The MAK Collection for Occupational Health and Safety

Methyl acrylate

MAK Value Documentation, addendum – Translation of the German version from 2017

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Methyl acrylate / Methyl prop-2-enoate

MAK Value Documentation

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the maximum concentration at the workplace (MAK value) of 5 ml/m³ for methyl acrylate [96-33-3] considering the endpoints local and developmental toxicity as well as genotoxicity. Available publications and unpublished study reports are described in detail. The critical effect in a two-year inhalation study with rats was reserve cell hyperplasia with loss of ciliated and olfactory cells in the transitional nasal epithelium at the lowest concentration of 15 ml/m³. In a two-generation reproduction toxicity study with a NOAEC of 5 ml/m³, degeneration with regeneration of the olfactory epithelium, hyperplasia of the transitional epithelium as well as hyperplasia and hypertrophy of the goblet cells were observed. A lower confidence limit of the benchmark dose for an extra risk of 5% increase of the critical effect incidence ($BMDL_{05}$) of 6.8 ml/m³ as a substitute for a NOAEC was calculated from the data of the two-year inhalation study. Since 2014, the Commission uses an empirical approach to set MAK values for substances with critical effects on the upper respiratory tract or the eyes. According to this approach, the MAK value for methyl acrylate has been lowered to 2 ml/m³. As local effects are critical, the assignment to Peak Limitation Category I and the excursion factor of 2 are confirmed, in analogy to ethyl acrylate. The NOAECs for developmental toxicity in rats and rabbits are sufficiently high so that damage to the embryo or foetus is unlikely when the MAK value is not exceeded. Thus, methyl acrylate is classified in Pregnancy Risk Group C. The substance is clastogenic in vitro but not in vivo and was not carcinogenic in a 2-year inhalation study in rats. There are only a few cases of contact sensitization in humans but there is a positive result in a local lymph node assay. Data on airway sensitization are still not available. Methyl acrylate remains designated with "Sh". Skin absorption was calculated to contribute significantly to the systemic toxicity and methyl acrylate is designated with an "H".

Keywords

methyl acrylate; acrylic acid methyl ester; methyl propenate; methyl 2-propenoate; 2-propenoic acid methyl ester; mechanism of action; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; allergenic effects; reproductive toxicity; fertility; developmental toxicity; genotoxicity; carcinogenicity; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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Methyl acrylate

[96-33-3]

Supplement 2017

MAK value (2016)	**2 ml/m³ (ppm) ≙ 7.1 mg/m³**
Peak limitation (2000)	**Category I, excursion factor 2**
Absorption through the skin (2016)	**H**
Sensitization (1984)	**Sh**
Carcinogenicity	**–**
Prenatal toxicity (2016)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
1 ml/m³ (ppm) ≙ 3.572 mg/m³	**1 mg/m³ ≙ 0.28 ml/m³ (ppm)**

The MAK value for methyl acrylate was derived in 1985 from a 90-day inhalation study in rats with a NOAEC (no observed adverse effect concentration) of 23 ml/m³ and a LOAEC (lowest observed adverse effect concentration) of 124 ml/m³ and from a 2-year inhalation study in rats (Klimisch and Reininghaus 1984; see documentation "Methyl acrylate" 1993). This study has in the meantime been published (Reininghaus et al. 1991) and the study report has been made available to the Commission (BASF AG 1985 a). In this study, the critical effect caused by exposure to methyl acrylate was found to be local irritation of the nasal mucosa, and reserve cell hyperplasia with the loss of olfactory and ciliated cells was identified as the most sensitive end point. A NOAEC was not determined in this study; the LOAEC was 15 ml/m³. However, the NOAEC can be approximated by extrapolating the dose-effect relationship using the "benchmark" approach. This extrapolation is carried out in this supplement. Up until this point, methyl acrylate was classified in Pregnancy Risk Group D. Three new studies of this end point have been conducted, which have made a re-evaluation of the Pregnancy Risk Group necessary. In addition, germ cell mutagenicity is assessed.

Documentation for methyl acrylate was published in 1986 (documentation "Methyl acrylate" 1993), followed by a supplement reviewing the sensitizing effect of the substance in 1999 (supplement "Methyl acrylate" 2001) and one reviewing peak limitation in 2000 (supplement "Methylacrylat" 2000, available in German only).

Mechanism of Action

In vitro studies have demonstrated that the hydrolysis of acrylate esters and the formation of acrylic acid associated with this is a detoxification mechanism. There were no significant differences between methyl acrylate, ethyl acrylate and *n*-butyl acrylate with regard to hydrolysis rates and their reaction with nucleophiles (Miller et al. 1985; Roos 2015).

Decisive for the toxicity of acrylates and methyl acrylates is not the release of the acid but the reactivity of the Michael system (α,β-unsaturated compounds) with nucleophilic compounds such as glutathione (McCarthy and Witz 1997; McCarthy et al. 1994). In vitro, sulfhydryl groups that are not bound to proteins are depleted.

Toxicokinetics and Metabolism

Absorption, distribution, elimination

Methyl acrylate is readily absorbed after oral, dermal and inhalation exposure and distributed throughout the body (OECD 2008). Two hours after oral doses of ^{14}C-labelled methyl acrylate were given to rats, most of the radioactivity was detected in the liver, kidneys, plasma and erythrocytes (Sapota 1993). Using the models of Fiserova-Bergerova et al. (1990), Guy and Potts (1993) and Wilschut et al. (1995), flux values were calculated for a saturated aqueous solution that correspond with absorbed amounts of 1670 mg, 195 mg and 315 mg, respectively, assuming 1-hour exposure of 2000 cm^2 of skin.

The metabolic pathway of methyl acrylate is hydrolysis by carboxyesterases to form acrylic acid and methanol (OECD 2008).

After oral or intraperitoneal administration, more than 90% of the methyl acrylate was eliminated within 72 hours, primarily via the lungs as carbon dioxide (> 50%) and via the kidneys (40%–50%) as products of glutathione conjugation (OECD 2008).

Effects in Humans

Repeated exposure

An unpublished case-crossover study at the workplace was conducted to determine whether the occupational exposure limit for methyl acrylate of 5 ml/m^3 would protect against irritation of the eyes and respiratory tract. A total of 15 employees took part, 10 of whom were production workers, 4 were intermittently exposed workers and 1 was an industrial hygienist who had had no notable previous exposure to methyl acrylate. As each 8-week production cycle was followed by a break of 2 weeks, each participant served as their own control. Irritation was determined by spirometry, peak expiratory flow (PEF), ophthalmological examinations and the reporting of symptoms by the participants. The available abstracts do not provide any details about the procedure used to divide the employees into high, middle and low exposure groups. The high exposure group (no details about the number of

employees) was exposed to an average methyl acrylate concentration of 2 ml/m³ (7.2 mg/m³). During certain tasks of 2 to 5 minutes in duration, peak exposures of 30 to 126 ml/m³ (107 to 451 mg/m³) were determined. There were no differences in the results of the ophthalmological examinations before and after exposure. Symptoms of irritation in the eyes were of low intensity and even though at the end of the shift the incidence was higher in workers exposed to high concentrations (4.4/100 person days in comparison with 1.4/100 person days in the low concentration group), the increase in incidence was not statistically significant. The examination of lung function parameters revealed no significant changes; a relatively high level of bronchial responsiveness had already been detected in all test persons prior to the start of the production phase (ECETOC 1998; OECD 2008; SCOEL 2004). This study is not suitable for the derivation of a MAK value because of the small number of examined persons, high peak concentrations that are probably responsible for the mild symptoms of irritation in the eyes, and the inadequate description of the exposure conditions and the effects.

Allergenic effects

There are only a few clinical findings available for methyl acrylate and most of these are incompletely documented. However, it has been established that methyl acrylate has a sensitizing effect on the skin of humans because several cases of sensitization induced by patch tests or through accidental contact have been described (supplement "Methyl acrylate" 2001). Methyl acrylate is not commercially available as a test preparation. This is probably the reason why no additional case studies with positive patch test findings have been published since the 1999 supplement (supplement "Methyl acrylate" 2001) and specifically why there are no clinico-epidemiological studies of affected or possibly exposed collectives. However, a number of studies have been conducted in which specially produced methyl acrylate test preparations were tested in conjunction with sensitization by dimethyl fumarate. Positive reactions were obtained in individual patients with preparations containing 0.06% methyl acrylate and in 1 case with a 0.006% preparation; it is very likely that these were immunological cross-reactions (Giménez-Arnau et al. 2009; Lammintausta et al. 2010).

No findings are available for sensitization of the airways.

Genotoxicity

In a prospective cohort study, 60 workers employed in the production of acrylic acid, acrylic acid esters and acrylate dispersions and 60 controls were investigated from 1992 to 1999. The average period of exposure was 13 ± 5 years. Exposure to acrylonitrile, *n*-butyl alcohol, *n*-butyl acrylate, ethyl acrylate, methyl acrylate, methyl methacrylate, toluene and styrene was determined by personal passive dosimetry. The measured concentrations of all substances were generally low. In the case of methyl acrylate, 90% of the individual values were below 0.06 ml/m³, just under 10% were between 0.06 and 0.28 ml/m³. The maximum concentration was 2.8 ml/m³. In the clinical, haematological and biochemical examinations, no differences were

found between the group of exposed workers and the group of workers not exposed that could be attributed to exposure to the above-listed chemicals. Cytogenetic examination of pairs of peripheral lymphocytes from exposed workers did not reveal genotoxic effects. Throughout the test period, more chromosomal aberrations were observed in exposed persons than in control persons; this difference was statistically significant (Tuček et al. 2002; Williams and Iatropoulos 2009). No differentiation was made between smokers and non-smokers and there was exposure to a mixture of substances. For this reason, this study cannot be used as evidence that methyl acrylate has a genotoxic effect.

Animal Experiments and in vitro Studies

Acute toxicity

Inhalation

Exposure of 5 male and 5 female Wistar rats to methyl acrylate concentrations of 10.8 mg/l (10 832 mg/m³; 3032.96 ml/m³) for 4 hours was lethal for all males and for 2 females. Exposure was nose-only. The symptoms observed in the animals were reduced breathing, diaphragmatic breathing, wheezing, breathing sounds, red, crusty eyes and noses, salivation, sallow skin, piloerection, hyperexcitability, tremor and poor general health. The lungs of 2 of the deceased animals were dark red in colour; in addition, partial lung collapse and hyperexpansion of the lungs with gaseous content was observed in 1 animal. Abnormal gaseous content in the stomach and intestines was found in 4 of the deceased animals. The animals died either directly on the day of exposure or 1 to 2 days later. The LC_{50} for the rat was therefore below 3000 ml/m³ in this study (BAMM 2012). Other LC_{50} studies in rats and mice are listed in the REACH dataset that is available to the public. According to this, the values for rats of both sexes are in the range from 3600 to 6500 mg/m³ (1000 to 1820 ml/m³, respectively) and those for mice are in the range from 5100 to 5700 mg/m³ (1430 to 1600 ml/m³, respectively) (ECHA 2016).

Subacute, subchronic and chronic toxicity

Inhalation

A 90-day study and a 2-year study in Sprague Dawley rats have been carried out with methyl acrylate. The MAK value of 5 ml/m³ that has been valid up until this point was derived from these studies. Other inhalation studies have in the meantime been conducted; these likewise found that methyl acrylate induces effects on the olfactory epithelium of treated animals. The available inhalation studies are shown in Table 1.

The following describes recent studies and a short summary of each of the studies that were included in the documentation from 1986.

In the developmental toxicity study in rabbits described in detail in the Section "Developmental toxicity", degeneration and atrophy of the olfactory epithelium were observed in dams after exposure to the medium concentration of 15 ml/m³ and

Table 1 Studies of the effects caused by irritation after inhalation exposure to methyl acrylate

Exposure period	Species, strain, number	NOAEC [ml/m³]	LOAEC [ml/m³]	Histopathological effects in the respiratory tract	References
developmental toxicity **23 days** 6 hours/day, 7 days/week	rabbit, Himalayan, 25	5	15	degeneration and atrophy of the olfactory epithelium	Acrylate Task Force 2010
range-finding study for the 2-generation study ♂: **42 days** ♀: about **12 weeks** 6 hours/day, 7 days/week	rat, Sprague Dawley, 12 ♂, 12 ♀	–	25	degeneration of the olfactory epithelium, very slight necrosis of olfactory epithelial cells, multifocal hyperplasia of the transitional epithelium	Acrylate REACH Task Force 2009
90 days 6 hours/day, 5 days/week	rat, Sprague Dawley, 10 ♂, 10 ♀	23 124	124 242	body weight gains ↓, relative lung and liver weights (♀) ↑, no effects on the respiratory tract atrophy (and necrosis) of the olfactory epithelium (follow-up examination)	BASF 1978, 1980
2-generation study ♂: about **12 weeks**, ♀: **4.5 months** 6 hours/day, 7 days/week	rat, Sprague Dawley, 27 ♂, 27 ♀	5	25	multifocal hyperplasia of the transitional epithelium; multifocal degeneration (with regeneration) of the olfactory epithelium, hyperplasia and hypertrophy of the goblet cells in the respiratory epithelium	Acrylate REACH Task Force 2009
12, 18 months, 2 years 6 hours/day, 5 days/week	rat, Sprague Dawley, 86 ♂, 86 ♀ 12 months: 10 ♂, 10 ♀ 18 months: 15 ♂, 15 ♀	$BMDL_{05}$ ♂: 6.8 ♀: 17	15	reserve cell hyperplasia with the loss of olfactory or ciliated cells in the olfactory epithelium	BASF AG 1985 a; Reininghaus et al. 1991

$BMDL_{05}$: lower 95% confidence limits of the benchmark concentrations for a 5% increase in incidence

above (plane of section III: 0/25, 0/25, 4/25, 25/25; plane of section IV: 0/25, 0/25, 0/25, 21/25). Concentrations of 0, 5, 15 and 45 ml/m³ were tested (Acrylate Task Force 2010). A NOAEC for effects on the respiratory tract of 5 ml/m³ was determined in this study with pregnant rats.

In an unpublished 90-day study conducted in 1978, 20 Sprague Dawley rats per sex and group were exposed to methyl acrylate concentrations of 0, 23, 124, 242 and 626 ml/m³ for 6 hours a day, on 5 days a week. A NOAEC of 23 ml/m³ was determined in this study. Only slight effects, such as reduced body weight gains and increased relative lung and liver weights, were observed in the females at concentrations of 124 ml/m³; however, these findings lacked a histopathological correlate. At the beginning of the study, irritation of the nose and eyes as well as dyspnoea were observed in the animals of the group exposed to the next-higher concentration; in addition, reduced body weight gains and an increase in the relative lung and liver weights were determined. Exposure to the high concentration was lethal for all animals and caused severe mucosal irritation, bloody discharge from the eyes and nose and severe dyspnoea. Histopathological examination revealed atrophy of the respiratory epithelium, keratinization of the transition zone between the respiratory and olfactory epithelium, rhinitis, tracheitis, pulmonary hyperaemia and bronchopneumonia (documentation "Methyl acrylate" 1993). The study report did not include information about the number of planes of section for the nose. As this study was conducted in 1978, it is possible that the scope of the examination does not comply with today's standards and the effects of the substance in the nose may not all have been detected.

For a more precise description of the damage, the nasal mucosa was prepared again for a histological follow-up examination. An additional cross-section was taken from all animals of the control group and from 10 animals per group and sex, except for animals of the low concentration group. In addition, a sagittal section was taken from 2 animals per sex. As the nasal mucosa was mechanically damaged while opening the nasal cavity at the time of section, it was not possible to obtain undamaged nasal tissue from all of the animals for the follow-up examination. Therefore, according to the authors, the exact number of animals with substance-related damage to the nasal mucosa is probably somewhat higher. Histopathological examination did not reveal any effects on the olfactory nasal mucosa after exposure to 23 and 124 ml/m³. The epithelium was atrophic in all 4 animals of the 242 ml/m³ group from which a sagittal section was taken (2 males and 2 females); in 1 male, it was disintegrated in the dorsocaudal area and necrotic. In the high concentration group, atrophy of the epithelium was found in 1 animal and purulent-necrotic rhinitis was observed in 3 of 4 animals. Epithelial metaplasia of the olfactory epithelium and, in many cases, widespread and deep-seated necrosis of the nasal mucosa, mainly in the dorsomediocaudal region, and cell vacuolization were found. Changes to the olfactory bulb were not observed. The authors pointed out that in order for the characteristic damage to develop, both higher concentrations of the substance as well as longer periods of exposure were necessary (BASF 1980). This means that an intensification of the effects with an increase in the exposure period is to be assumed.

In the 2-generation study in Sprague Dawley rats described in the Section "Fertility", a concentration-dependent increase in the incidence and severity of histopathological damage to the nasal tissue was observed in the parent animals of both gen-

erations after exposure to methyl acrylate concentrations of 0, 5, 25 and 75 ml/m³. The males were exposed for about 12 weeks, the females for about 4.5 months. The results are summarized in Table 2. In this study, the NOAEC for histopathological damage to the nasal area was 5 ml/m³ (Acrylate REACH Task Force 2009).

The MAK value was derived in 1985 from a 2-year inhalation study in Sprague Dawley rats, the irritation threshold observed in humans of 0.25 mg/l (around 75 ml/m³) and the findings from the 90-day study (see above) (Klimisch and Reininghaus 1984; see documentation "Methyl acrylate" 1993). The 2-year inhalation study has in the meantime been published (Reininghaus et al. 1991) and the study report has been made available to the Commission (BASF AG 1985 a). The study is described in more detail in the following. In this study, the critical effect of methyl acrylate was local irritation of the nasal mucosa, which induced atrophy and hyperplasia of the olfactory epithelium.

The animals were whole-body exposed daily to concentrations of 0, 15, 45 and 135 ml/m³ for 6 hours a day, on 5 days a week, for an exposure period of 12, 18 or 24 months. The body weights were significantly reduced (–4% in comparison with the controls) in the animals exposed to concentrations of 135 ml/m³. In the low concentration group, slight atrophy and beginning of reserve cell hyperplasia were observed in only a small number of animals. At the higher concentrations, hyperplasia with a loss of olfactory and ciliated cells in the most anterior region of the olfactory epithelium (roof of the dorsal nasal meatus) was detected in almost all of the animals (see Table 3).

A NOAEC was not determined in this study. The LOAEC for local irritation was 15 ml/m³, which was the lowest concentration tested.

Reserve cell hyperplasia with a loss of olfactory or ciliated cells was identified as the most sensitive end point after exposure for 24 months; a NOAEC is not available for this end point. For this reason, the BMDS software 2.3.1 of the US EPA was used to obtain values of 6.8 and 17 ml/m³, respectively, for the lower 95% confidence limits of the benchmark concentrations for a 5% increase in the incidence ($BMDL_{05}$) of this end point in male rats (3-degree polynomial multistage model with parameter restrictions) and in female rats (log-logistic model with parameter restrictions) (Figures 1 and 2). The original report also includes the total incidences of spontaneous deaths and moribund sacrifices. However, as it is unclear at which time point during exposure these occurred, only those animals that were examined after 24-month exposure are included in the calculation.

Summary

On the basis of the available studies, it was found that histopathological damage to the olfactory and transitional epithelium of rats and rabbits is induced at concentrations of 15 ml/m³ and above. A NOAEC of 5 ml/m³ was determined in a recent, valid 2-generation study with daily, 6-hour exposure of rats.

Table 2 Histopathological damage to the nasal area in a 2-generation study with Sprague Dawley rats (Acrylate REACH Task Force 2009)

		male				female			
concentration (ml/m³)		0	5	25	75	0	5	25	75
number of animals		27	27	27	27	27	27	27	27
olfactory epithelium									
degeneration, olfactory nerve, multifocal									
minimal	F0	0	0	**1**	**11**	0	0	0	**8**
	F1	0	0	0	**14**	0	0	0	**14**
slight	F0	0	0	0	**14**	0	0	0	**19**
	F1	0	0	0	**13**	0	0	0	**12**
degeneration, focal									
minimal	F0	0	0	0	0	2	1	4	0
	F1	0	0	1	0	3	2	4	0
degeneration, multifocal									
minimal	F0	0	0	0	0	0	1	**7**	0
	F1	0	0	**6**	0	0	1	**8**	0
degeneration with regeneration, multifocal									
minimal	F1	0	0	0	0	0	0	0	**1**
slight	F0	0	0	**1**	**12**	0	0	0	**8**
	F1	0	0	0	**13**	0	0	0	**14**
moderate	F0	0	0	0	**15**	0	0	0	**19**

Table 2 (continued)

		male				female			
concentration (ml/m³)		0	5	25	75	0	5	25	75
inflammation, chronic, active, multifocal									
minimal	F0	1	0	2	**15**	0	0	1	**20**
	F1	0	0	0	**14**	0	0	1	**8**
slight	F0	0	0	0	**1**	0	0	0	0
	F1	0	0	0	0	0	0	0	0
mineralization, focal									
minimal	F0	0	0	0	**1**	0	0	0	**2**
	F1	0	0	**1**	**1**	0	0	0	0
mineralization, multifocal									
minimal	F0	0	0	**1**	**5**	0	0	0	**2**
	F1	0	0	**1**	**15**	0	0	**1**	**14**
necrosis of individual cells, focal									
minimal	F0	1	0	1	0	1	0	3	0
	F1	0	0	0	0	1	0	1	0
multifocal									
minimal	F0	0	0	**1**	**26**	0	1	**2**	**26**
	F1	0	0	**1**	**24**	0	0	**4**	**27**

Table 2 (continued)

		male				female			
concentration (ml/m³)		0	5	25	75	0	5	25	75
ulcer, focal									
minimal	F0	0	0	0	**4**	0	0	0	**1**
	F1	1	0	0	**1**	0	0	0	0
transitional epithelium									
hyperplasia, multifocal									
minimal	F0	3	4	**17**	**12**	2	1	**23**	**24**
	F1	4	4	**18**	**8**	9	6	**23**	**24**
slight	F0	0	0	0	**15**	0	0	**2**	**3**
	F1	0	0	**2**	**19**	1	0	0	**1**
squamous metaplasia, multifocal									
minimal	F0	0	0	0	**5**	0	0	0	0
	F1	0	0	0	0	0	0	0	0
respiratory epithelium									
hyperplasia and hypertrophy, goblet cells, diffuse									
minimal	F0	1	0	**4**	1	0	1	**8**	**10**
	F1	0	0	0	**6**	7	8	11	**16**
slight	F0	0	0	**1**	**22**	0	0	**13**	**11**
	F1	0	0	0	**3**	3	1	5	2

Table 2 (continued)

		male				female			
concentration (ml/m^3)		0	5	25	75	0	5	25	75
inflammation, chronic, active, multifocal									
minimal	F0	0	0	0	0	0	0	1	**5**
	F1	0	0	0	0	0	0	0	0
mineralization, focal									
slight	F0	0	0	0	0	0	0	0	**1**
	F1	0	0	0	0	0	0	0	0

Values printed in bold type are considered to have been caused by the treatment

Table 3 Effects in the nasal cavity of rats (plane of section II) after inhalation exposure to methyl acrylate (BASF AG 1985 a; Reininghaus et al. 1991)

		Number of males with effects/analysed preparations				Number of females with effects/analysed preparations			
Effects	Time (month)	0 ml/m³	15 ml/m³	45 ml/m³	135 ml/m³	0 ml/m³	15 ml/m³	45 ml/m³	135 ml/m³
reserve cell hyperplasia[a]	12	0/10	0/ 9	0/10	0/10	0/10	0/ 9	0/10	0/10
	18	0/14	0/14	0/15	0/15	0/15	0/15	0/15	0/15
	24	0/46	2/49	1/53	0/52	0/48	0/48	3/46	0/46
	total	0/70	2/72	1/78	0/77	0/73	0/72	3/71	0/71
reserve cell hyperplasia[b]	12	0/10	0/ 9	9/10	10/10	0/10	0/ 9	6/10	10/10
	18	0/14	0/14	15/15	15/15	0/15	0/15	11/15	15/15
	24	0/46	4/49	49/53	52/52	0/48	0/48	41/46	46/46
	total	0/70	4/72	73/78	77/77	0/73	0/72	68/71	71/71
atrophy	12	0/10	0/ 9	0/10	0/10	0/10	0/ 9	0/10	0/10
	18	0/14	6/14	0/15	0/15	0/15	0/15	3/15	0/15
	24	0/46	3/49	0/53	0/52	0/48	0/48	0/46	0/46
	total	0/70	9/72	0/78	0/77	0/72	0/72	3/71	0/71

[a] without the loss of olfactory or ciliated cells
[b] with the loss of olfactory or ciliated cells

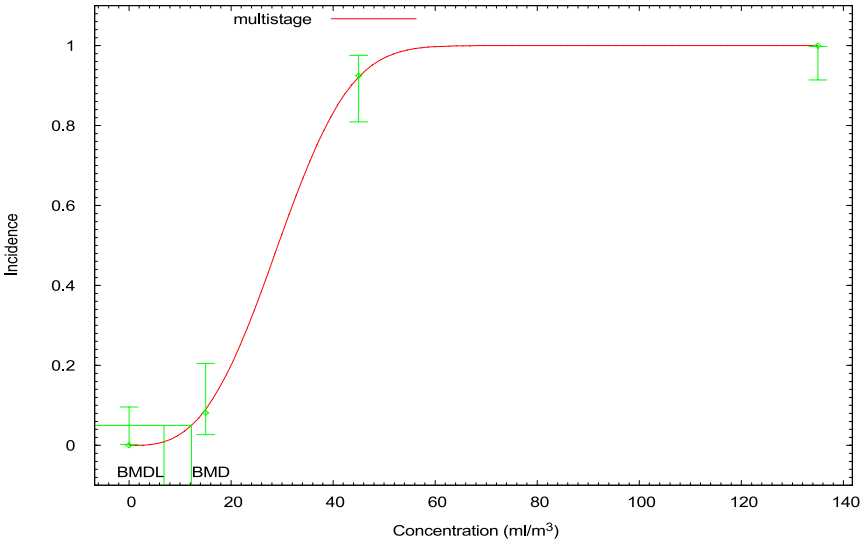

Figure 1 BMD calculation for reserve cell hyperplasia with the loss of functional epithelium, male rats, BMD = 12 ml/m^3, $BMDL_{05}$ = 6.8 ml/m^3, 3-degree polynomial multistage model with parameter restrictions

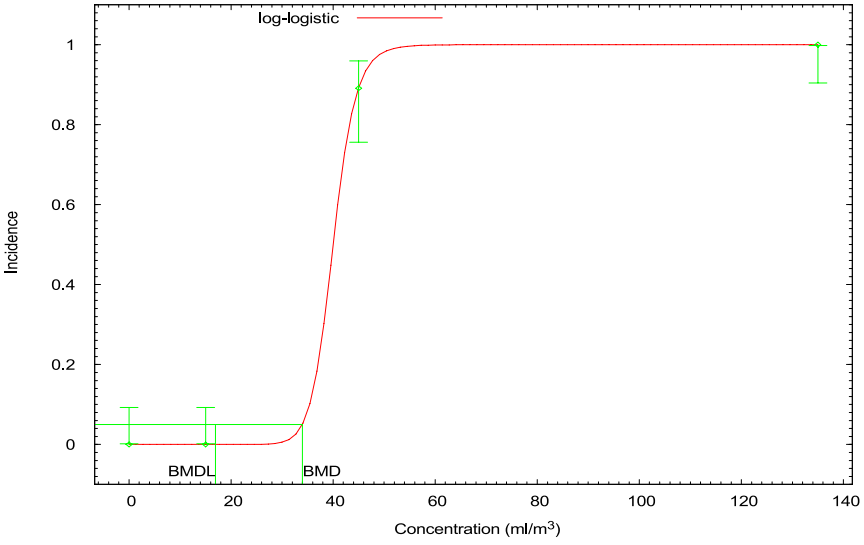

Figure 2 BMD calculation for reserve cell hyperplasia with the loss of functional epithelium, female rats, BMD = 34 ml/m^3, $BMDL_{05}$ = 17 ml/m^3, log-logistic model with parameter restrictions

Allergenic effects

Sensitizing effects on the skin

A local lymph node assay in CBA/Ca mice yielded an EC3 value of 19.6 for methyl acrylate tested in acetone/olive oil (4:1) (Dearman et al. 2007). Methyl acrylate was therefore found to be a weak contact allergen in this test system.

Sensitizing effects on the airways

There are no data available.

Reproductive and developmental toxicity

Fertility

In a range-finding study for the 2-generation study described below, 12 Sprague Dawley rats per sex and group were exposed to methyl acrylate concentrations of 0, 25, 75 and 150 ml/m^3 for 6 hours a day, on 7 days a week. The males were treated for a total of 42 days, beginning 4 weeks before mating. The females were exposed for a total of 12 weeks, also beginning 4 weeks before mating and lasting until the end of lactation with an exposure-free period between gestation day 21 and lactation day 4. Histopathological damage to the nasal tissue was found in the parent animals after exposure to the low concentration and above; reduced feed consumption, delayed body weight gains and a concentration-dependent decrease in terminal body weights were observed in the next-higher concentration group. The terminal body weights were reduced also in the offspring of this group (see Table 4; Acrylate REACH Task Force 2009).

In a 2-generation study carried out in compliance with OECD Test Guideline 416, 27 Sprague Dawley rats per sex and group were exposed by inhalation to methyl acrylate concentrations of 0, 5, 25 and 75 ml/m^3 in whole-animal exposure chambers for 6 hours a day, on 7 days a week, beginning 10 weeks before mating and lasting until the end of lactation. The only exception were the dams; they were not exposed to the substance from gestation day 20 to lactation day 4. At the end of lactation, the F1 parent animals were selected from among the offspring and then exposed to methyl acrylate using the same procedure as for the F0 generation, beginning in postnatal week 4 and lasting until weaning of the F2 generation. No treatment-related fatalities, clinical signs, or pathological or histological changes in the reproductive organs of the F0 or F1 generations were observed. Sperm parameters and the oestrus cycle remained unchanged. Body weight gains, feed consumption and the terminal body weights of the male and female F0 and F1 parent animals of the high concentration group were reduced in comparison with the controls. However, although the terminal body weights were reduced in the male F0 parent animals, the decrease was not statistically significant. The relative testis and epididymis weights of the male F0 animals and the relative liver and brain weights of the female F0 animals were increased in comparison with the controls. In the F1 generation, the relative weights of the brain, testes, seminal vesicles with coagulating glands and the epididymis in the males and the relative weights of the adrenal gland and brain

in the females were increased. Histopathological effects were observed in the nasal tissues of parent animals of the F0 and F1 generations at concentrations of 25 ml/m^3 and above; the increase in the incidence and severity of these effects was dependent on the concentration. An exact description of these effects can be found in the Section "Subacute, subchronic and chronic toxicity". The following parameters remained unchanged by the treatment: mating, conception, fertility, gestation indices, post-implantation losses, the onset of mating, the length of gestation, litter size, the sex ratio and postnatal survival indices. The time of vaginal opening and preputial separation in the offspring was similar to that in the controls (see Table 4; Acrylate REACH Task Force 2009).

The NOAEC for local toxicity in the parent animals of the F0 and F1 generations was determined to be 5 ml/m^3 on the basis of histopathological effects in the nasal tissues. The NOAEC for systemic effects in the parent animals and offspring was 25 ml/m^3 on the basis of reduced body weights. The NOAEC for fertility was 75 ml/m^3, the highest concentration tested.

Developmental toxicity

Studies of developmental toxicity are summarized in Table 5.

Groups of 25 pregnant Sprague Dawley rats (controls: 27) were exposed daily to methyl acrylate concentrations of 0, 25, 50 and 100 ml/m^3 for 6 hours a day, from gestation days 6 to 20. Maternal feed consumption and body weight gains were decreased after exposure to the medium concentration and above; after the uterus weights were subtracted, the dams were found to even have lost body weight. A concentration-dependent decrease in foetal body weights was likewise observed; this decrease was statistically significant in the high concentration group. A malformation (craniorhachischisis) was found in 1 foetus of the 100-ml/m^3 group; this malformation was not considered to have been caused by the substance. There was no incidence of skeletal variations induced by the substance. In this study, the NOAEC for maternal toxicity was 25 ml/m^3, the NOAEC for developmental toxicity was 50 ml/m^3 (Saillenfait et al. 1999).

Groups of 25 pregnant Himalayan rabbits were exposed daily to methyl acrylate concentrations of 0, 5, 15 and 45 ml/m^3 for 6 hours a day from gestation day 6 to 28. Foetuses were examined on gestation day 29. No effects on developmental toxicity parameters or on the foetuses were observed up to the high concentration. Degeneration and atrophy of the olfactory epithelium (plane of section III: 0/25, 0/25, 4/25, 25/25; plane of section IV: 0/25, 0/25, 0/25, 21/25) were detected in the dams at the medium concentration of 15 ml/m^3 and above. The NOAEC for systemic maternal toxicity was 15 ml/m^3 because the damage to the nasal epithelium was so severe at concentrations of 45 ml/m^3 that this probably induced stress in the dams. The NOAEC for developmental toxicity was 45 ml/m^3, the highest concentration tested (Acrylate Task Force 2010).

Table 4 Multi-generation study with inhalation exposure to methyl acrylate

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 12 ♂, 12 ♀	**range-finding study for the 2-generation study** 0, 25, 75, 150 ml/m³, whole-body ♂: 42 days ♀: about 12 weeks 6 hours/day, 7 days/week	**25 ml/m³ and above**: histopathological damage to nasal tissue **75 ml/m³ and above**: parent animals: feed consumption ↓, concentration-dependent reduction in terminal body weights (♂: –7%, ♀: –2% in comparison with the controls), body weight gains ↓ offspring: concentration-dependent reduction in terminal body weights (♂: –4%, ♀: –9% in comparison with the controls) **150 ml/m³**: parent animals: breathing sounds after exposure offspring: body weights ↓ in comparison with the controls (PND 14)	Acrylate REACH Task Force 2009
rat, Sprague Dawley, 27 ♂, 27 ♀	**2-generation study**, 0, 5, 25, 75 ml/m³, 6 hours/day, 7 days/week whole-body OECD 416	**5 ml/m³: NOAEC parental toxicity** **25 ml/m³ and above**: parent animals F0, F1: histopathological damage to nasal tissue (see Table 1) **75 ml/m³**: parent animals F0, F1: **NOAEC fertility**, feed consumption ↓, body weight gains ↓, terminal body weights ↓ parent animals F0: ♂: relative testis and epididymis weights ↑, ♀: relative brain and liver weights ↑ parent animals F1: ♂: relative weights of brain, testes, seminal vesicles and epididymis ↑, ♀: relative brain and adrenal gland weights ↑, absolute thyroid weights ↓ offspring F0, F1: body weight gains ↓	Acrylate REACH Task Force 2009

PND: postnatal day

Table 5 Studies of developmental toxicity after inhalation exposure to methyl acrylate

Species, strain, number per group	Exposure	Findings	References
rat, Sprague Dawley, 25–27 ♀	**GD 6–20**, 0, 25, 50, 100 ml/m³, whole-body, examination GD 21	**25 ml/m³**: dams: **NOAEC maternal toxicity** **50 ml/m³**: foetuses: **NOAEC developmental toxicity** **50 ml/m³ and above**: dams: feed consumption ↓, body weight gains ↓, terminal body weights ↓ **100 ml/m³**: foetuses: body weights ↓; 1 foetus with craniorhachischisis	Saillenfait et al. 1999
rabbit, Himalayan, 25 ♀	**GD 6–28**, 0, 5, 15, 45 ml/m³, whole-body, examination GD 29	**5 ml/m³**: dams: **NOAEC local maternal toxicity** **15 ml/m³**: dams: beginning degeneration and atrophy of the olfactory epithelium (4/25) **45 ml/m³**: dams: degeneration and atrophy of the olfactory epithelium (25/25) foetuses: **NOAEC developmental toxicity**	Acrylate Task Force 2010
rat, Sprague Dawley, 27 ♂, 27 ♀	**2-generation study**, 0, 5, 25, 75 ml/m³, whole-body, 6 hours/day, 7 days/week, 2 generations (19 weeks per generation) OECD 416	**5 ml/m³**: parent animals: **NOAEC local toxicity** **25 ml/m³**: parent animals: **NOAEC systemic toxicity** offspring: **NOAEC developmental toxicity** findings see Table 4	Acrylate REACH Task Force 2009

GD: gestation day

In the 2-generation study already described in the Section "Fertility", the body weights of the offspring were comparable to those of the control group up to postnatal day 14. At the next test time point (postnatal day 21), the body weights of the offspring of both generations were reduced in the high concentration group in comparison with the values for the control group (Acrylate REACH Task Force 2009). The NOAEC for local toxicity in parent animals of the F0 and F1 generations was determined to be 5 ml/m³ on the basis of adverse histopathological effects in the nasal tissue. The NOAEC for developmental toxicity and systemic toxicity in parent animals and offspring was 25 ml/m³ because of the reduced body weights at 75 ml/m³.

Summary

The NOAEC for developmental toxicity in rabbits was 45 ml/m³, the highest concentration tested. Histopathological damage to the olfactory epithelium was observed in all dams of this exposure group (NOAEC for maternal toxicity = 5 ml/m³). In a developmental toxicity study in rats, the NOAEC for developmental toxicity was determined to be 50 ml/m³ because reduced foetal weights were observed after exposure to methyl acrylate concentrations of 100 ml/m³. The NOAEC for maternal toxicity was 25 ml/m³ because reduced feed consumption and body weight gains were found at methyl acrylate concentrations of 50 ml/m³. In a 2-generation study with Sprague Dawley rats, the local NOAEC for parent animals of both generations was 5 ml/m³ in view of adverse histopathological damage in the nose. The NOAEC for developmental toxicity was 25 ml/m³ because of reduced body weights of the offspring at 75 ml/m³. Therefore, the two values derived for the NOAEC for developmental toxicity in rats are consistent.

Genotoxicity

Numerous in vitro and in vivo studies of genotoxicity have become available since the documentation of 1986 was published (documentation "Methyl acrylate" 1993). In order to be able to assess germ cell mutagenicity, a brief summary of all the available studies follows.

In vitro

Methyl acrylate did not induce mutations in Salmonella typhimurium (documentation "Methyl acrylate" 1993; IARC 1999).

The induction of chromosomal aberrations was observed in L5178Y mouse lymphoma cells, CHO and CHL cells (cell lines derived from Chinese hamster ovary and lung). Small colonies were induced in the $TK^{+/-}$ test with L5178Y mouse lymphoma cells, which suggests that methyl acrylate has a clastogenic effect or is cytotoxic. No mutations were induced in the HPRT or XPRT assays with CHO cells. Testing was carried out in mammalian cells without the addition of a metabolic activation system (SCOEL 2004).

In vivo

In Drosophila melanogaster larvae given methyl acrylate via the diet, negative results were obtained in the SLRL assay (test for sex-linked recessive lethal mutations) (Zimmering et al. 1989).

After methyl acrylate was administered to BALB/c mice by intraperitoneal injection in two doses of 37.5 to 300 mg/kg body weight separated by an interval of 24 hours, micronuclei formation in the bone marrow was induced in high dose groups. Concurrently a significant decrease in the ratio of polychromatic to normochromatic erythrocytes was observed, which suggests that these doses induce cytotoxicity (Przybojewska et al. 1984). A positive result was obtained also for ethyl acrylate which was tested at the same time. However, this result could not be reproduced in another study that tested higher intraperitoneal doses in BALB/c and C57BL/6 mice (10 per group; 2 × 738 mg/kg body weight or 2 × 812 mg/kg body weight) (see supplement "Ethyl acrylate" 2016). Negative results were yielded by other micronucleus tests with inhalation exposure of male ddY mice (methyl acrylate concentrations of 1300 and 2100 ml/m^3, 3 hours, sampling 18, 24, 30, 48 or 72 hours after treatment) (Sofuni et al. 1984) or treatment with single or 4 oral doses (single doses of 62.5, 125 or 250 mg/kg body weight, 6 animals per group; 4 doses of 125 mg/kg body weight and day, 4 animals per group, sampling 24 hours after treatment) (Hachiya et al. 1982; OECD 2008).

Carcinogenicity

In the 2-year inhalation study already reviewed in the documentation published in 1986 (documentation "Methyl acrylate" 1993), carcinogenic effects were not observed in Sprague Dawley rats that were exposed to methyl acrylate concentrations of 0, 15, 45 and 135 ml/m^3 for 6 hours a day, on 5 days a week. At the end of the 2-year treatment period, the number of males and females examined were, respectively, 46 and 49 in the control group, 50 and 48 in the low concentration group, 53 and 47 in the medium concentration group and 52 and 46 in the high concentration group (Reininghaus et al. 1991).

Manifesto (MAK value/classification)

The critical effects of exposure to methyl acrylate are reserve cell hyperplasia with the loss of cilia and olfactory cells, degeneration with regeneration of the olfactory epithelium, hyperplasia of the transitional epithelium, and hyperplasia and hypertrophy of the goblet cells in the respiratory epithelium of rats.

MAK value. No data have been reported for sensory irritation in humans that would be relevant to the evaluation. A workplace study with 15 test persons exposed to methyl acrylate is not suitable for the derivation of a MAK value because of the small number of persons investigated, the high peak concentrations that were probably responsible for the irritation caused by the substance and an insufficient description of the exposure conditions and effects. The original report of this study

is not available. The derivation of the MAK value is therefore based on the findings from animal studies.

A NOAEC of 5 ml/m³ was determined in a 2-generation study with daily exposure of Sprague Dawley rats, the males for a total of about 12 weeks and the females for about 4.5 months. In the group exposed to the next-higher concentration of 25 ml/m³, multifocal hyperplasia of the transitional epithelium and hyperplasia and hypertrophy of the goblet cells in the respiratory epithelium were reported in the parent animals of both generations. Also, degeneration with regeneration of the olfactory epithelium was observed. Effects on the transitional epithelium between the olfactory and respiratory epithelium were found in exposed rats in the 2-year inhalation study with a LOAEC of 15 ml/m³. A $BMDL_{05}$ of 6.8 ml/m³ was calculated from this study for male rats. On the basis of the overall data provided by the two studies and taking into consideration the daily exposure of the rats in the 2-generation study, the MAK value is derived from the $BMDL_{05}$ of 6.8 ml/m³ from the 2-year study. Using the approach of Brüning et al. (2014) for the extrapolation of the effects on the olfactory and respiratory epithelium of rats to humans (1:3) and the application of the preferred value approach, a MAK value of 2 ml/m³ is derived.

The findings are consistent with those of the 2-year study with ***n*-butyl acrylate** (BASF 1984; BASF AG 1985 b; Reininghaus et al. 1991). In the case of **ethyl acrylate** primarily effects on the olfactory epithelium of F344 rats were observed at concentrations of 25 ml/m³ in a 27-month study. No effects were recorded in a 2-year study that tested only the one concentration of 5 ml/m³ (Miller et al. 1985).

The hydrolysis of the acrylates investigated is a detoxification mechanism. For this reason, the reaction with nucleophiles and not the release of the acid is decisive for the toxicity of these acrylates. In vitro studies of the reaction with nucleophiles found that methyl acrylate, ethyl acrylate and *n*-butyl acrylate have similar levels of reactivity, which supports the MAK value of 2 ml/m³ that has been established for these substances. This is further supported by the NOAEC of 2 ml/m³ for sensory irritation determined in a study with exposure of test persons to ethyl acrylate (supplement "Ethyl acrylate" 2016).

Adverse effects caused by the metabolite methanol, which has a MAK value of 200 ml/m³, are not to be expected at the level of the MAK value established for methyl acrylate.

Peak limitation. The substance remains classified in Peak Limitation Category I; this classification was made on the basis of local effects. In vitro studies of the reaction with nucleophiles found that ethyl acrylate and methyl acrylate have similar levels of reactivity. For this reason, an excursion factor of 2 has been established for methyl acrylate in analogy to that for ethyl acrylate because no studies in test persons are available for methyl acrylate. In a valid study in test persons, no irritation of the eyes and nose could be detected after 4-hour exposure to ethyl acrylate concentrations averaging 2.5 ml/m³ and peak concentrations of twice that value (supplement "Ethyl acrylate" 2016).

Prenatal toxicity. In a study of the toxic effects on prenatal development carried out in rats and rabbits according to OECD Test Guideline 414, reduced foetal weights were observed concurrently with maternal toxicity after the exposure of rats to methyl acrylate concentrations of 100 ml/m³. In rabbits, the NOAEC for

developmental toxicity was 45 ml/m³, the highest concentration tested. At this concentration, histopathological damage to the olfactory epithelium was observed in all dams. In a 2-generation study with Sprague Dawley rats, the LOAEC for developmental toxicity was determined to be 75 ml/m³ on the basis of the reduced weight of the offspring. After inhalation exposure, the NOAEC for toxic effects on prenatal development was 50 ml/m³ in rats, 45 ml/m³ in rabbits and 25 ml/m³ in a 2-generation study in rats. As the 25-fold, 23-fold and 13-fold margins between these values and the MAK value of 2 ml/m³ (7.1 mg/m³) are sufficiently large, methyl acrylate has been classified in Pregnancy Risk Group C.

Carcinogenicity. No other data have become available for the carcinogenic effects of methyl acrylate since the documentation of 1986 was published (documentation "Methyl acrylate" 1993). No carcinogenic effects were observed in the 2-year inhalation study in rats. Methyl acrylate has therefore not been classified in any of the categories for carcinogenic substances.

Germ cell mutagenicity. No data for germ cells are available. Methyl acrylate did not induce gene or point mutations in bacteria and mammalian cells. Methyl acrylate had a clastogenic effect in vitro. These positive results were not confirmed in vivo. Overall, methyl acrylate is not assumed to be a germ cell mutagen. Methyl acrylate has therefore not been classified in any of the categories for germ cell mutagens.

Absorption through the skin. Model calculations (see Section "Toxicokinetics and Metabolism") yielded dermal absorption values of up to 1670 mg in humans after exposure to a saturated aqueous solution and assuming 1-hour exposure of 2000 cm² of skin. On the basis of the systemic NOAEC of 135 ml/m³ (482 mg/m³) from the 2-year study in rats (documentation "Methyl acrylate" 1993), a respiratory volume of 10 m³ at the workplace and after extrapolation of this value to the human (1/2) taking into consideration the higher respiratory volume at the workplace in comparison with exposure of animals at rest (1/2), this results in a systemically tolerable amount of about 1205 mg. As the absorption of methyl acrylate through the skin is thus higher than 25% of the systemically tolerable amount, the substance is designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. The only data available for the contact-sensitizing effects of methyl acrylate are the case reports that were included in the supplement from 1999 (supplement "Methyl acrylate" 2001). However, the positive result in a local lymph node assay confirms that the substance has skin-sensitizing potential. Data for the sensitization of the respiratory passages are not available. Methyl acrylate is therefore designated with "Sh" but not with "Sa" (for substances which cause sensitization of the skin or airways).

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