The MAK Collection for Occupational Health and Safety

Methyl acetate

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

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

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Methyl acetate

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 work place (MAK value) of methyl acetate [79-20-9] of 100 ml/m³ considering the critical endpoint respiratory tract irritation. A 28-day study with rats shows a NOAEC for degeneration and necrosis of the olfactory epithelium of 350 ml/m³. A chronic NAEC of 125 to 167 ml/m³ can be extrapolated. 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 NAEC would correspond to a concentration of 63 to 84 ml/m³ for work place air. However, acetic acid resulting from the local enzymatic cleavage of methyl acetate by carboxylesterases is responsible for the effects to the olfactory epithelium, and not the substance itself. Thus, the activity of rat and human carboxylesterases is decisive in the respiratory tract irritation of methyl acetate. Based on a comparative analysis on vinyl acetate, in which rat olfactory enzyme activity was shown to be almost equivalent to that in humans, the same is assumed for methyl acetate and the interspecies extrapolation step is deemed unnecessary. The MAK value is retained at 100 ml/m³. As local effects are critical, the assignment to Peak Limitation Category I and the excursion factor of 4 are also retained.

Keywords

methyl acetate; acetic acid methyl ester; (sub)acute toxicity; (sub)chronic toxicity; irritation; peak limitation; prenatal toxicity; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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Methyl acetate

[79-20-9]

Supplement 2016

MAK value (2005)	**100 ml/m³ (ppm) ≙ 310 mg/m³**
Peak limitation (2005)	**Category I, excursion factor 4**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (1997)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
log K_{OW}[1)]	0.18 (SRC 2014)
Solubility	243 000 mg/l water at 20 °C (SRC 2014)
pKa value	no data
1 ml/m³ ≙ 3.07 mg/m³	**1 mg/m³ ≙ 0.325 ml/m³**

For the derivation of MAK values for substances with effects on the upper airways and eyes, since 2014 the Commission has been using a procedure based on physiological and empirical aspects (Brüning et al. 2014), in which also the criteria for categorization as a sensory irritant are described. The MAK value has been re-evaluated on the basis of this procedure.

For methyl acetate, documentation is available from 1997 (documentation "Methylacetat" 1997, available in German only) and supplements from 1989 (on exposure during pregnancy) (documentation "Sammelkapitel MAK-Werte und Schwangerschaft" 1989, available in German only), 2001 (supplement "Methyl acetate" 2002) and 2006 (supplement "Methylacetat" 2006, available in German only).

Since the last supplement, only a review by Heldreth et al. (2012) has been published; however, it does not provide any new data relevant for the derivation of a MAK value.

1) octanol/water partition coefficient.

Animal Experiments and in vitro Studies

Subacute, subchronic and chronic toxicity

In the 28-day inhalation study in rats according to OECD Test Guideline 412 already described in detail in the supplement from 2006 (supplement "Methylacetat" 2006, available in German only) which was used for the derivation of the MAK value, groups of 10 Sprague Dawley rats per sex were exposed to methyl acetate concentrations of 0, 75, 350 or 2000 ml/m^3 for 6 hours a day, on 5 days per week for 4 weeks. At 2000 ml/m^3, degeneration and necrosis of the olfactory epithelium were observed in 10 of 10 male animals and 9 of 10 female animals. There were no such changes in the olfactory epithelium in any of the animals of the two lower concentration groups or in the control group. Other effects in the high concentration group were decreased body weight gains and decreased food consumption. At the concentration of 350 ml/m^3, changed absolute and relative adrenal and thymus weights were found, which developed in counter directions in the two sexes and did not correlate with histological changes. The NOAEC (no observed adverse effect concentration) derived for degeneration and necrosis of the olfactory epithelium was 350 ml/m^3 (Celanese 1999).

Local effects on skin and mucous membranes

Skin

In a study of acute skin irritation carried out according to OECD Test Guideline 404 in three rabbits, 0.5 ml undiluted methyl acetate (purity: 99.9%) was tested. The average irritation scores after 30 to 60 minutes and after 24, 48 and 72 hours were 0.2 for erythema (maximum score: 4) and 0 for oedema (maximum score: 4). The erythema was completely reversible within 48 hours after removal of the patches. Methyl acetate was classified as not irritating to the skin (unpublished study from 1988; ECHA 2014).

Eyes

In a study of acute eye irritation carried out according to OECD Test Guideline 405 in three rabbits, 0.1 ml undiluted methyl acetate (purity: 99.9%) was used. The average irritation scores after 24, 48 and 72 hours were 1.3 for the cornea (maximum score: 4), 1.0 for the iris (maximum score: 2), 2.7 for the conjunctiva (maximum score: 3), and 1.8 for chemosis (maximum score: 4). All changes were reversible within 7 days. The substance was classified as irritating to the eyes (unpublished study from 1988; ECHA 2014).

Manifesto (MAK value/classification)

The critical effect of methyl acetate is local irritation of the olfactory epithelium in the rat.

MAK value. In a 28-day inhalation study in rats, degeneration and necrosis of the olfactory epithelium occurred at the highest methyl acetate concentration of 2000 ml/m³. The NOAEC for this effect was 350 ml/m³. No long-term study is available. In the supplement from 2006 the question as to whether long-term exposure would lead to an increase in the severity of effects was discussed in detail. The substance was compared with vinyl acetate, as it likewise causes lesions in the olfactory epithelium after inhalation as the critical effect. Due to their structural relationship and the similarity of the effects, a common mode of action (cleavage of the ester group, release of acetic acid) can be assumed. The calculated NAEC (no adverse effect concentration) for long-term exposure to methyl acetate is in the range of 125 to 167 ml/m³ (supplement "Methylacetat" 2006, available in German only).

Following the procedure of Brüning et al. (2014) for the extrapolation of effects on the olfactory epithelium in rats to humans, a NAEC of 63 to 84 ml/m³ is obtained from the calculated NAEC of 125 to 167 ml/m³ (see above). In the case of methyl acetate, however, the damage to the nasal tissue is to be attributed to the acetic acid formed locally by cleavage of the ester and not to methyl acetate itself. The cleavage is caused by carboxylesterases (supplement "Methylacetat" 2006, available in German only). Therefore, for the toxicity of methyl acetate, it is not the higher-level exposure to methyl acetate of the tissue that is decisive, but the activity of the carboxylesterases in the olfactory epithelium leading to the formation of the toxic metabolite acetic acid. For vinyl acetate it has been shown that the levels of carboxylesterase activity in the olfactory epithelium of rats and humans are similar (Bogdanffy et al. 1998). The same can be assumed for the enzymatic cleavage of methyl acetate to acetic acid. Therefore, for the derivation of the MAK value for methyl acetate, there is no need for an additional margin to the NOAEC from the rat study. The MAK value of 100 ml/m³ (310 mg/m³) is thus confirmed.

Peak limitation. Classification in Peak Limitation Category I has been retained because the MAK value was derived on the basis of local irritation. The excursion factor of 4 can be retained as no irritation was observed in an earlier volunteer study after 5-minute exposure to 350 ml/m³, and slight tracheal irritation was described only after concentrations of 4000 ml/m³ and above. This is supported by the large margin between the MAK value and the LOAEC (lowest observed adverse effect concentration) of 2000 ml/m³ obtained in the 5-day study carried out as a preliminary experiment for the 28-day study. The 5-day study is described in great detail in the supplement from 2006 (supplement "Methylacetat" 2006, available in German only).

Prenatal toxicity. There are no new data available for the developmental toxicity of the substance. As the MAK value has been retained, also classification in Pregnancy Risk Group C has been confirmed.

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