The MAK Collection for Occupational Health and Safety

Methacrylic acid

MAK Value Documentation, addendum – Translation of the German version from 2016

A. Hartwig[1,*], MAK Commission[2,*]

[1] *Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Institute of Applied Biosciences, Department of Food Chemistry and Toxicology, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Building 50.41, 76131 Karlsruhe, Germany*

[2] *Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany*

* *email: A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)*

Keywords: methacrylic acid; MAK value; mammary carcinomas; peak limitation; developmental toxicity; irritation; respiratory epithelium; toxicity

Citation Note: Hartwig A, MAK Commission. Methacrylic acid. MAK Value Documentation, addendum – Translation of the German version from 2016. MAK Collect Occup Health Saf [Original edition. Weinheim: Wiley-VCH; 2018 Apr;3(2):481-496]. Corrected republication without content-related editing. Düsseldorf: German Medical Science; 2025. https://doi.org/10.34865/mb7941e6018_w

Republished (online): 12 Dec 2025

Originally published by Wiley-VCH Verlag GmbH & Co. KGaA; https://doi.org/10.1002/3527600418.mb7941e6018

Addendum completed: 25 Feb 2015

Published (online): 24 Apr 2018

The commission established rules and measures to avoid conflicts of interest.

Methacrylic acid

MAK Value Documentation

A. Hartwig[1, *], MAK Commission[2, *]

DOI: 10.1002/3527600418.mb7941e6018

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 work place (MAK value) of methacrylic acid of 5 ml/m³, considering all toxicity endpoints. Available unpublished study reports and publications are described in detail. The critical effects of methacrylic acid are goblet cell hyperplasia/hypertrophy in the respiratory epithelia and reduced body weight gain in rats, probably a secondary effect of the irritation at 350 ml/m³ in a 90-day 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 NOAEC of 100 ml/m³ corresponds to a work place air concentration of 33 ml/m³. As the goblet cell hyperplasia is judged to be adaptive and its incidence is not significantly increased, the MAK value is elevated to 50 ml/m³. Since local effects are critical, the assignment to Peak Limitation Category I and the excursion factor 2 are confirmed. Studies with the read-across methyl methacrylate which is cleaved to methacrylic acid show that damage to the embryo or foetus is unlikely when the MAK value for methacrylic acid is observed, and the assignment to pregnancy risk group C is confirmed. Methacrylic acid and methyl methacrylate are not genotoxic. Carcinogenicity studies with methacrylic acid are lacking but methyl methacrylate is not carcinogenic. Skin contact does not contribute significantly to systemic toxicity and sensitization is not expected.

Keywords

2-methylacrylic acid; 2-methylpropenoic acid; 2-methylene propionic acid; 2-methyl-2-propenoic acid; mechanism of action; toxicokinetics; metabolism; (sub)acute toxicity; (sub) chronic toxicity; irritation; 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

Author Information

[1] Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Department of Food Chemistry and Toxicology, Institute for Applied Biosciences, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Geb. 50.41, 76131 Karlsruhe, Germany

[2] Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany

* Email: A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)

Methacrylic acid

[79-41-4]

Supplement 2016

MAK value (2015)	**50 ml/m³ (ppm) ≙ 180 mg/m³**
Peak limitation (2005)	**Category I, excursion factor 2**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2005)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**

1 ml/m³ (ppm) ≙ 3.572 mg/m³ **1 mg/m³ ≙ 0.280 ml/m³ (ppm)**

Since the documentation from 2006 (documentation "Methacrylic acid" 2010), studies have been carried out which make a re-evaluation of the substance necessary. Also studies with methacrylic acid methyl ester are used in the evaluation of a number of systemic end points. Cleavage of the ester by carboxylesterases is assumed to be complete, as the competing reaction with glutathione plays a minor role. For this reason, no great difference is to be expected in the bioavailability of the amount of methacrylic acid released from methacrylic acid methyl ester, compared with the absorption of methacrylic acid itself (documentation "Methacrylic acid" 2010). After inhalation, the target tissue of both substances is the upper respiratory tract. In the upper respiratory tract of rats, deposition of methacrylic acid methyl ester is 10% to 20% (supplement "Methyl methacrylate" 2010); that of methacrylic acid is 95% (Section 3.1). Therefore, the assessment of systemic end points using inhalation studies with methacrylic acid methyl ester probably represents an overestimation of the systemic exposure to methacrylic acid, as a much smaller amount of methacrylic acid enters the lungs and consequently reaches the blood.

1 Toxic Effects and Mode of Action

Methacrylic acid has mainly local effects. It is corrosive on the skin and in the eyes. In a 90-day inhalation study with Sprague Dawley rats, slight hypertrophy or hyperplasia of goblet cells of the respiratory epithelium of the nose was observed in 2 female animals at the concentration of 350 ml/m³. At the same time, non-specific systemic effects were found, such as, for example, reduced body weights in male and female rats at the end of the study and a statistically significant reduction in body weight gains in male rats during the study. In humans, there is no clear evidence of contact sensitization; corresponding animal studies yielded negative results. Studies of sensitizing effects of methacrylic acid on the respiratory tract are not available. A developmental toxicity study in rats did not produce such effects up to the highest concentration of 300 ml/m³. There are no fertility studies available with methacrylic acid; in an oral 2-generation study with methacrylic acid methyl ester in rats, however, no effects on fertility and development of the offspring were found at dose levels up to 400 mg/kg body weight and day. A Salmonella mutagenicity test with methacrylic acid yielded negative results. There are no other investigations available of the genotoxicity and carcinogenicity of the substance. A comparison with the data for methacrylic acid methyl ester shows that no hazard is to be expected for these end points.

2 Mechanism of Action

The local effects in the nose can be explained by the acidic character of the substance. Also, the double bond can presumably react with nucleophiles (for example glutathione), as demonstrated in the case of acrylic acid (Esterbauer et al. 1975). This reaction, however, is probably comparatively slow, as methacrylates are less reactive than acrylates (Osman et al. 1988). Under physiological conditions, methacrylic acid (pKa 4.66) exists mainly in dissociated form as a methacrylate anion, which further reduces its nucleophilic reactivity as a result of the shift in the charge of the carboxylate group in the direction of the double bond.

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

In rats, 95% of the methacrylic acid inhaled under conditions in which the flow is unidirectional is deposited in the upper respiratory tract. This suggests that methacrylic acid affects the upper respiratory tract and hardly reaches the lungs. This assumption is confirmed by the results of the 90-day study (documentation "Methacrylic acid" 2010, Section 5.2.1).

In the case of the human nasal tract, the retention of 78% of the methacrylic acid has been predicted after exposure to 10 to 80 ml/m³ and the exposure of the human olfactory tissue is expected to be 2 to 3 times lower than that of rats. Because of various weaknesses, the model was, however, criticized (documentation "Methacrylic acid" 2010).

A pharmacokinetic model has been developed and validated for methacrylic acid. On the basis of the kinetics determined in the validation study with Fischer-344 rats, the half-life in blood after intraperitoneal administration of 10 and 20 mg/kg body weight was 1.7 minutes. The PBPK model revealed a half-life in blood of 2.5 minutes for humans after simulation under comparable conditions (intravenous injection of 10 mg/kg body weight) (ECHA 2014 a). This is consistent with the observation in hip operations using bone cement containing methacrylic acid methyl ester that the maximum concentration of methacrylic acid, as the primary metabolite of methacrylic acid methyl ester, is reached within the first five minutes, after which time methacrylic acid does not continue to accumulate. At this point in time, the concentration of methacrylic acid methyl ester is approximately as high as the methacrylic acid concentration (Crout et al. 1979). Unfortunately, only the maximum, but not the further kinetics, were documented. Thus, it must be assumed that at least 50% is cleaved to form methacrylic acid, but presumably cleavage is complete, as the competing reaction with glutathione is of minor importance (documentation "Methyl methacrylate" 1992).

In a skin permeation study with isolated epidermis from Wistar rats, a maximum permeation rate of 23 825 ± 2839 µg methacrylic acid/cm² and hour and the absorption of 93% of the applied dose within 24 hours were determined. The maximum permeation rate was attained during the first four hours. In a further study with the intact skin of Wistar rats, the maximum permeation rate was 4584 ± 344 µg methacrylic acid/cm² and hour, and 70% of the applied dose was absorbed within 24 hours. In this study, the maximum permeation rate occurred between 5 and 8 hours. Here, 100 µl/cm² was applied occlusively, although the test guideline recommends a maximum of only 10 µl/cm². For human epidermis, a penetration rate of 812 µg/cm² and hour was estimated from the data for other methacrylates; in the case of human full-thickness skin this was 327 µg/cm² and hour (ECHA 2014 a). Controls of the epidermal preparations after the end of exposure were not carried out. On the basis of the data with human epidermis and assuming standard conditions (exposure for one hour, area of skin 2000 cm²), the amount of methacrylic acid taken up would be 1600 mg. Data for the dermal penetration of methacrylic acid esters cannot, however, be extrapolated to methacrylic acid because the lipophilicity of the substances differ. Also, the investigations with rat skin are difficult to evaluate, as they were carried out with undiluted methacrylic acid, which is corrosive on the skin, consequently resulting in increased uptake. By comparison: with 4% **acrylic acid** in water (a non-irritating concentration), the experimentally determined penetration rate for human full-thickness skin is 28.9 µg/cm² and hour (ECHA 2014 b). To evaluate the absorption through the skin, therefore, this flux for acrylic acid is taken as a basis. Assuming the exposure of a 2000 cm² area of skin for 1 hour, this would correspond to an absorbed amount of about 60 mg.

3.2 Metabolism

There are no studies available for the metabolism of methacrylic acid. It is assumed that methacrylic acid reacts with coenzyme A and is then converted to (S)-3-hy-

droxyisobutyryl-CoA. It then rapidly enters the citric acid cycle (documentation "Methyl methacrylate" 1992).

4 Effects in Humans

There are no valid data available for repeated exposure to the substance (documentation "Methacrylic acid" 2010).

In various contact sensitization studies, no clear evidence of such an effect in humans was found (documentation "Methacrylic acid" 2010). Since then, more recent studies have not been conducted.

For all other end points there are no data available with methacrylic acid.

The results of the studies of reproductive toxicity and genotoxicity carried out with **methacrylic acid methyl ester** are regarded as invalid or ambiguous. Epidemiological studies do not indicate that methacrylic acid methyl ester has carcinogenic effects (documentation "Methacrylic acid" 2010).

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

In a study carried out according to OECD Test Guideline 403, a 4-hour LC50 of 7100 mg methacrylic acid/m^3 (1988 ml/m^3) was obtained in rats. Weight loss occurred, and gross-pathologically visible irritation of the respiratory tract was described (documentation "Methacrylic acid" 2010). The RD_{50} in mice (30 minutes exposure) was 22 000 ml methacrylic acid/m^3. Even at the low concentration of 4900 ml/m^3, signs of mild sensory irritation were found after the first few minutes of exposure; at 9400 ml/m^3 and above the irritation was described as moderate to severe from the beginning of exposure (ECHA 2014 a). For **acrylic acid**, an RD_{50} of 685 ml/m^3 was reported in mice after an exposure time of 30 minutes (WHO 1997).

5.1.2 Oral administration

Most of the oral LD50 values for rats, mice and rabbits were below 2000 mg/kg body weight. When diluted solutions were applied, these values were slightly higher than 2000 mg/kg body weight (documentation "Methacrylic acid" 2010).

5.1.3 Dermal application

In a range-finding study with rabbits, doses of 500 mg/kg body weight were not lethal. Doses of and above 1000 mg/kg body weight were lethal (documentation "Methacrylic acid" 2010). The corrosive effects of the substance could have caused the lethal effects.

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

In a 90-day study with animals not specified as pathogen-free (SPF), groups of 10 B6C3F1 mice, SD rats and F344 rats per strain, sex and concentration were exposed in whole-body chambers to methacrylic acid concentrations of 0, 20, 100 or 300 ml/m³ for 6 hours a day, on 5 days a week (CIIT 1984). A further 10 animals per strain, sex and concentration were exposed to the same concentrations for 4 days and examined on day 5. The findings in the 300 ml/m³ groups were: reduced body weight gains in male F344 rats and in both sexes of mice, and reduced food consumption in male F344 rats (in each case about 10%). The reduced body weights in rats are therefore directly related to the reduced food intake and this is not to be seen as a direct systemic toxic effect. Reduced leukocyte counts and increased alkaline phosphatase activity were recorded in female mice. In the male F344 rats, the blood urea nitrogen was increased. As these effects did not occur consistently, a relationship with the exposure is not plausible. In the male animals of both rat strains and in both sexes of mice, the absolute liver weights were reduced. The relative liver weights were reduced only in the mice, but significant only in the male animals and without histopathological changes. Therefore, the decrease in absolute liver weights in rats is a sequel of the reduced body weights and not an independent effect. For systemic effects, therefore, the NOAEC (no observed adverse effect concentration) was 300 ml/m³ in rats and 100 ml/m³ in mice.

Microscopic findings in the nose after 4 and 90 days of exposure are given below in Table 1 and Table 2. After 4 days, histopathological signs of irritation in the nasal cavity could be seen. In the 300 ml/m³ group of F344 rats, exudate, goblet cell hyperplasia, focal ulceration, hyperkeratosis and acute necrosis were observed. In the B6C3F1 mice, the effects were acute rhinitis, acute necrosis, exudate and ulceration. At concentrations of 20 ml/m³ and above, rhinitis occurred also in F344 rats, and epithelial vesicles, acute rhinitis and hyperkeratosis were found also in the SD rats.

In the 90-day study, the findings were similar: in the rats, rhinitis, exudate and epithelial hyperplasia were observed, but the findings were not concentration-dependent. Rhinitis would be a plausible effect of methacrylic acid, as it occurred also after the 4-day exposure. As, however, also control animals in the 90-day study (and in the 4-day study with SD rats) were affected, this makes interpretation of the data in both rat strains difficult. While a NOAEC of 100 ml/m³ was derived in the F344 rats, exudate and epithelial hyperplasia occurred in SD rats even at 20 ml/m³, but neither finding was concentration-dependent. The reason for rhinitis in control SD rats even after the 4-day exposure is not clear. It can be assumed that the findings in the nose were the result of a viral infection and that a direct effect of the substance is less probable, so that the significance of these studies with regard to the upper respiratory tract is questionable. In the mice, rhinitis, exudate and ulceration did not occur until concentrations of 300 ml/m³. After 90 days, in the middle and high concentration groups of mice, degeneration of the olfactory epithelium occurred in section levels B and C. Deposits of an orange to pink-coloured material were found in the cytoplasm of ciliated cells (sustentacular cells). In severe cases, there was a subsequent loss of ciliated cells. In mice, the NOAEC was 20 ml/m³ for local effects

Table 1 Findings in the nasal cavity of rats in the 4-day study (CIIT 1984)

	Concentration [ml/m³]			
	0	20	100	300
Findings in section level A:				
F344 rats				
acute rhinitis				
♂	0/10	4/10	2/10	9/10
♀	0/10	2/10	4/10	7/10
SD rats				
epithelial vesicles				
♂	1/9	2/10	4/10	1/10
♀	0/10	0/10	5/10	1/9
acute rhinitis				
♂	2/9	3/10	4/10	6/10
♀	0/10	2/10	4/10	6/9
exudate				
♂	0/9	1/10	0/10	3/10
♀	0/10	0/10	0/10	3/9
focal ulceration				
♂	0/9	0/10	0/10	1/10
♀	0/10	0/10	0/10	1/9
hyperkeratosis				
♂	0/9	1/10	2/10	2/10
♀	0/10	1/10	3/10	7/9

because of the findings in the olfactory epithelium. A reliable NOAEC for SD rats cannot be derived from the study.

To clarify the ambiguous findings with SD rats in the 1984 study, a further 90-day study was performed. Groups of 10 SD rats per sex and concentration, this time specific-pathogen-free (SPF) animals, were exposed in whole-body chambers to methacrylic acid concentrations of 0, 20, 40, 100 or 350 ml/m³ for 6 hours a day, on 5 days a week. The study was carried out according to the OECD Test Guideline 413, and included a functional observational battery (FOB) and an investigation of the sperm count, sperm motility and morphology. The findings in the 350 ml/m³ groups were: reduced body weight gains in the male rats from day 7, reduced terminal body weights in both sexes compared with the values for the controls (♂: –12% ($p < 0.01$), ♀: –7% ($p < 0.05$)), and reduced food intake (–13%) and food efficiency in the male animals. The reduced body weights in the male rats are to be seen as a direct result of the reduced food intake and not as a direct systemic toxic effect. In the female rats, the food intake was below that of the control group, especially in the second half of the study, although the reduction was not statistically significant. Histopathology revealed slight hypertrophy or hyperplasia of the goblet cells of the respiratory nasal epithelium of the anterior part of the nose in two females of the 350 ml/m³ group; this was the only relevant finding. Changes in organ weights at

Table 2 Findings in the nasal cavity of rats and mice in the 90-day study (CIIT 1984)

	Concentration [ml/m³]			
	0	20	100	300
Findings in section level A:				
F344 rats				
acute rhinitis				
♂	5/10 (1.2)*	6/9 (1.33)	4/10 (1.25)	9/9 (2.1)
♀	5/10 (1.2)	9/10 (1.44)	1/10 (2)	7/10 (1.5)
exudate				
♂	1/10	1/9	0/10	4/9
♀	0/10	0/10	0/10	4/10
SD rats				
acute rhinitis				
♂	5/10 (1)	6/10 (1.5)	10/10 (1.3)	8/10 (1)
♀	2/10 (1)	4/10 (2)	2/10 (1.5)	7/10 (1.14)
exudate				
♂	0/10	2/10	7/10	4/10
♀	0/10	2/10	2/10	4/10
epithelial hyperplasia				
♂	0/10	3/10	5/10	3/10
♀	0/10	1/10	1/10	3/10
B6C3F1 mice				
acute rhinitis				
♂	0/10	0/10	0/10	4/9 (1)
♀	0/10	0/10	0/10	3/10 (1)
exudate				
♂	0/10	0/10	0/10	4/9
♀	0/10	0/10	0/10	2/10
ulceration				
♂	0/10	0/10	0/10	3/9
♀	0/10	0/10	0/10	2/10
Findings in section level B:				
B6C3F1 mice				
degeneration of the olfactory epithelium				
♂	0/10	0/10	1/10	1/10
♀	0/10	0/10	1/10	9/10
Findings in section level C:				
B6C3F1 mice				
degeneration of the olfactory epithelium				
♂	0/10	0/9	1/10	8/10
♀	0/10	0/10	3/10	9/10

* severity (1–5, minimal to severe) indicated in brackets

the high concentration (350 ml/m³), such as a reduction in the absolute epididymis and relative heart and brain weights in the males and in the absolute liver and relative brain and lung weights in the females were regarded either as sequelae of the reduced body weights or as random findings, and not as direct, substance-induced effects, as there were no histopathological correlates to the changes in organ weights (BASF SE 2008).

The slight hypertrophy or hyperplasia of the goblet cells in the respiratory epithelium observed at the high concentration (350 ml/m³) is a physiological reaction to exposure to an irritating substance and is not a substance-specific adverse effect, but an adaptive response. It is a proliferative, but not a pre-neoplastic effect (Monticello et al. 1990; Renne et al. 2009; Rogers 1994). The increased differentiation of stem cells of the basal epithelial layer to goblet cells (instead of to columnar cells) is a physiological process, and reversible at any time, and serves to increase the production of mucus as a reaction to the exposure. It is, however, not clarified how findings of this type develop with prolonged exposure. Goblet cell hyperplasia is to be seen as a marker of subclinical irritation, which is also to be avoided as the increased production of mucus in the nose is not desirable at the workplace. This would, however, be an adaptive effect, and not adverse in the same way as damage to tissue, so would be regarded as an "annoyance to be avoided". Based on the slight effects on body weights and the nose of female animals, the NOAEC was therefore 100 ml/m³ and the LOAEC (lowest observed adverse effect concentration) 350 ml/m³ in this medium-term inhalation study with SD rats.

Overall, the findings obtained with SPF and non-SPF rats support the assumption that the not clearly concentration-dependent histopathological findings in treated, but also in untreated animals of the earlier study are related to infections in the respiratory tract of the animals not spec pathogen-free. Histopathological changes in the epithelial structure and in goblet cells resulting from infections such as those described, for example, by Norlander et al. (1994), Westrin et al. (1992) and by Stierna and Carlsöö (1990), would provide an explanation for the absent or unclear dependency of the findings on the test concentration used. A number of other studies with inhalation exposure are available but do not meet present-day requirements as regards the documentation and methods used (EU 2002). These studies are therefore not presented here.

In a long-term study with **methacrylic acid methyl ester** in rats and mice, a NOAEC of 25 ml/m³ (supplement "Methyl methacrylate" 2010) was obtained.

Conclusions:

For the reasons presented above, of the studies with rats, only the new 90-day inhalation study with a NOAEC of 100 ml/m³ can be considered relevant to the evaluation. For mice, the NOAEC for local effects was 20 ml/m³ because of the findings in the olfactory epithelium.

As regards the different NOAECs for rats and mice, the following evaluation from the documentation for acrylic acid from 2006 (documentation "Acrylic acid" 2010) can be used:

In a 13-week inhalation study (6 hours/day for 5 days/week), groups of 15 male and 15 female F344 rats and B6C3F1 mice were exposed to acrylic acid concentrations of 5, 25 or 75 ml/m³. Ten animals per group were examined histopathological-

ly (nose: 4 section levels). The NOAECs for systemic effects were 5 ml/m³ in female mice and 75 ml/m³ in male mice and rats. Only lower body weight gains were observed, but no systemic organ or tissue damage. As a result of slight histological damage to the olfactory epithelium, the LOAEC was given as 5 ml/m³ in mice. No effects on the nasal mucosa were observed in the two low concentration groups in rats. The NOAEC for local irritation was thus 25 ml/m³ (Miller et al. 1981).

In a study carried out as a result of these findings, groups of 15 female B6C3F1 mice were exposed to acrylic acid vapour concentrations of 0, 5 or 25 ml/m³ for 15 days for 6 or 22 hours a day and also to 25 ml/m³ for 4.4 hours a day. Ten animals were sacrificed at the end of exposure and the remaining 5 after a 6-week recovery phase. Clinical parameters were investigated but only the nasal cavity was examined histopathologically. Exposure to 5 ml/m³ for 6 hours caused no changes. Both 5 ml/m³ for 22 hours and 25 ml/m³ for 4.4, 6 and 22 hours led to concentration and time-related changes to the olfactory epithelium consisting of atrophy, basal cell hypertrophy, necrosis and degeneration of Bowman's glands. The findings obtained after 22-hour exposure to 5 ml/m³ and after 4.4-hour and 6-hour exposure to 25 ml/m³ were completely reversible after 6 weeks. In contrast, the animals of the 25 ml/m³ group were found to have localized areas in which the olfactory epithelium had turned into respiratory-like epithelium (respiratory metaplasia) after 22-hour exposure (Lomax et al. 1994; Rohm and Haas Company 1994). The findings from this 15-day study show that at most a slight increase in the effects with time must be assumed as regards irritation of the olfactory epithelium. With the exception of the very slight changes to the olfactory epithelium at 5 ml/m³ in the medium-term study, the effects observed were similar after 15 and 90 days.

In a study with male F344 rats and B6C3F1 mice designed to detect differences between the species, the animals were exposed to acrylic acid concentrations of 75 ml/m³ in whole-animal exposure chambers for 6 hours a day, for 4 days. On day 5, nose-only exposure was carried out for 6 hours. The respiratory rate decreased by about the same extent in both species (rats between 16% and 23%; mice between 32% and 37%). The effect on the inhaled volume was only very slight in rats (93% to 103% of the values of the control animals); in mice it was also only slightly affected. The minute volume decreased by about 23% in rats and 27% to 34% in mice. For mice, an 88% higher tissue dose per time unit (3.5–3.8 mg/min and cm² compared with 1.8–2.1 mg/min and cm² in rats) was calculated from the concentration, the surface area of the nasal cavity and the respiratory minute volume. Lesions of the respiratory tract, which were limited to the nasal section and mainly affected the olfactory epithelium, were found in both species. The lesions were more pronounced in mice than in rats. The animals were treated with tritium-labelled thymidine 18 hours after the last exposure to acrylic acid to determine the effects on olfactory cell proliferation. Cell division was increased 17 times in mice and 4 times in rats (Barrow 1984, 1986; Swenberg et al. 1987).

In the case of both acrylic and methacrylic acid, the mouse is the considerably more sensitive species. The qualitative and quantitative difference in sensitivity between the rat and the mouse is explained by the greater irritative effect of both substances on the olfactory region in the mouse caused by the greater exposure of the tissue in this species. The level of exposure in the olfactory epithelium in hu-

mans is even lower than that in rats (Brüning et al. 2014). The effects on the olfactory epithelium of mice are therefore not comparable with the situation in humans.

Overall, only the new 90-day inhalation study in rats with a NOAEC of 100 ml/m³ is considered to be relevant for humans.

5.2.2 Oral administration

Only inadequately documented data are available (ECHA 2014 a).

5.2.3 Dermal application

Systemic effects after repeated dermal application were not investigated (documentation "Methacrylic acid" 2010), and more recent data are not available.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

After application for only 3 minutes, undiluted methacrylic acid is corrosive on the skin of rabbits (documentation "Methacrylic acid" 2010).

5.3.2 Eyes

Undiluted methacrylic acid is corrosive in the eyes of rabbits (documentation "Methacrylic acid" 2010).

5.4 Allergenic effects

In a modified Buehler test, a maximization test and a modified single injection adjuvant test according to Polak (footpad test), methacrylic acid was not found to have sensitizing effects on the skin (documentation "Methacrylic acid" 2010).

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

There are no fertility studies available for methacrylic acid. In both 90-day studies, no evidence of effects on the sex organs of the treated animals was found (Section 5.2.1; BASF SE 2008; CIIT 1984). No conspicuous findings were obtained in the complementary examination of sperm morphology and motility in the new 90-day inhalation study (BASF SE 2008).

In a 2-generation study with Wistar rats carried out according to OECD Test Guideline 416 with gavage doses of **methacrylic acid methyl ester** of 0, 50, 150 or 400 mg/kg body weight, no effects of the test substance on fertility and the development of the offspring were found up to and including the highest dose (BASF SE 2009).

5.5.2 Developmental toxicity

In an inhalation study with SD rats exposed to methacrylic acid concentrations of 0, 50, 100, 200 or 300 ml/m³ (gestation days 6–20, 6 hours/day, in analogy to OECD Test Guideline 414), food intake and body weight gains were reduced in the dams during exposure at the high concentration. No clinical findings were reported. Examination of the foetuses for skeletal and visceral anomalies did not reveal any unusual findings (Saillenfait et al. 1999).

Numerous studies with **methacrylic acid methyl ester**, including two carried out according to OECD Test Guideline 414 with concentrations up to 400 ml/m³ in mice or 2000 ml/m³ in rats, provided no evidence of developmental toxicity (supplement "Methyl methacrylate" 2010).

5.6 Genotoxicity

In the documentation from 2006 (documentation "Methacrylic acid" 2010), the data were evaluated as follows: The results of a Salmonella mutagenicity test with the strains TA98, TA100, TA1535 and TA1537 were negative for concentrations of up to 4 mg/plate. Higher concentrations were cytotoxic (EU 2002). As no other studies with methacrylic acid are available, investigations with the structurally similar **methacrylic acid methyl ester** are used for the evaluation. These showed that in vitro the ester has clastogenic potential only at cytotoxic doses and in vivo (dominant lethal test, micronucleus test) is not genotoxic (supplement "Methyl methacrylate" 2010; EU 2002). Therefore, for methacrylic acid, clastogenic potential is only to be expected in vitro at cytotoxic dose levels. In vivo, genotoxic potential is not to be expected (supplement "Methyl methacrylate" 2010; EU 2002).

Positive results were obtained in some in vivo chromosomal aberration tests with methacrylic acid methyl ester. These are, however, difficult to evaluate because of methodological limitations or implausible results (supplement "Methyl methacrylate" 2010). More recent studies are not available.

5.7 Carcinogenicity

In the documentation from 2006 (documentation "Methacrylic acid" 2010) the data were evaluated as follows: There are no studies available for the carcinogenicity of methacrylic acid. Valid inhalation studies with **methacrylic acid methyl ester** in rats and hamsters do not suggest the substance has carcinogenic potential, but indicate that it causes local irritation (supplement "Methyl methacrylate" 2010). For this reason, methacrylic acid is also unlikely to have carcinogenic potential (EU 2002). More recent studies are not available.

6 Manifesto (MAK value/classification)

The critical effects are goblet cell hyperplasia, as a marker for subclinical irritation of the respiratory epithelium, and the reduced body weights at the end of the 90-day study after concentrations of 350 ml/m³ (BASF SE 2008).

MAK value. The data in humans are insufficient for establishing a MAK value for methacrylic acid. The two earlier 90-day studies in rats are not considered to be relevant to the evaluation because of confounding, resulting from an infection of the airways (Section 5.2.1). Degeneration of the olfactory epithelium was found only in mice, for which the NOAEC was 20 ml/m³. However, the olfactory system of mice, compared with that in rats, is subject to higher levels of exposure, and that of rats in turn to higher levels of exposure than that of humans. Therefore, these findings in mice are not comparable with the human situation (Section 5.2.1).

The basis for deriving a MAK value is the NOAEC of 100 ml/m³ (357 mg/m³) from the more recent 90-day inhalation study with SD rats. The LOAEC was 350 ml/m³; at this concentration lower terminal body weights and in some cases a significant reduction in food intake were determined, and in two female rats slight hyperplasia or hypertrophy of the goblet cells in the respiratory epithelium were found. As regards the question of an increase in the effects with time, for shorter exposure periods only data with limited reliability are available for methacrylic acid, as there was probably a confounding airway infection in the 4-day studies. On the other hand, the 4-day study with F344 rats, in which no rhinitis occurred in the control animals, yielded a LOAEC of 20 ml/m³ after 4 days. In the 90-day study with this rat strain, in which rhinitis was found also in the control animals, a NOAEC of 100 ml/m³ was obtained, indicating that there was no increase with time in rhinitis induced by methacrylic acid. In addition, it was demonstrated for acrylic acid that the increase in the severity of rhinitis with time was only slight (Section 5.2.1; documentation "Acrylic acid" 2010). As the incidence of the findings in the nasal epithelium in the recent 90-day study was still below the significance level, the severity was low and the effects in the respiratory epithelium are regarded as adaptive, the difference between the NOAEC and the occurrence of these findings can in this case be smaller than that given in Brüning et al. (2014) (1:3) for the extrapolation of the data to humans. Therefore, from the NOAEC of 100 ml/m³ (357 mg/m³), a MAK value of 50 ml/m³ (178 mg/m³) can be derived for humans. The MAK value of methacrylic acid is five times higher than that of acrylic acid (10 ml/m³); this is supported also by the markedly higher RD_{50} of methacrylic acid (22 000 ml/m³) compared with the RD_{50} of acrylic acid (685 ml/m³). If the reduced body weights are taken as the relevant end point for the evaluation, a MAK value of 50 ml/m³ would likewise be obtained from the NOAEC of 100 ml/m³ according to the standard procedure used by the Commission, as the reduction in body weights was accompanied by a reduction in food intake, which does not indicate a direct systemic effect, but presumably a secondary effect due to irritation.

Peak limitation. Methacrylic acid causes both systemic and local effects. It is possible that the systemic effect is a secondary effect of irritation. Methacrylic acid is therefore classified in Peak Limitation Category I with an excursion factor of 2, as the effects observed at the LOAEC are only very weak and even at 100 ml/m³ (357 mg/m³) the safety margin is still adequate.

Prenatal toxicity. In a developmental toxicity study carried out in analogy to OECD Test Guideline 414 in SD rats, no developmental toxicity was found at the high methacrylic acid concentration of 300 ml/m³. At this concentration, the food intake and body weight gains of the dams were reduced (Saillenfait et al. 1999). The

NOAEC for developmental toxicity is therefore higher than 300 ml methacrylic acid/m³. Other developmental toxicity studies are not available for this substance. It is assumed that **methacrylic acid methyl ester** is completely hydrolysed, or at least to 50% (Section 3.1), by carboxylesterases to form methacrylic acid. Therefore, studies with this substance are also included in the evaluation. In a developmental toxicity study in rats carried out according to OECD Test Guideline 414, no developmental toxicity was found at the high methacrylic acid methyl ester concentration of 2028 ml/m³, at which maternal toxicity occurred in the form of reduced body weight gains (Solomon et al. 1993). The NOAEC for developmental toxicity is therefore more than 2028 ml methacrylic acid methyl ester/m³. The studies with methacrylic acid methyl ester in mice are not included in the evaluation because of the inadequate documentation, especially the absence of a description of the methods and the tabulation of results. The same applies to the remaining studies with rats, as already described in the supplement to methacrylic acid methyl ester (supplement "Methyl methacrylate" 2010). Teratogenic effects were not found in animals with either of the two substances. The difference between the highest methacrylic acid concentration tested of 300 ml/m³ and the MAK value of 50 ml/m³ is 6-fold. The methacrylic acid methyl ester concentration of 2028 ml/m³ corresponds, in the case of complete cleavage, to 2028 ml methacrylic acid/m³ and represents a 41-fold difference to the MAK value of 50 ml/m³. Even if only 50% cleavage is assumed, the NOAEC is higher than the MAK value by a factor of 20. As the difference to the MAK value is sufficiently large, methacrylic acid methyl ester was not found to cause developmental toxicity and the NOAEC for methacrylic acid is higher than 300 ml/m³, the classification of methacrylic acid in Pregnancy Risk Group C is retained.

Carcinogenicity. There are no studies available for the carcinogenicity of methacrylic acid. Valid inhalation studies with **methacrylic acid methyl ester** in rats and hamsters do not suggest the substance has carcinogenic potential, but indicate that it causes local irritation. For this reason, methacrylic acid is also unlikely to have carcinogenic potential.

Germ cell mutagenicity. For methacrylic acid, only one Salmonella mutagenicity test with negative results is available. As for **methacrylic acid methyl ester**, clastogenic potential is to be expected for methacrylic acid only in vitro at cytotoxic concentrations. No genotoxic effects are to be expected in vivo (EU 2002). Therefore, methacrylic acid is not classified in one of the categories for germ cell mutagens.

Absorption through the skin. Methacrylic acid is corrosive on the skin. In a study to determine the acute dermal toxicity in rats, deaths occurred at 1000 mg/kg body weight. However, absorption through injured skin cannot be excluded and may have distorted the results. There are no suitable data available for the skin penetration of diluted, no longer irritating methacrylic acid. For this reason, the data for the structural analogue acrylic acid are used. Assuming the exposure for one hour of a 2000 cm² area of human full-thickness skin to an acrylic acid concentration of 4%, which is probably no longer irritating to the skin, the dermal uptake of 60 mg has been estimated. In the case of exposure at the level of the MAK value, which was derived also as a result of the systemic toxicity, 1780 mg methacrylic acid

is absorbed at an assumed 100% absorption by inhalation and a respiratory volume of 10 m^3. Therefore, dermal exposure does not contribute significantly to the systemic toxicity, and methacrylic acid is not designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. As described in the documentation from 2006 (documentation "Methacrylic acid" 2010), there is no clear evidence that methacrylic acid has contact-sensitizing effects in humans. In animal studies, negative findings were obtained. More recent data are not available, and there are also no studies of the sensitizing effects of methacrylic acid on the airways. Therefore, methacrylic acid is not designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

7 References

Barrow CS (1984) Species differences in toxicology of the nasal passages: acrylic acid and dimethylamine. CIIT Act 4: 1–5

Barrow CS (1986) Quantitation of nasal "dose" with formaldehyde, acrylic acid, and dimethylamine. in: Barrow CS (Ed.) Toxicology of the nasal passages, Hemisphere Publishing Corporation, Washington, 113–122

BASF SE (2008) Methacrylic acid, subchronic 90-day inhalation study in Sprague Dawley rats vapor exposure. Study No. 50I0581/06069 from Experimentelle Toxikologie der BASF SE on behalf of Methacrylates Toxicology Committee of CEFIC MMA Sektorgruppe, unpublished report

BASF SE (2009) Methyl methacrylate – Two-generation reproduction toxicity study in Wistar rats oral administration (gavage); Study No. 73R0751/07101 from Experimentelle Toxikologie der BASF SE on behalf of Methacrylate REACH Task Force, unpublished report

Brüning T, Bartsch R, Bolt HM, Desel H, Drexler H, Gundert-Remy U, Hartwig A, Jäckh R, Leibold E, Pallapies D, Rettenmeier AW, Schlüter G, Stropp G, Sucker K, Triebig G, Westphal G, van Thriel C (2014) Sensory irritation as a basis for setting occupational exposure limits. Arch Toxicol 88: 1855–1879

CIIT (Chemical Industry Institute of Toxicology) (1984) 90-Day vapor inhalation toxicity study of methacrylic acid in B6C3F1 mice, Sprague-Dawley rats and Fischer-344 rats. FYI-OTS-0685-0415, NTIS, Alexandria, VA, USA

Crout DHG, Corkill JA, James ML, Ling RSM (1979) Methyl methacrylate metabolism in man. The hydrolysis of methyl methacrylate to methacrylic acid during total hip replacement. Clin Orthop Relat Res 141: 90–95

ECHA (European Chemicals Agency) (2014 a) Information on registered substances. Dataset on methacrylic acid (CAS Number 79-41-4), joint submission, first publication 04.03.2011, last modification 12.09.2014,
http://echa.europa.eu/web/guest/information-on-chemicals

ECHA (European Chemicals Agency) (2014 b) Information on registered substances. Dataset on acrylic acid (CAS Number 79-10-7), joint submission, first publication 04.03.2011, last modification 12.09.2014,
http://echa.europa.eu/web/guest/information-on-chemicals

Esterbauer H, Zollner H, Scholz N (1975) Reaction of glutathione with conjugated carbonyls. Z Naturforsch Teil C 30: 466–473

EU (European Union) (2002) Risk assessment report, methacrylic acid, 1st priority list, Volume 25, Office for Official Publications of the European Communities, Luxemburg

Lomax LG, Brown DW, Frederick CB (1994) Regional histopathology of the mouse nasal cavity following two weeks of exposure to acrylic acid for either 6 or 22 hours per day. Toxicologist 14: 312

Miller RR, Ayres JA, Jersey GC, McKenna MJ (1981) Inhalation toxicity of acrylic acid. Fundam Appl Toxicol 1: 271–277

Monticello TM, Morgan KT, Uraih L (1990) Nonneoplastic lesions in rats and mice. Environ Health Perspect 85: 249–274

Norlander T, Westrin KM, Stierna P (1994) The inflammatory response of the sinus and nasal mucosa during sinusitis: implications for research and therapy. Acta Otolaryngol, Suppl 515: 38–44

Osman R, Namboodiri K, Weinstein H, Rabinowitz JR (1988) Reactivities of acrylic and methacrylic acids in a nucleophilic addition model of their biological activity. J Am Chem Soc 110: 1701–1707

Renne R, Brix A, Harkema J, Herbert R, Kittel B, Lewis D, March T, Nagano K, Pino M, Rettinghausen S, Rosenbruch M, Tellier P, Wohrmann T (2009) Proliferative and nonproliferative lesions of the rat and mouse respiratory tract. Toxicol Pathol 37: 5S–73S

Rogers DF (1994) Airway goblet cells: responsive and adaptable front-line defenders. Eur Respir J 7: 1690–1706

Rohm and Haas Company (1994) Acrylic acid: regional histopathology of the mouse nasal cavity following 15 days of exposure to acrylic acid either 6 or 22 hours per day. Toxicology Department, Report No. 93R-199, unpublished study

Saillenfait AM, Bonnet P, Gallissot F, Peltier A, Fabriès JF (1999) Developmental toxicities of methacrylic acid, ethyl methacrylate, n-butyl methacrylate, and allyl methacrylate in rats following inhalation exposure. Toxicol Sci 50: 136–145

Solomon HM, McLaughlin JE, Swenson RE, Hagan JV, Wanner FJ, O'Hara GP, Krivanek ND (1993) Methyl methacrylate: inhalation developmental toxicity study in rats. Teratology 48: 115–125

Stierna P, Carlsöö B (1990) Histopathological observations in chronic maxillary sinusitis. Acta Otolaryngol 110: 450–458

Swenberg JA, Gross EA, Randall HW (1987) Localization and quantitation of cell proliferation following exposure to nasal irritants. in: Barrow CS (Ed.) Toxicology of the nasal passages, Hemisphere Publishing Corporation, Washington, 291–300

Westrin KM, Norlander T, Stierna P, Carlsöö B, Nord CE (1992) Experimental maxillary sinusitis induced by Bacteroides fragilis. A bacteriological and histological study in rabbits. Acta Otolaryngol 112: 107–114

WHO (World Health Organization) (1997) Acrylic acid. IPCS – Environmental health criteria No 191, WHO, Geneva

completed 25.02.2015