentration of 74 ppm (266 mg/m^3) has been cited as being irritating to the eyes, nose and throat of humans (Deichmann and Gerarde, 1969), but without reference to the original study.

Milton et al. (unpublished; ACGIH 2001) reported on a case-crossover study over an 8-week period. The test subjects were ten production workers, four partially exposed workers, and an occupational hygienist who had minimal exposure previous. Each individual served as his/her own "unexposed" control because there was a 2-week turnaround time between the production cycles of methylacrylate. Average exposure was 2 ppm, with peaks of 12.6 to 30 ppm lasting 2 to 5 minutes for the highest exposure job category. Area sampling found a mean level of 5.4 ppm with a minimum of 0.6 ppm and a maximum of 17.2 ppm. Highest peak exposures occurred during the tasks of "sampling" (to 115 ppm) and during "inhibitor inhibition" (to 122 ppm). Subjects were examined by an ophthalmologist at the onset of the study and after 8 week of production for corneal changes. No corneal changes noted. All subjects had mild to moderate blepharitis and conjunctivitis at the beginning and throughout the study. Although not statistically significant, the incidence of reported increased eye irritation by the end of the shift (4.4/100 person days) was greater in the higher exposed group than in the lower (1.4/100 person days). Other reported symptoms were described as being of low occurrence and intensity, except for fatigue. 50% of all subjects had bronchial hyperactivity at the start of the study. Changes in metacholine challenge were described as small and tending to decrease; the largest increase was seen in the occupational hygienist who was the only subject without prior occupational exposure to methyl acrylate. Baseline spirometry is described as unremarkable; there was a borderline significant (p=0.06) reduction in peak flow drop across workshifts in the combined medium- and high-exposure groups as compared to the low-exposure group. This study is not adequate for OEL setting due to the low number of subjects, high peak exposures (which are usually responsible for irritating effects) and insufficient exposure and effect characterisation of the low, medium, and high exposure groups.

Several cases of occupationally-related contact dermatitis have been described for methylacrylate (DFG, 1993, Sokolowski, 1977). A single accidental exposure to undiluted methylacrylate can also cause

sensitization (Kanerva *et al.*, 1993). An allergic genesis of methylacrylate induced sensitisation was demonstrated in one case (Cavelier *et al.*, 1981). Sensitizing effects of methylacrylate were also shown in guinea pigs in a test with epicutaneous induction of methylacrylate (modified Draize test) and in various test protocols with intradermal induction of methylacrylate together with adjuvant (modified maximization test, Polak test, split adjuvant test) (Bull *et al.*, 1985, Parker and Turk 1983, Parker *et al.*, 1985). Guinea pigs treated once epicutaneously on the ear with methylacrylate produced marked reactions and lymphocyte proliferation in the lymph nodes (Bull *et al.*, 1985). For further details see DFG (2001). There are no data available for sensitizing effects on the respiratory passages.

In a prospective cohort study a group of 60 workers exposed to chemical substances in the production of acrylic acid, acrylic acid esters and acrylate dispersions, and 60 controls, were followed up from 1992 to 1999. The average exposure period was 13±5 years. Exposure to acrylonitrile, n-butanol, butyl acrylate, ethyl acrylate, methyl acrylate, methyl methacrylate, toluene, and styrene was determined by personal passive dosimetry. The measured concentrations were generally low, occasionally exceeding maximum allowable concentrations. Less than 10% of the samples from personal passive dosimetry showed methylacrylate concentrations over 0.2 mg/m^3 (0.06 ppm). The results of the clinical, haematological and biochemical examination of the workers have not revealed any marked differences between the exposed and control groups that could be attributable solely to the acrylate exposure (Tuček *et al.,* 2002).

Recommendation:

There are no human data available which are adequate for proposing occupational exposure limits.
The study of Reininghaus *et al*. (1991), establishing a LOAEL of 15 ppm (54 mg/m^3), for slight irritation of the olfactory epithelium in rats, was considered to be the best available basis for proposing occupational exposure limits. In view of the mild nature of this localised lesion, observed in a well-conducted study and the very steep concentration-response-curve beyond 15 ppm, an uncertainty factor of 2 was considered appropriate to allow for the absence of a NOAEL and of human data. This is in accordance with the calculated BMDL of 14 ppm. Taking into account the preferred value approach, the recommended 8-hour TWA is 5 ppm (18 mg/m^3). A STEL (15 mins) of 10 ppm (36 mg/m^3) was proposed to limit peaks of exposure which could result in irritation.

No “skin” notation was considered necessary since methylacrylate is irritating to the skin and absorption through the skin was only slowly after dermal application.

Methylacrylate should be recognised as a skin sensitizer.

At the levels recommended, no measurement difficulties are foreseen.

Key Bibliography:

ACGHI (American Conference of Governmental Industrial Hygienists) (2000). Methyl acrylate.

Amtower, A.L., Brock, K.H., Doerr, C.L., Dearfield, K.L. and Moore, M.M. (1986). Genotoxicity of three acrylate compounds in L5178Y mouse lymphoma cells. Environ. Mutagen. Suppl. 6, 4.

Bull, J.E., Parker, D., Turk, J.L. (1985) Predictive value of assessment of lymph node weight and T-lymphocyte proliferation in contact sensitivity in acrylates. J. Invest. Dermatol. 85, 403–406.

Cavelier, C., Jelen, G., Hervé-Bazin, B., Foussereau, J. (1981). Irritation et allergie aux acrylates et méthacrylates. Première partie: monoacrylates et monométhacrylates simples. Ann. Dermatol. Venereol. (Paris) 108, 549–556.

Deichmann, W.B. and Gerarde, H.W. (1969). Toxicology of Drugs and Chemicals, p75, Academic Press, New York.

DFG (Deutsche Forschungsgemeinschaft) (1993). Occupational Toxicants, Critical Data Evaluatuation for MAK Values and Classification of Carcinogens, Methyl acrylate, Volume 6, 253–262.

DFG (Deutsche Forschungsgemeinschaft) (2001). Occupational Toxicants, Critical Data Evaluation for MAK Values and Classification of Carcinogens, Methyl acrylate, Volume 16, 177–180.

Hachiya, N., Taketami, A., Takizawa, Y. (1982). Ames test and mouse bone marrow micronucleus test on acrylic resin monomer and other additives. Jpn. J. publ. Health 29, 236–239.

IARC (1999) Methyl acrylate. IARC Monogr. Eval. Carcinog. Risks. Hum., Vol. 71 Pt 3, 1489–1496.

Ishidate, M., Sofuni, T., Yoshikawa, K. (1981). Chromosomal aberration test *in vitro* as a primary screening tool for environmental mutagens and/or carcinogens. Gann Monogr. Canc. Res. 27, 95–108.

Kanerva, L., Jolanki, R., Estlander, T. (1993). Accidental occupational sensitization caused by methyl acrylate. Eur. J. Dermatol. 3, 195–198.

Moore, M.M., Amtower, A., Doerr, C.L., Brock, K.H., Dearfield, K.L. (1988). Genotoxicity of acrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate, and ethyl methacrylate in L5178Y mouse lymphoma cells. Environ. Mol. Mutagen. 11, 49–63.

Moore, M.M., Harrington-Brock, K., Doerr, C.L., Dearfield, K.L. (1989). Differential mutant quantitation at the mouse lymphoma tk and CHO hgprt loci. Mutagenesis 4, 394–403.

Moore, M.M., Parker, L., Huston, J., Harrington-Brock, K., Dearfield, K.L. (1991). Comparison of mutagenicity results for nine compounds evaluated at the hgprt locus in the standard and suspension CHO assays. Mutagenesis 6, 77–85.

Oberly, T.J., Huffman, D.M., Scheuring, J.C., Garriott, M.L. (1993). An evaluation of 6 chromosomal mutagens in the AS52/XPRT mutation assay utilizing suspension culture and soft agar cloning. Mutat. Res. 319, 179–187.

Parker, D., Turk, J.L. (1983). Contact sensitivity to acrylate compounds in guinea pigs. Contact Dermatitis 9, 55–60.

Parker, D., Long, P.V., Bull, J.E., Turk, J.L. (1985). Epicutaneous induction of tolerance with acrylates and related compounds. Contact Dermatitis 12, 146–154.

Przybojewska, B., Dziubaltowska, E. and Kowalski, Z. (1984). Genotoxic effects of ethyl acrylate and methyl acrylate in the mouse evaluated by the micronucleus test. Mutat. Res. 135, 189–191.

Reininghaus, W., Koestner, A. and Klimisch, H.-J. (1991). Chronic toxicity and oncogenicity of inhaled methyl acrylate and n-butyl acrylate in Sprague-Dawley rats. Fd. Chem. Toxicol. 29, 329–339.

Saillenfait, A.M., Bonnet, P., Gallissot, F., Protois, J.C., Peltier, A., Fabries, J.F. (1999). Relative developmental toxicities of acrylates in rats following inhalation exposure. Toxicol Sci 48, 240–254.

Seutter, E., Rijntjes, N.V.M. (1981). Whole-body autoradiography after systemic and topical administration of methyl acrylate in the guinea pig. Arch. Dermatol. Res. 270, 273–284.Sofuni, T., Hayashi, M., Matsuoka, A., Sawada, M., Hatanaka, M., Ishidate, M. Jr. (1984a). Cytogenetic effects of gaseous and volatile chemicals on mammalian cells in vitro and in vivo. I. Chromosome aberration tests in cultured mammalian cells (Japanese). Eisei Shikenjo Hokoku 102, 77–83.

Sofuni, T., Hayashi, M., Matsuoka, A., Sawada, M., Hatanaka, M., Ishidate, M. Jr. (1984b). Cytogenetic effects of gaseous and volatile chemicals on mammalian cells in vitro and in vivo. II. Micronucleus tests in mice (Japanese). Eisei Shikenjo Hokoku 102, 84–90.

Sokolowski, F. (1977) Allergie auf Methylacrylat nach Hauttests (talk). Berufs-Dermatosen 25, 92.

Tuček, M., Tenglerova, J., Kollarova, B., Kvasnickova, M., Maxa, K., Mohyluk, I., Svandova, E., Topolcan, O., Vlasak, Z., Cikrt, M. (2002). Effect of acrylate chemistry on human health. Int. Arch. Occup. Environ. Health 75, Suppl 1, 67–72.