Methyl methacrylate

Supplement 2006

MAK value (1988)	**50 ml/m^3 (ppm) ≙ 210 mg/m^3**
Peak limitation (2000)	**Category I, excursion factor 2**
Absorption through the skin	**–**
Sensitization (1984)	**Sh**
Carcinogenicity	**–**
Prenatal toxicity (1985)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
Synonyms	methacrylic acid methyl ester methyl α-methyl acrylate methyl 2-methylpropenoate methyl 2-methyl-2-propenoate MMA
Chemical name (CAS)	2-methyl-2-propenoic acid methyl ester
CAS number	80-62-6
1 ml/m^3 (ppm) ≙ 4.2 mg/m^3	**1 mg/m^3 ≙ 0.238 ml/m^3 (ppm)**

This supplement is based on EU Risk Assessment Report 22 (EU 2002), the IUCLID Dataset (ECB 2000), Concise International Chemical Assessment Document 4 (WHO 1998) and an IARC assessment (IARC 1994).

These reports provide detailed, comprehensive data. Therefore, only studies relevant to the evaluation are listed in the present supplement.

1 Toxic Effects and Mode of Action

Methyl methacrylate (MMA) is widely used in cement for dental and surgical prostheses. The substance is a colourless, flammable liquid with a severely irritating,

The MAK-Collection Part I: MAK Value Documentations, Vol. 26. DFG, Deutsche Forschungsgemeinschaft

ISBN: 978-3-527-32306-7

pungent and fruitlike smell and an odour threshold of 0.21 ml/m^3. Since methyl methacrylate is easily polymerized or copolymerized by light, heat, ionizing radiation or chemical catalysts, it is almost always present with inhibitor additives.

Methyl methacrylate is irritating to the skin and mucous membranes. Narcotic effects, disorders of the central nervous system (CNS) and CNS depression were observed after higher doses.

In a carcinogenicity study carried out by the National Toxicology Program (NTP) with F344 rats and B6C3F$_1$ mice, no carcinogenic effects were detected after methyl methacrylate concentrations of up to 1000 ml/m^3.

On the basis of reliable case reports of the allergenic effects of methyl methacrylate on the skin and of contact sensitization in guinea pigs, methyl methacrylate is designated with an "Sh".

In vitro studies suggest that methyl methacrylate produces clastogenic effects.

In a prenatal developmental toxicity study with rats exposed by inhalation, no developmental toxicity was found up to the highest concentration of 2000 ml/m^3.

2 Mechanism of Action

The mitochondria are regarded as the main intracellular target of methyl methacrylate. If isolated rat liver mitochondria are incubated with methyl methacrylate, oxygen consumption increases. This is the result of an uncoupling of the mitochondrial respiratory chain, as seen from the expected influence on state 4 and state 3 respiration. State 4 respiration is stimulated. As has been reported for organic solvents, methyl methacrylate attacks complex I of the respiratory chain close to the rotenone binding site. This means that substrates which are oxidized in conjunction with NADH inhibit the flow of electrons and thus also ATP synthesis. Unlike classical uncouplers, methyl methacrylate stimulates the Mg^{2+}-dependent ATPase bound to the inner mitochondrial membrane. Structural changes of the inner membrane, as found with non-ionic detergents, were observed by electron microscopy. The release of enzymes indicates disintegration of the membrane (Bereznowski 1994).

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

The toxicokinetics of methyl methacrylate seem to be similar in humans and test animals (EU 2002).

3.1.1 Inhalation

After exposure of rats to methyl methacrylate concentrations of 0, 90, 437 or 2262 mg/m^3 (0, 21, 104 or 538 ml/m^3) by inhalation, 10 % to 20 % of the substance was deposited in the lower respiratory tract and metabolized there (EU 2002).

3.1.2 Ingestion

Methyl methacrylate is rapidly absorbed and distributed after ingestion. Single gavage doses of methyl methacrylate of 8 mmol/kg body weight (800 mg/kg body weight) led to maximum serum concentrations between 10 and 15 minutes after administration (Bereznowski 1995).

After administration of 5.7 and 120 mg/kg body weight of radioactively-labelled methyl methacrylate to rats, 76 % to 88 % of the radioactivity was exhaled within 10 days; 4.7 % to 7.2 % was found in the urine and 1.7 % to 3.0 % in the faeces; the remaining radioactivity was detected in the liver and adipose tissue (EU 2002).

3.1.3 Dermal absorption

Methyl methacrylate is irritating to the skin and, according to the authors, can be absorbed effectively via the skin (Rajaniemi 1986). An *in vitro* study with human (heat-separated) epidermis in a static diffusion model showed that methyl methacrylate can be absorbed through the skin and absorption is increased by occlusion. About 10 mg undiluted methyl methacrylate/cm^2 was applied for a period of 30 hours. The maximum absorption rates were measured during the first hour and were 274 µg/cm^2 and hour under occlusive conditions and 107 µg/cm^2 and hour under non-occlusive conditions. These values dropped to 152 and 3.48 µg/cm^2 and hour during the next 10 hours. Only a small amount of the dose applied penetrated the skin under non-occlusive conditions (0.56 %); this implies that methyl methacrylate evaporates from the surface of the skin (Cefic 1993).

3.1.4 Other routes of absorption

Since cement containing methyl methacrylate is used in surgery, e.g. as cement for artificial hip joints, there are numerous studies dealing, for example, with the composition of the cement (Morita *et al.* 1998), its effects on biological systems (Elmaraghy *et al.* 1998) and the determination of methyl methacrylate in blood (Gentil *et al.* 1993; Hand *et al.* 1998). These studies are not described here because they are not appropriate for deriving a MAK value.

Methyl methacrylate and methacrylic acid can be detected in the blood for a short period of time after the use of cement containing methyl methacrylate. In one study the half-life of methyl methacrylate in the blood was specified to be 47 to 55 minutes

(Svartling *et al*. 1986). In a more recent study, methyl methacrylate was no longer found in the blood after only 3 and 6 minutes. The initial and terminal half-lives were specified as being 0.3 and 3 minutes, respectively (Gentil *et al*. 1993).

3.2 Metabolism

The 1984 MAK documentation describes the metabolism of methyl methacrylate. Methyl methacrylate is hydrolyzed to methacrylic acid by carboxylesterases. Methacrylic acid is transformed via physiological metabolic pathways and enters the citric acid cycle via methylmalonyl-CoA and succinyl-CoA. Methyl methacrylate may, however, also react directly with glutathione and other sulfhydryl groups ("Methyl methacrylate", Volume 3, present series).

3.3 Species differences

In rats, hamsters and humans, methyl methacrylate is hydrolyzed to methacrylic acid by carboxylesterases, for example in the nasal mucosa. The local toxicity is attributed to the acid that is formed. Pre-treatment of rats with bis(*p*-nitrophenyl)phosphate, a carboxylesterase inhibitor, clearly reduced the severity of the nasal lesions. Investigations with rat, hamster and human nasal tissues have shown that carboxylesterases are mainly localized in goblet cells and Bowman's gland in rats, but are more generally distributed in the human olfactory epithelium. In all three species, the enzyme activity is higher in the olfactory tissue than in the respiratory tissue, by a factor of 3 in rats and humans and a factor of 12 in hamsters. The rate of metabolism of methyl methacrylate *in vitro* (V_{max}) was similar in the olfactory epithelium of rats and hamsters, but about 7 to 13 times lower in humans. In respiratory tissues, the rate of metabolism in humans was at least 6 times lower than that in the rat. The authors conclude from these findings that the level of exposure of the olfactory epithelium is lower in humans than in rats or hamsters (Mainwaring *et al*. 2001). However, it must be noted that human nasal explants were available from only 5 persons.

Mathematical models (physiologically based pharmacokinetic, PBPK) were developed to describe the dosimetry of methyl methacrylate in nasal epithelial tissue. Among other things, airflow patterns within the nose, nasal compartmentation and the distribution of the carboxylesterases in the different nasal cell types were taken into account. Assuming that the carboxylesterases are distributed in different amounts in the human nose, the models used predict 3 to 8 times lower methyl methacrylate doses in human tissue compared with those in the rat even at an increased respiration rate and the same methyl methacrylate concentrations (Andersen *et al*. 2002; EU 2002).

4 Effects in Humans

4.1 Repeated exposures

Inhalation

Irritation of the upper respiratory tract and eyes and possible CNS effects were reported in humans after exposure to methyl methacrylate concentrations of up to 250 ml/m^3. Individual publications described CNS effects and hypotension after inhalation of methyl methacrylate concentrations of about 36 to 83 ml/m^3 at the workplace for up to 11 years; functional disorders (CNS, cardiovascular system, liver and blood count) were reported after even lower occupational exposure. Since no information was provided about controls, exposure concentrations, the exposure period or smoking habits, these reports cannot be used to evaluate possible effects of methyl methacrylate ("Methyl methacrylate", Volume 3, present series).

In 91 workers exposed to person-related 8-hour mean levels of methyl methacrylate of between 4 ± 2.2 and 49 ± 26.2 ml/m^3, no significant changes in symptoms (coughing or sputum), pulmonary function, allergic reactions, blood pressure or haematology were found compared with the findings for 43 control persons. Slightly altered levels for cholesterol, albumin and total bilirubin were found particularly in the high dose group; the authors considered these findings to be clinically irrelevant. The reduced serum glucose levels that were also observed in the high exposure group were found to be reproducible; according to the authors, they must be substantiated by a properly matched control group. Changes to the skin and nervous system were also mentioned, although they were not statistically significant (NIOSH 1976; "Methyl methacrylate", Volume 3, present series). They were probably caused by dermal exposure to methyl methacrylate. The reduced serum glucose levels may be the result of the influence of shift work and circadian differences in glucose metabolism (Morgan *et al*. 2003).

A more recent study carried out between 1991 and 1993 at the Röhm factory included all 211 male workers involved in acrylic sheet production and mainly exposed to methyl methacrylate. The workers had to fill in a questionnaire and were subjected to anamnesis and rhinoscopy every six months. The workers were on average 37 years old and had spent an average of 8.8 years in acrylic sheet production. 34 % of the workers had been exposed for more than 10 years, and 16 % for more than 20 years. The current mean values for methyl methacrylate were specified to be 3 to 40 ml/m^3, earlier 8-hour means were specified to be 10 to 70 ml/m^3. The analyses were person-related. Short-term 5 to 15-minute exposure peaks were reported to be 100 to 300 ml/m^3, in one case 680 ml/m^3 (Röhm 1994). Tables giving the results of analyses of short-term exposures for 1991 and 1992 show that short-term levels were below 100 ml/m^3 in most cases. Only 3 of the 60 values reported were above 100 ml/m^3 (683, 142 and 115 ml/m^3) (Degussa 2004). The workplaces were categorized according to the median person-related exposure level (8-hour average value): Area 4: 3 to 10 ml methyl methacrylate/m^3 (7 workers); Area 3:

10 to 20 ml/m^3 (128 workers); Area 2: 20 to 30 ml/m^3 (20 workers); Area 1: 30 to 40 ml/m^3 (56 workers). Area 0 consisted of 57 newly hired workers who had presumably been exposed to methyl methacrylate several times before the examination and could therefore not be used as a control group (Degussa 2005). The workers reported no irritation, nor did rhinoscopy reveal nasal lesions. However, a few workers from Area 2 and Area 3 complained of impaired nasal breathing, dryness in the nose and burning or itching of the eyes or lacrimation in conjunction with exposure to methyl methacrylate; in these areas, there was a high rate of air exchange with low humidity caused by the exhaust air system (see Table 1). Comparable methyl methacrylate-related effects were not observed in workers of Area 1 with a higher level of exposure to methyl methacrylate caused by a lower rate of air exchange. Some workers who reported effects such as impaired nasal breathing, dryness in the nose, burning of the eyes or lacrimation attributed these mainly to peak exposures to methyl methacrylate, which were above 100 ml/m^3. There were no reports of changes to the nasal cavity epithelium or irritant effects on the upper respiratory tract that could clearly have been caused by long-term exposure to methyl methacrylate. An impaired sense of smell that could not be attributed to other causes, such as an acute cold or allergic rhinitis, was described by 2 workers of Area 2. One of these workers was later subjected to the Rhino-Test® (Muttray *et al.* 1997; see below), but his sense of smell was not impaired. The second worker could not be examined since he had apparently left the company. Workplace-related sensitization was not reported although the entire group included 27 atopics (12.8 %) with known allergies. Four workers had respiratory sensitization to enzymes, flowers or animal hair, 13 workers, 6 of them in the control group, had hay fever, 6 workers had dermal sensitization to antibiotics, animal hair, chromium and nickel and 4 workers had a food allergy. The authors point out the limitations of the study: The questionnaires were not evaluated and the data could not be evaluated statistically because there was no comparable control group (Röhm 1994).

Despite the described limitations, the above study provides evidence that no exposure-induced irritation of the eyes or respiratory tract occurs after exposure to methyl methacrylate concentrations of up to 40 ml/m^3. Irritation was observed only at higher concentrations, which, according to the authors, were more than 100 ml/m^3.

Table 1. Findings in workers from acrylic sheet production (supplemented according to Röhm 1994)

Complaints (finding No.)	8-hour average values for methyl methacrylate [ml/m^3] (current//earlier concentrations)				
		3–10//<10–30 1–6 hours/day	10–20//20–60 1–5 hours/day	20–30//40 6 hours/day	30–40//50–70 4–5 hours/day
	Area 0	Area 4	Area 3	Area 2	Area 1
No. of workers	57	7	128	20	56
Nose					
rhinitis (1)	1 (1.8 %)	1 (14 %) *not MMA-induced*	5 (3.9 %) subjective, 2 (1.6 %) of these clinically confirmed *not MMA-induced*		3 (5.4 %) subjective, 1 (1.8 %) of these clinically confirmed *not MMA-induced*
impaired nasal breathing (2)	3 (5.5 %) subjective; 2 (3.6 %) clinically confirmed		14 (11 %) subjective, 4 (3.3 %) of these clinically confirmed **7× possibly MMA-induced**	2 (10 %) subjective, 0 (–) of these clinically confirmed *not MMA-induced*	13 (23 %) subjective, 7 (12.5 %) of these clinically confirmed *not MMA-induced*
dry nose (3)		1 (14 %) subjective; 0 (–) clinical	18 (14 %) subjective, 6 (4.7 %) of these clinically confirmed **5× possibly MMA-induced**	7 (35 %) subjective, 1 (5.0 %) of these clinically confirmed **3× possibly MMA-induced** (1× confirmed), **2 of these impaired sense of smell**	4 (7.1 %) subjective, 2 (3.6 %) of these clinically confirmed *not MMA-induced*
frequent nose bleeding (6)	2 (3.6 %)		2 (1.6 %)		2 (3.6 %) *not MMA-induced*
impaired sense of smell (7)	1 (1.8 %) *not MMA-induced*		2 (1.6 %) *not MMA-induced*	2 (9.5 %) **2× possibly MMA-induced;** 1× not confirmed in secondary examination	2 (3.6 %) *not MMA-induced*
burning/itching of eyes or lacrimation (10+11)	1 (1.8 %) *not MMA-induced*		8 (6 %) **2× possibly MMA-induced**	2 (9.5 %) **1× MMA-induced (peak exposure)**	5 (9 %) *not MMA-induced*

In 1994, a Rhino-Test® with six aromas to determine hyposmia (diminished sense of smell) was carried out in 175 workers from the Röhm factory to examine whether degeneration of the nasal epithelium together with a resulting loss of the sense of smell had occurred in workers exposed to methyl methacrylate. The average exposure period was 9.6 ± 7.1 years. Up to 1988, the 8-hour mean values were between 25 and 100 ml/m^3, and from 1988 to 1994 they were 10 to 50 ml/m^3. The workers were exposed almost exclusively to methyl methacrylate; only two workers also had short-term exposures to formaldehyde up to 1990, four workers had been exposed to acrylonitrile and two other workers to formaldehyde and acrylonitrile. The proportion of smokers was higher in the exposed workers (58.3 %) than in the 88 control persons (34.1 %). In the group of exposed workers, only one worker (0.6 %), who suffered from sinusitis on the day of examination, was observed to have hyposmia. The number of workers (merely six) who from 1981 to 1994 had left the company for occupationally-related health problems was small (Muttray *et al.* 1997). This study indicates that no impairment of the sense of smell occurs, at least after exposure to methyl methacrylate concentrations of up to 50 ml/m^3.

In 8 of 40 workers who had been exposed to average methyl methacrylate concentrations of 18.5 or 21.6 ml/m^3 (range 9–21 ml/m^3 or 11.9–38.5 ml/m^3) in two factories for 5 to 10 years, or more than 10 years, an increased incidence of chronic coughing was observed compared with that in 2 of 45 control persons with the same smoking habits. Spirometric findings did not differ between exposed and control persons before the workshift, but deteriorated during the workshift in both the controls and the workers exposed to methyl methacrylate. The decline in the maximal expiratory flow at 50 % of forced vital capacity (MEF_{50}) and the ratio of MEF_{50} to maximal expiratory flow were significant in the workers exposed to methyl methacrylate compared with in the control persons. The authors attributed the increased incidence of chronic coughing and the slight respiratory obstruction to exposure to methyl methacrylate (Marez *et al.* 1993). The EU Risk Assessment Report draws attention to the small population, the lack of data about possible exposure to other irritant substances, and other inadequacies, and expresses doubts about how exposure was recorded (EU 2002). Exposure was determined only by static devices, not by personal air sampling, and the inadequate data give rise to doubts about the analytical methods used. This study is therefore not suitable for deriving a threshold value.

In a biological monitoring study, 32 male workers were examined who were exposed to methyl methacrylate concentrations of between 0.4 and 112 ml/m^3 with a geometric mean of 6.1 ml/m^3 and a median of 5.3 ml/m^3. Four workers were exposed to concentrations of more than 50 ml/m^3 and one of them was exposed to concentrations above 100 ml/m^3. No changes in haematological or biochemical parameters were found in the serum; nor was there a statistically significant difference in the prevalence of symptoms compared with those in 16 workers not exposed. Only 6 exposed workers reported frequent coughing with sputum and 4 workers reported throat irritation. Four of the 6 workers who complained of coughing and sputum and all 4 workers with throat irritation belonged to the "high" exposure group (5–112 ml/m^3; median 18 ml/m^3); however, the workers with these symptoms were not always those exposed to the highest concentrations (no other details) (Mizunuma *et al.* 1993). There are no details about the

current or earlier 8-hour mean values or peak exposures to which the workers with symptoms were exposed. Nor is there any information about smoking habits. Therefore, the data cannot be used for deriving a threshold value.

In a dental laboratory, methyl methacrylate concentrations from 4.09 to 30.64 mg/m^3 (0.26–7.29 ml/m^3) were determined in the breathing zones of 8 workers. Sixteen analyses of methyl methacrylate in the air yielded concentrations between 3.68 and 38.42 mg/m^3 (0.88–9.14 ml/m^3). Persons who worked with methyl methacrylate for 20 to 30 minutes—kneading the mass containing methyl methacrylate with their bare hands—complained of the unpleasant smell and occasional eye irritation (Korczynski 1998). Since no data are available about the methyl methacrylate concentrations present when the workers complained of eye irritation, these findings cannot be used for an assessment of methyl methacrylate.

4.2 Local effects on skin and mucous membranes

Dental technicians who used liquid methyl methacrylate reported dermal lesions and finger paresthesia (Rajaniemi 1986; Seppalainen and Rajaniemi 1984).

4.3 Allergenic effects

4.3.1 Sensitizing effects on the skin

In a Belgian hospital, a total of 13833 patients were patch tested between 1978 and 1999. A reaction to (meth)acrylate was observed in 54 of a total of 7369 patients who reacted to at least one substance; 5 also reacted to 2 % methyl methacrylate in petrolatum. The number of persons tested with methyl methacrylate was not documented (Geukens and Goossens 2001). In a British hospital, 352 patients were tested with 2 % methyl methacrylate in petrolatum in the period from 1983 to 1998; 17 of them produced a reaction (Tucker and Beck 1999). Between January 1988 and October 2002, a reaction to at least one (meth)acrylate was observed in a total of 75 patients of an American hospital. A reaction to 2 % methyl methacrylate in petrolatum was also observed in 19 of 56 patients whose data could be evaluated (Sood and Taylor 2003). In another American hospital, a total of 472 patients were tested with 2 % methyl methacrylate in petrolatum between July 1994 and June 1999; 3 of 54 workers employed in a health-care related field and 3 of 418 persons not employed in health-care professions produced reactions (Shaffer and Belsito 2000). In 2001 and 2002, 4900 patients were tested with 2 % methyl methacrylate in petrolatum in a North American multicentre study; 1.4 % produced a positive result. For the periods from 1996 to 1998 and 1998 to 2000, the authors specify the proportion of reactions as being 1.6 % of 4099 persons and 1.4 % of 5812 persons tested, respectively (Pratt *et al.* 2004).

In a study of 27 patients who had contact with artificial fingernails, including 16 cosmeticians, 4 of the 21 persons tested reacted to 2 % methyl methacrylate in

petrolatum and 25 of 27 to 2 % 2-hydroxyethyl methacrylate in petrolatum (Constandt *et al*. 2005). According to a Swedish study, a reaction to 2 % methyl methacrylate in petrolatum was observed in 16 of 109 dental personnel examined between 1995 and 1998. All 16 patients also reacted to 2-hydroxethyl methacrylate and 15 of them to ethylene glycol dimethacrylate as well (Wrangsjö *et al*. 2001). Of 79 dentists and 46 dental nurses who were tested in a Polish hospital between 1990 and 2000, 8 reacted to 2 % methyl methacrylate in petrolatum. All eight also produced a reaction to ethylene glycol dimethacrylate (Kiec-Swierczynska and Krecisz 2002). A reaction was observed in 20 of the 271 patients tested with 2 % methyl methacrylate in petrolatum at the Finnish Institute of Occupational Health between 1985 and 1995 (Kanerva *et al*. 1997). In a Finnish multicentre evaluation carried out in the period from 1994 to 1998, a reaction was reported in 28 of 2607 patients tested. A further 15 reactions were classified as questionable or irritant (Kanerva *et al*. 2001). Reactions to methyl methacrylate were observed in 2 of 49 Korean dental technicians, 22 of whom had contact dermatitis (Lee *et al*. 2001). Between 1992 and 1995, 143 dental technicians were tested with 2 % methyl methacrylate in petrolatum in the clinics of the Information Network of Departments of Dermatology (Informationsverbund Dermatologischer Kliniken); 18 of them (12.6 %) produced a reaction (Schnuch *et al*. 1998*)*. However, these patients belong to the collective whose test results were already included in the 1997 documentation ("Methyl methacrylate", Volume 16, present series).

There are also individual case reports of sensitization to methyl methacrylate and reactions in patch tests in 2 dental nurses (Kanerva and Estlander 1998; Kanerva *et al*. 1998), 1 female patient with acute eczema in the contact area of a plastic catheter (Saccabusi *et al*. 2001), 1 patient with an erythematous-oedematous reaction in the contact area of an adhesive for a surgical earthing plate containing 2-hydroxyethyl acrylate and 2-hydroxyethyl methacrylate (Miranda-Romero *et al*. 1998), 1 female patient with erythematous skin changes with blisters after application of artificial nails (Mowad and Ferringer 2004), another female patient with skin reactions to components of artificial fingernails (Casse *et al*. 1998) and in several patients intolerant to dental prostheses (Bauer and Wollina 1998; Giroux and Pratt 2002; Lunder and Rogl-Butina 2000; Ruiz-Genao *et al*. 2003). The clinical relevance of the patch test reactions described in these reports is unclear in most cases as the affected patients almost always reacted to several (meth)acrylates, especially ethylene glycol dimethacrylate, and the level of methyl methacrylate in the products was only rarely specified. One female patient with anamnestic evidence of intolerance to fingernail materials containing acrylate and a temporarily inserted dental filling was subjected to a test to identify whether it would be possible to implant a knee prosthesis with bone cement containing methacrylate. For this purpose, the patient was patch tested with 2 % and 4 % mixtures of a liquid methyl methacrylate preparation (with *N*,*N*-dimethyl-*p*-toluidine, hydroquinone and chlorophyll); methacrylate copolymer powder (with di-benzoyl peroxide, zirconium dioxide and chlorophyll); and with a patch of the polymerized cement. After 72 hours there was an indurated erythematous reaction to the cement and the two methyl methacrylate preparations (Kaplan *et al*. 2002). In another study (Hochman and Zalkind 1997), a female patient with suspected intolerance to a dental prosthesis and a dentist who exhibited intolerance reactions while working with materials containing acrylate

were apparently tested with undiluted methyl methacrylate, with the effect that the positive findings obtained cannot be evaluated. Another positive test result with methyl methacrylate in one worker with skin changes induced by an adhesive containing acrylic acid and methyl methacrylate (Bang Pedersen 1998) was not adequately documented. Four reactions to 1 % methyl methacrylate were observed in the patch testing of 520 patients with mucosal alterations which might have been caused by dental prostheses. Clinical relevance was specified for two of these reactions, but there are no details (Vilaplana and Romaguera 2000).

One female patient with a 4-year history of lesions of the palate associated with a dental prosthesis reacted to none of the acrylates or methacrylates in the patch test after 2 or 4 days. After 3 weeks, the patient went to hospital again because she had an unpleasant feeling in the test area. The repeated testing led to 3+ reactions to 2 % methyl methacrylate, 0.1 % ethyl and butyl acrylate and 2 % 2-hydroxyethyl methacrylate in petrolatum after 4 days, which the authors considered to be evidence of sensitization caused by the patch test (Vozmediano and Manrique 1998). In another case, a 1+ reaction to methyl methacrylate, which was observed only after 38 days, was reported in a female dental technician (Fowler 1999).

Methyl methacrylate was used in studies in which the effects of contact sensitizing substances on the maturation and cytokine secretion of human dendritic cells and the migration of Langerhans' cells were investigated in excised human skin to evaluate the applicability of *in vitro* test methods. In these studies, methyl methacrylate led to less pronounced effects than ethylene glycol dimethacrylate, hydroxypropyl methacrylate and 2-hydroxyethyl methacrylate (Rustemeyer *et al*. 2003).

4.3.2 Sensitizing effects on the respiratory tract

A 48-year-old female worker exposed to methyl methacrylate in the processing of an adhesive containing methyl methacrylate developed workplace-related dyspnoea and rhinorrhoea as well as other symptoms. A 30-minute provocation test, in which the patient applied "one or four ml" of the adhesive to an area of 10 × 10 cm in an exposure chamber, led to a 24 % decrease in the peak expiratory flow (PEF) only after 8 hours. Up to the seventh hour, the reduction in PEF was about 16 % at most and was also lower in subsequent determinations with the exception of the analysis after 12 hours (about –18 %). A 46-year-old dental technician who had been in the profession for 20 years reported tiredness and respiratory symptoms such as a cough and chest tightness which disappeared when she was ill or on holiday, but recurred within one week after she had returned to her job. A workplace-related provocation test, during which the patient processed a prosthesis made of 10 ml methacrylate powder (probably polymethyl methacrylate) and 10 ml methacrylate liquid, led to a dual reaction with a decrease in the PEF of a maximum 26 % (no other details). The grinding of a "piece of methacrylate" (probably polymethyl methacrylate) led to a delayed 15 % decrease in the PEF in another female worker, who developed asthmatic symptoms after exposure for one month to (poly)methyl methacrylate in the manufacture of hearing aids. The authors determined an increase in non-specific respiratory tract reactivity in the histamine test after the

provocation (Savonius *et al.* 1993a, 1993b). A recent communication reported occupationally induced hypersensitivity pneumonitis in a 20-year-old and a 24-year-old female dental technician. Dyspnoea and coughing occurred in both employees a few weeks or about half a year after beginning training. The blood gas analysis revealed hypoxaemia (65 and 55 mm Hg), and pulmonary function tests showed the diffusion capacity to be reduced and in one case the total lung capacity to be reduced (67 % of the expected level). The 20-year-old patient was exposed to a methyl methacrylate aerosol two months later. There was a 30 % increase in lymphocytes in the bronchioalveolar lavage (BAL) fluid, and pulmonary function tests revealed a 20 % decrease in the diffusion capacity for carbon monoxide (TLCO). No other findings were communicated. About four weeks after the symptoms had subsided in the second patient as a result of oral corticosteroid therapy, she returned to her laboratory workplace, and one day later a pronounced cough recurred. After another two days, she was re-examined in hospital, and hypoxaemia (58 mm Hg), an increase in the lymphocyte count in the BAL fluid, reduced forced vital capacity (2.0 l; 50 %) and reduced forced expiratory volume in the first second (FEV_1; 0.85 l; 24 %) were again found (Scherpereel *et al.* 2004).

A 44-year-old secretary reported experiencing respiratory symptoms (rhinorrhoea, dyspnoea and coughing attacks) for the past two years 15 to 20 minutes after beginning copying on a black and white copier with a toner containing a polymer of styrene and *n*-butyl methacrylate. The histamine test revealed non-specific bronchial hyperreactivity ($PC_{20(histamine)}$: 2.16 mg/ml). In a workplace-related provocation test, respiratory symptoms (dyspnoea) occurred after 18 minutes. The FEV_1 was reduced at this time by 21 %, after 1 hour by 24 % and after 4 hours by 19 %. In a provocation test with methyl methacrylate, which was heated to 80°C, a FEV_1 decrease of 30 % occurred after 1 hour and a 24 % decrease after 5 hours. Provocation tests with polystyrene and potato flour induced no respiratory symptoms or spirometric alterations. The nasal lavage fluid contained an increased amount of eosinophils only after the workplace-related provocation and after provocation with methyl methacrylate. In addition, the two provocation tests led to an increase in the permeability index (from 6.5 % to 16.1 % and from 9.1 % to 19.7 %) after 24 hours (Wittczak *et al.* 2003).

Hoarseness and sore throat, as well as nasal symptoms and dyspnoea, occurred in a 48-year-old dental nurse after almost 27 years of exposure to acrylates. Prick tests with ubiquitous allergens, acrylates (no other details), chloramine-T and latex and a provocation test with a mixture of 2-hydroxyethyl methacrylate and bisphenol A diglycidyl methacrylate yielded negative results. Pulmonary function tests did not reveal abnormal findings. Provocation tests with liquid methyl methacrylate (10 drops; trade product with stabilizers and other additives) and with polymethyl methacrylate powder (10 ml; trade product) led to mucosal alterations not described in detail and to symptoms of the upper respiratory tract, indicating rhinitis and pharyngitis. An increase in airway resistance (70 %) was determined rhinomanometrically. However, the FEV_1 decrease was only 6 % at most, and the PEF was reduced by 20 % 16 hours after provocation. PEF monitoring revealed no workplace-related changes. After about two years of continued work with reduced exposure to acrylates and local corticosteroid therapy, further PEF monitoring revealed fluctuations of 350–470 l/min on working days and

420–460 l/min on work-free days; the authors concluded from this that the patient had occupational asthma (Piirilä *et al.* 1998).

A female dental technician developed dyspnoea, wheezing, coughing and rhinorrhoea 6 to 8 months after her first contact with preparations containing methyl methacrylate. At the time of examination, the patient had already been exposed to methyl methacrylate for 13 years. Prick tests with ubiquitous allergens yielded negative results. Pronounced stridor and dyspnoea and a decrease in the FEV_1 and PEF occurred in the provocation test with methyl methacrylate. In the nasal lavage fluid there was an increase in leukocytes, eosinophils and basophils and an increase in the eosinophilic cationic protein and mast cell tryptase (Wittczak *et al.* 1996).

In a cross-sectional study, the pulmonary function parameters of 19 male dental technicians exposed to methyl methacrylate concentrations of 0.16 to 4.38 ml/m^3 (TWA; arithmetic mean: 1.40 ml/m^3; geometric mean: 0.91 ml/m^3) were compared with those of 9 male workers not exposed. Peak exposures of a maximum 37.71 ml/m^3 occurred during the processing of thermosetting resins. In the group of exposed persons, the parameters FVC and FEV1.0 (determined as %FVC/Ht and %FEV1.0/Ht) were reduced and the workers specified a higher incidence of respiratory symptoms (coughing) (Nishiwaki *et al.* 2001). Since no immunological investigations were carried out, the study cannot be used for assessing the sensitizing effects of methyl methacrylate on the respiratory tract. The same applies to other studies in which respiratory functions were monitored in workers exposed to methyl methacrylate or possible respiratory symptoms were recorded but no provocation tests or other immunological investigations were carried out among the specific workers (see also EU 2002).

4.4 Reproductive toxicity

Male and female workers exposed to methyl methacrylate and vinyl chloride reported sexual disorders that were not specified in detail. Since these studies are only available as abstracts and there are no further details, they cannot be used for assessment (EU 2002).

The EU Risk Assessment Report describes a study of a cohort of women who had been occupationally exposed to methyl methacrylate from 1976 to 1985. The evaluation of a total of 502 pregnancies, for example, revealed an increased incidence of spontaneous abortions among women exposed to more than 20 mg/m^3 (about 5 ml/m^3) and asphyxia, malformations (no other details) and stillbirths among the newborn babies of women exposed to below 10 mg/m^3 (about 2.5 ml/m^3). Since the study is based only on retrospective data and there are no details of controls or workplace and exposure conditions, it is not possible to attribute the described effects to an exposure to methyl methacrylate. Therefore, this study cannot be used for assessment (EU 2002).

4.5 Genotoxicity

The number of SCEs (sister chromatid exchanges) was increased in 31 workers exposed to methyl methacrylate (7.85 ± 2.66) compared with the number in 31 controls adjusted for age and smoking behaviour (7.49 ± 2.33). The incidence of SCEs was significantly increased only in the group of workers exposed to peak methyl methacrylate concentrations of 114 to 400 ml/m^3. Responsible for this increase were some cells with a large number of SCEs (Marez *et al*. 1991). As a result of methodological inadequacies, the specified exposure concentrations are questionable (see Section 4.1: Marez *et al*. 1993).

4.6 Carcinogenicity

Large mortality studies were carried out in two US companies involved in acrylic sheet production (Collins *et al*. 1989; Walker *et al*. 1991). The cohorts were exposed mainly to ethyl acrylate and methyl methacrylate. There was co-exposure to ethylene dichloride, methylene chloride and acrylonitrile. Increased mortality resulting from colon cancer was significant in one factory and not significant in the other. A non-significant increase in rectal cancer was identified in the first factory. The increases were most obvious in the workers from the earliest production period and in workers with the highest exposure levels. There was, however, no relationship between the tumour risk and increasing methyl methacrylate exposure (IARC 1994).

5 Animal Experiments and *in vitro* Studies

5.1 Acute toxicity

5.1.1 Inhalation

The 4-hour LC_{50} for rats is 29800 mg/m^3 (7092 ml/m^3) (EU 2002).

Mice were exposed to methyl methacrylate concentrations of 740 to 33000 ml/m^3 for 30 minutes to determine the RD_{50}. The respiratory rates were not consistently reduced by more than 25 % at any exposure concentration (ACGIH 2001). Therefore, no RD_{50} could be determined.

Female F344 rats exposed to methyl methacrylate concentrations of 200 ml/m^3 for 6 hours were found to have lesions in the nasal olfactory epithelium characterised by degeneration and atrophy (Mainwaring *et al*. 2001).

5.1.2 Ingestion

Oral LD_{50} values of 8 to 10 ml/kg body weight (7552–9440 mg/kg body weight) were obtained in rats (EU 2002).

5.1.3 Dermal absorption

The dermal LD_{50} was greater than 5000 mg/kg body weight in rabbits under occlusive conditions (EU 2002).

5.2 Subacute, subchronic and chronic toxicity

Inhalation

Most of the available studies with repeated administration have already been described in the 1984 MAK documentation ("Methyl methacrylate", Volume 3, present series). What follows is a description of relevant studies published since that time; for comparison, the earlier studies relevant to the evaluation are described below.

Groups of 5 female F344 rats were exposed to methyl methacrylate concentrations of 0, 110 or 400 ml/m^3 in whole-body exposure chambers for 6 hours per day, for 1, 2, 5, 10 or 28 days. Animals were examined 4, 13, 24 or 36 weeks after the end of exposure to assess the reversibility of the findings. The only finding in both exposure groups was damage to the olfactory epithelium. The lesions induced by methyl methacrylate concentrations of 110 ml/m^3 were reversible during the exposure period. The lesions caused by 400 ml/m^3 were repaired after 13 weeks, but minimal respiratory metaplasia was observed, and there were focal adhesions between the septum and turbinates and between the turbinates themselves (Hext *et al*. 2001).

Degeneration of the olfactory epithelium, bronchopneumonia, interstitial pneumonia, haemorrhages, atelectasis, oedema, emphysema and bronchial epithelial hyperplasia occurred after exposure of at least 10 rats per group to methyl methacrylate concentrations of 0 or 1000 ml/m^3 for 6 hours per day, on 5 days per week for 4 weeks, under poor and normal ventilation conditions. Bronchopneumonia with abscesses was observed only in rats under poor ventilation conditions; in addition, glutathione levels were significantly decreased and malondialdehyde levels were significantly increased in rats of this group. No difference was observed in superoxide dismutase activity. According to the authors, the poor air exchange rate led to higher concentrations; they point out that adequate protection systems should be in place in operating theatres, which is rarely the case in Turkey (Aydin *et al*. 2002).

In a carcinogenicity study of the NTP ("Methyl methacrylate", Volume 3, present series), groups of 50 male F344 rats were exposed to methyl methacrylate concentrations of 0, 500 or 1000 ml/m^3, female rats were exposed to methyl methacrylate concentrations of 0, 250 or 500 ml/m^3 and male and female $B6C3F_1$ mice were exposed to 0, 500

or 1000 ml/m^3 over 102 weeks, for 6 hours per day, on 5 days per week. Body weight gains were reduced in animals of all exposure groups, and there were non-neoplastic lesions in the nasal cavity. Rats and mice were found to have inflammation of the nasal cavity and degeneration of the olfactory epithelium; mice also had hyperplasia of the nasal cavity epithelium (Chan *et al*. 1988). No NOAEL was obtained in this study.

In a combined chronic toxicity and carcinogenicity study carried out by Rohm and Haas in 1979, groups of 70 male and 70 female F344 rats were exposed to methyl methacrylate concentrations of 0, 25, 100 or 400 ml/m^3 for 2 years. Ten animals from each group were investigated after 13 and 52 weeks. Body weight gains were reduced only in the females of the high exposure group from the 52nd week. Haematological and clinicochemical parameters and urinalyses were unchanged. Histopathological changes were observed only in the nasal cavity. The nasal tissues—three to four sections per animal—were re-evaluated in 1992 and 1997 (Lomax *et al*. 1997). Sections of trachea, pharynx and larynx were no longer preserved. Degeneration, atrophy, hyperplasia, inflammation and metaplasia in the olfactory epithelium and hyperplasia and inflammation in the respiratory epithelium were observed in the animals of the two high exposure groups (Table 2). The NOAEL in this study was 25 ml/m^3 (EU 2002).

Table 2. Incidence of nasal lesions in F344 rats after exposure for two years to methyl methacrylate (EU 2002; Lomax *et al*. 1997)

Findings	Methyl methacrylate concentration (ml/m^3)							
	males				females			
	0	25	100	400	0	25	100	400
olfactory epithelium								
number of animals examined (n)	39	47	48	38	44	45	41	41
basal cell hyperplasia (%)	13	6	69	87	0	2	44	76
degeneration/ atrophy (%)	0	0	86	100	0	0	59	95
chronic mucosal and submucosal inflammation (%)	0	0	35	76	0	0	12	61
metaplasia (%)	0	0	2	39	0	0	17	51
respiratory epithelium								
number of animals examined (n)	44	47	48	42	45	45	41	42
Bowman's gland and goblet cell hyperplasia (%)	2	0	2	60	0	0	2	21
chronic mucosal and submucosal inflammation (%)	9	0	4	60	4	0	0	21

statistical significance of the findings not specified in the publication

In a carcinogenicity study carried out by Rohm and Haas in 1979, golden hamsters were exposed to methyl methacrylate concentrations of 0, 25, 100 or 400 ml/m^3 over 78 weeks, for 6 hours per day, on 5 days per week. The re-evaluation of the findings in 1997, in which two to four sections were evaluated per animal, revealed no nasal lesions (EU 2002; Lomax *et al*. 1997).

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

In a range-finding study with 2 rabbits, occlusive application of 0.5 ml undiluted methyl methacrylate for 4 hours was found to be weakly irritating to the skin. In addition, blanching, eschar formation and desiccation of the skin were reported (Rohm & Haas 1982).

Groups of 2 male rabbits were treated dermally for 24 hours with methyl methacrylate doses of 0, 200, 2000 or 5000 mg/kg body weight under occlusive conditions. Well-defined to severe erythema with blanching and moderate to severe oedema with pocketing were observed after 24 hours. After 14 days, skin irritation was still present in animals treated with methyl methacrylate doses of 2000 and 5000 mg/kg body weight. After 3 days, no irritation was observed in animals treated with methyl methacrylate doses of 200 mg/kg body weight. After 2 days, eschar formation was found in the animals of the 2000 and 5000 mg/kg groups. On day 12, eschar was observed to be sloughing off with new hair growth. Desiccation of the skin was observed in animals of all exposure groups (EU 2002).

5.3.2 Eyes

In a range-finding study with 2 rabbits, the instillation of 0.1 ml undiluted methyl methacrylate into the eyes led to conjunctival redness in both rabbits after 24 hours, which was no longer present after 72 hours (Rohm & Haas 1982). No effects on the iris or cornea were observed in another study with 6 rabbits (EU 2002).

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

All animals produced a reaction in a modified maximization test with two groups of 5 animals (intradermal induction with 10 % methyl methacrylate in corn oil/physiological saline, epicutaneous induction with 25 % methyl methacrylate in sunflower oil; challenge occlusively on day 14 with 25 % methyl methacrylate in corn oil, occlusively

with 25 % methyl methacrylate in DMSO/corn oil and on day 28 non-occlusively with 25 % methyl methacrylate in DMSO/ethanol or non-occlusively with 50 % methyl methacrylate in DMSO/ethanol) (Rustemeyer *et al*. 1998). Two of 14 female Hartley guinea pigs reacted in another modified maximization test (intradermal and epicutaneous inductions with 10 % methyl methacrylate in olive oil; challenge occlusively with 1 % methyl methacrylate in acetone). After challenge with 1 % methyl methacrylate in acetone, no reaction was observed in 10 animals which had been treated with 1 % or 0.1 % methyl methacrylate preparations for induction (Kanazawa *et al*. 1999). Further positive findings were obtained in a modified Freund's Complete Adjuvant (FCA) test. In this test, a total of 300 µl 10 % methyl methacrylate in FCA/water (1:1) was injected intradermally into both flanks (2 × 50 µl) and the ears (2 × 50 µl) and necks (100 µl) of groups of 5 animals for induction. Challenge was carried out on day 14 by occlusive application of 25 µl of a preparation of 25 % methyl methacrylate in corn oil or in DMSO/corn oil and on day 28 by non-occlusive application of 25 % methyl methacrylate in DMSO/ethanol (4:1) or a preparation of 50 % methyl methacrylate in DMSO/ethanol. Ten of 10 and 9 of 10 animals reacted after occlusive and non-occlusive challenge treatment, respectively. Almost all of the animals sensitized with methyl methacrylate also reacted to 10 % ethylene glycol dimethacrylate. There were markedly fewer cross-reactions with 2-hydroxyethyl methacrylate and 2-hydroxypropyl methacrylate (Rustemeyer *et al*. 1998). In later studies with the modified FCA test, male and female inbred guinea pigs (no other details) were also sensitized with 10 % methyl methacrylate in FCA/water (1:1) and reacted to 50 % methyl methacrylate in DMSO/ethanol (4:1) after non-occlusive challenge treatment. However, if 175 µl undiluted methyl methacrylate was administered orally to the animals 26, 20 and 14 days before the beginning of sensitization, it was possible to induce tolerance, which was manifest in the clearly less pronounced reaction to the challenge treatment (Rustemeyer *et al*. 2001).

5.4.2 Sensitizing effects on the respiratory tract

There are no data available for sensitization of the respiratory tract induced by methyl methacrylate.

5.5 Reproductive toxicity

5.5.1 Fertility

There are no valid studies of fertility available.

Long-term inhalation studies with rats and mice and an oral long-term study with the administration of methyl methacrylate in drinking water revealed no histopathological changes in the male or female sex organs (see Section 5.2).

5.5.2 Developmental toxicity

Rats

In a prenatal developmental toxicity study carried out according to OECD Test Guideline 414, groups of 27 pregnant CD rats (Sprague-Dawley) were exposed to methyl methacrylate concentrations of 0, 99, 304, 1178 or 2028 ml/m^3 for 6 hours a day, on days 6 to 15 of gestation. Reduced feed consumption and reduced maternal body weight gains were recorded in all exposure groups throughout the exposure period. The minimal reductions in body weight gain observed on days 6 to 8 of gestation after 99 and 304 ml/m^3 were transient. The incidences of foetuses with variations and retardations per litter were somewhat higher in all exposed groups than in the control group, but there was no clear relationship to the concentration. A significant increase was observed only for the incidence of variations (particularly of rudimentary 14th ribs) at the second highest concentration of 1178 ml/m^3. Here, 3 foetuses from two litters were found to have malformations (1× omphalocoele of the abdomen and 2× enlarged adrenal glands) compared with 1 foetus in the control group (duplication of the hypothalamus). The authors do not regard the findings as substance-induced as there was no dose-response relationship, and they conclude that there was no substance-related embryotoxicity or foetotoxicity even at concentrations that resulted in maternal toxicity (Solomon *et al.* 1993).

In two independent tests carried out by Imperial Chemical Industries Limited (ICI) in 1977, rats were exposed to methyl methacrylate concentrations of 0, 100 or 1000 ml/m^3 and to 0, 25, 100 or 1000 ml/m^3 on days 6 to 15 of gestation. The no observed adverse effect concentration (NOAEC) for maternal toxicity was specified to be 1000 ml/m^3. The authors reported an increase in the number of early resorptions in the high exposure group in both tests and of late resorptions in only one test. The authors derived a NOAEC of 100 ml/m^3 from their results. Because of this study's limitations (insufficient randomization of test animals, inadequate test protocol and poor documentation), the authors' interpretations could not be followed in the Risk Assessment Report (EU 2002).

Another inhalation study with rats (Nicholas *et al.* 1979) is not useful because of the high, toxic concentration of methyl methacrylate administered of 110000 mg/m^3 (26180 ml/m^3) for 17 or 54 minutes per day. Exposure led to deaths, loss of body weight and reduced feed consumption in the dams. Early resorptions were observed. Foetal body weights were reduced, crown–rump lengths were shorter and there were haematomas and retarded ossification (EU 2002).

The intraperitoneal injection of methyl methacrylate in doses of 0, 0.133, 0.266 or 0.443 ml/kg body weight (0, 126, 251 or 418 mg/kg body weight) on days 5, 10 and 15 of gestation revealed no maternal effects in rats. Compared with in untreated controls, there was a higher incidence of resorptions, and foetal body weights were slightly reduced, but all values were in the range of those of the control animals with intraperitoneal injection of water, saline or oil. The foetuses were found to have a higher, dose-dependent incidence of anomalies (haemangiomas) (2.3 %, 8.0 % and 16.7 %; controls 0–2 %), but no malformations or other effects of developmental toxicity (Singh *et al.* 1972). The haemangiomas were presumably the result of the irritant effects of the

substance after intraperitoneal injection and are therefore not relevant for the assessment of the developmental toxicity of methyl methacrylate under inhalation conditions.

Mice

The exposure of groups of pregnant CD-1 mice (n = 38, 32, 18) to methyl methacrylate concentrations of 0, 100 or 400 ml/m^3 for 6 hours per day, on days 4 to 13 of gestation, led only to slight, but statistically significant differences in the body weights of the foetuses (no other details); no teratogenic effects were induced (ICI 1980).

Exposure of 18 pregnant ICR mice to methyl methacrylate concentrations of 1330 ml/m^3 for 2 hours twice daily on days 6 to 15 of gestation revealed only slightly increased foetal weights, but no evidence of developmental toxicity. There are no data for maternal toxicity (McLaughlin *et al.* 1978).

Rabbits

In a study carried out by ICI in 1977, the intraperitoneal injection of 0.004, 0.04 or 0.4 ml/kg body weight (3.8, 38 or 376 mg/kg body weight) on days 6 to 18 of gestation led in rabbits to a high incidence of peritonitis (probably the result of the irritant effects of methyl methacrylate) and an increase in the respiration rate in the high dose group. In this dose group, also the foetal weights were significantly reduced and the number of resorptions was increased. There were no malformations (EU 2002).

5.6 Genotoxicity

5.6.1 *In vitro*

Methyl methacrylate yielded negative results in bacterial gene mutation tests (EU 2002; IARC 1994).

In vitro genotoxicity studies in mammalian test systems are shown in Table 3.

At concentrations with moderate toxicity, methyl methacrylate induced small colonies in the mouse lymphoma test without, but especially with S9 mix (Dearfield *et al.* 1991; Doerr *et al.* 1989; Myhr *et al.* 1990), which are evidence of a clastogenic effect of the substance. Similar evidence was obtained in the micronucleus test (Doerr *et al.* 1989) and in chromosomal aberration tests (Anderson *et al.* 1990; Doerr *et al.* 1989). However, in the studies by Doerr *et al.* (1989), positive effects were not related to the concentration tested but linked with severe toxicity. In contrast, “authentic clastogens” demonstrate very steep dose–response relationships. The SCE data showing more pronounced effects at a later time of preparation confirm these data. If the SCE data are considered separately, they have little relevance, but in the context of the other data they substantiate the presence of a genotoxic potential *in vitro*, which is detected only when there are also toxic effects.

Table 3. *In vitro* genotoxicity studies with methyl methacrylate in mammalian test systems (according to IARC 1994)

Test system		Concentration	Results		References
			without MA	with MA	
SCE	CHO cell line	5 µg/ml	–		Anderson *et al.* 1990
		16–1250 µg/ml	+		
		50–500 µg/ml		–	
		1600–5000 µg/ml		+	
gene mutation, $TK^{+/-}$ locus	mouse lymphoma cell line L5178Y	250–3000 µg/ml	(+)[1]		Dearfield *et al.* 1991
		500–1000 µg/ml		+[1]	
gene mutation, $TK^{+/-}$ locus	mouse lymphoma cell line L5178Y	250–3000 µg/ml	+[1]		Doerr *et al.* 1989; Moore *et al.* 1988
gene mutation, $TK^{+/-}$ locus	mouse lymphoma cell line L5178Y	125–250 nl/ml (118–235 µg/ml)	–		Myhr *et al.* 1990
		500–1000 nl/ml (470–940 µg/ml); toxic at 1500 nl/ml (1410 µg/ml)	+		
		125 nl/ml (118 µg/ml)		–	
		250–1500 nl/ml (235–1410 µg/ml)		+	
gene mutation, $TK^{+/-}$ locus	mouse lymphoma cell line L5178Y	up to 100 nl/ml (94 µg/ml)	–		EU 2002
		100–250 nl/ml (94–235 µg/ml)		(+)	
MN	mouse lymphoma cell line L5178Y	1000–3000 µg/ml	(+)[2]	not investigated	Doerr *et al.* 1989
CA	CHO cell line	up to 500 µg/ml	–		Anderson *et al.* 1990
		1600, 3000 µg/ml	+		
		160–1600 µg/ml		–	
		5000 µg/ml		+	
CA	mouse lymphoma cell line L5178Y	1000–3000 µg/ml	(+)[3]	not investigated	Doerr *et al.* 1989; Moore *et al.* 1988

CA: chromosomal aberrations; MA: metabolic activation; MN: micronuclei; SCE: sister chromatid exchange; +: positive; (+): weakly positive; –: negative

[1] small colonies

[2] a maximum of 25 % of cells with aberrations; negative controls 9 %

[3] a maximum of 39 % of cells with aberrations; negative controls 15 % and positive controls 47 %; "not all cultures yielded positive results" (no other details)

5.6.2 *In vivo*

A dominant lethal test carried out by ICI in 1976 yielded negative results after inhalation exposure of mice to methyl methacrylate concentrations of 100, 1000 or 9000 ml/m^3. The animals were exposed for 6 hours daily, on 5 days per week, for 8 weeks and mated weekly (EU 2002; "Methyl methacrylate", Volume 3, present series).

A micronucleus test with bone marrow cells of mice yielded negative results after single intraperitoneal methyl methacrylate doses of 4500 mg/kg body weight and after four intraperitoneal doses of 1100 mg/kg body weight (Hachitani *et al*. 1981).

A bone marrow chromosomal aberration test in rats yielded negative results after single intraperitoneal methyl methacrylate doses of 650 or 900 mg/kg body weight. Increased aberrations were reported after single intraperitoneal doses of 1300 mg/kg body weight (17 % with aberrations; controls 1.8 %), but it was not specified whether the evaluation was carried out including gaps. In another test with repeated intraperitoneal methyl methacrylate doses of 650 mg/kg body weight, positive findings were described after treatment for 2 and 4 weeks, and negative findings after 6 and 8 weeks (Fedyukovich and Egorova 1991). There is no plausible explanation for this unusual time–effect relationship; therefore, the findings are of questionable reliability (EU 2002).

Two bone marrow chromosomal aberration tests in rats were carried out by ICI in 1976 and 1979 (EU 2002). In the first test, positive findings were obtained after a single 2-hour exposure or after five 5-hour exposures to 9000 ml/m^3 by inhalation. No aberrations were observed after exposure to 100 or 1000 ml/m^3, although the 2-hour exposure, rather than the five exposures, led to a questionably positive result. In the second test, weakly positive findings were reported after exposure to 400 and 700 ml/m^3. These results cannot be assessed because positive findings were only obtained including gaps, and 11 % hydroquinone, which is genotoxic itself, was used in the tests.

5.7 Carcinogenicity

No carcinogenic effects were observed in a carcinogenicity study carried out by the NTP with F344 rats and B6C3F$_1$ mice with methyl methacrylate concentrations of up to 1000 ml/m^3 ("Methyl methacrylate", Volume 3, present series; Chan *et al*. 1988) or in carcinogenicity studies carried out by Rohm and Haas in F344 rats and golden hamsters with methyl methacrylate concentrations of up to 400 ml/m^3 (EU 2002).

6 Manifesto (MAK value, classification)

Clastogenic effects were observed in genotoxicity studies *in vitro* at toxic doses. To evaluate this finding, the results from *in vivo* studies are very important. Because of methodological limitations, these are problematical and of little use to the evaluation. Therefore, they cannot counter the suspicion resulting from the *in vitro* studies that the

substance has clastogenic effects. The carcinogenicity studies revealed no evidence of carcinogenic effects in either rats, mice or hamsters. On the basis of the available data, classification as a carcinogen is not required. Since there are only limited data, classification in one of the categories for germ cell mutagens is not possible.

In several studies with repeated exposures carried out in rats, distinct nasal lesions in the olfactory epithelium were observed at methyl methacrylate concentrations of 100 ml/m^3. A NOAEC of 25 ml/m^3 was obtained in a 2-year study. However, *in vitro* studies of the carboxylesterase level in the nose and PBPK models revealed higher exposure of the olfactory epithelium in rats than in humans. Therefore, only the results from studies of exposed persons are used for deriving the MAK value.

Studies of workers involved in acrylic sheet production who were almost exclusively exposed to methyl methacrylate revealed no rhinologically detectable irritant effects (Röhm 1994) or impairment of the sense of smell after an average 8.8 years of employment with 8-hour mean exposure values for methyl methacrylate of up to 40 ml/m^3 (Muttray *et al*. 1997). Sensory irritation was reported only after short-term exposure peaks of more than 100 ml/m^3 (Röhm 1994). On the basis of these results, the MAK value of 50 ml/m^3 has been retained.

Since local irritation occurred in workers only after short-term exposure peaks of more than 100 ml/m^3, Peak Limitation Category I with an excursion factor of 2 can be retained.

An *in vitro* study, in which an absorption rate of 107 µg/cm^2 and hour was determined, is available for the assessment of dermal absorption. This rate would correspond to the absorption of 214 mg methyl methacrylate after one hour of exposure of the hands and forearms (2000 cm^2). The systemic NOAEC is about 100 ml/m^3 (420 mg/m^3); reduced body weight gains were observed at 400 ml/m^3 in female rats in the carcinogenicity study. Assuming an inhaled volume of 10 m^3, the calculated amount absorbed by the skin is only 1/20 of the systemic NOEC (no observed effect concentration; 4200 mg), and dermal absorption thus makes no relevant contribution to systemic toxicity. Methyl methacrylate is, therefore, still not designated with an “H”.

Both the findings in humans which have been published since the 1997 MAK documentation and the results from animal studies demonstrate that methyl methacrylate has contact sensitizing potential. Some supplementary findings regarding effects on the respiratory tract in humans are also available. Nevertheless, these findings are not sufficient to establish that methyl methacrylate can induce sensitization of the respiratory tract. Methyl methacrylate is therefore still designated with an “Sh”, but not with an “Sa”.

Methyl methacrylate has to date been classified in Pregnancy Risk Group C. A prenatal developmental toxicity study in rats with exposure by inhalation that was carried out according to valid guidelines revealed no developmental toxicity up to the highest concentrations (> 2000 ml/m^3). Other prenatal developmental toxicity studies carried out in rats and rabbits are not of use to the evaluation because of their methodological inadequacies or unphysiological administration (intraperitoneal). Only early studies are available for mice. Although slight, but statistically significant differences in foetal weights were observed in a study in which mice were exposed to methyl methacrylate concentrations of 100 or 400 ml/m^3, another study revealed no

developmental toxicity other than increased foetal body weights at the only methyl methacrylate concentration tested of 1330 ml/m^3. In view of the findings obtained in inhalation studies with rats and mice, methyl methacrylate remains in Pregnancy Risk Group C.

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completed 09.03.2005