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Formic acid methyl ester

MAK Value Documentation, supplement – Translation of the German version from 2019

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

formic acid methyl ester; central nervous system; neurotoxicity; behavioural toxicity; nasal epithelium; MAK value; maximum workplace concentration; peak limitation; read-across

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), the Pregnancy Risk Group and the germ cell mutagenicity of formic acid methyl ester [107-31-3]. No neurobehavioral effects were observed in subjects exposed to 100 ml/m^3 for 8 hours at rest. After taking the increased respiratory volume at the workplace into account because the blood:air partition coefficient of formic acid methyl ester is > 5 (see List of MAK and BAT Values, Sections Ib and Ic), the MAK value of 50 ml/m^3 has been retained. Since a systemic effect is critical, Peak Limitation Category II is retained. As it is unclear whether the metabolites methanol and formic acid or formic acid methyl ester itself are responsible for the effects, the excursion factor has been set to the default value of 2 for substances with systemic effects. There are no developmental toxicity studies with formic acid methyl ester. Taking into consideration the data for the metabolites formic acid and methanol, damage to the embryo and foetus is unlikely if the MAK value for formic acid methyl ester is not exceeded. Therefore, formic acid methyl ester remains classified in Pregnancy Risk Group C. Formic acid methyl ester is not mutagenic in bacteria. No clastogenic effects were observed in vivo. Uptake via the skin can lead to systemic effects and formic acid methyl ester remains designated with "H". There are no clinical results for sensitization in humans and no sensitization tests in animals.

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MAK value (1996)	**50 ml/m³ (ppm) ≙ 120 mg/m³**
Peak limitation (2018)	**Category II, excursion factor 2**
Absorption through the skin (1996)	**H**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (1996)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**not established**
CAS Number	107-31-3
Vapour pressure at 25 °C	780 hPa (NLM 2021)
log K_{OW}	0.03 (NLM 2021)
Solubility in water at 25 °C	230 g/l (ECHA 2018)
1 ml/m³ (ppm) ≙ 2.492 mg/m³	**1 mg/m³ ≙ 0.401 ml/m³ (ppm)**

Documentation for formic acid methyl ester is available from 2003 (Hartwig 2013).

In 2016, the Commission began using a revised approach for assessing substances with a MAK value based on systemic effects and derived from inhalation studies in animals or studies with volunteers at rest; this new approach takes into account that the respiratory volume at the workplace is higher than under experimental conditions. This does not apply, however, to gases or vapours with a blood:air partition coefficient < 5 (see List of MAK and BAT Values, Sections Ib and Ic). The blood:air partition coefficient calculated for formic acid methyl ester using the formula of Buist et al. (2012) is 36.2. This supplement evaluates whether the MAK value and the pregnancy risk group for formic acid methyl ester need to be re-assessed as a result of the higher respiratory volume at the workplace. In addition, two inhalation studies in rats are discussed, which were carried out after the documentation from 2003 (Hartwig 2013), and germ cell mutagenicity is assessed.

Mechanism of Action

Effects on the central nervous system (CNS) are critical, caused either by formic acid methyl ester itself or by the cleavage product methanol (Hartwig and MAK Commission 2021). The delayed body weight gains in the 90-day study in rats with a concurrent reduction in feed consumption may be a secondary effect. The irritation of the nasal mucosa observed in animal experiments was probably caused by the metabolites formaldehyde and formic acid.

Toxicokinetics and Metabolism

Formic acid methyl ester is absorbed mainly via the lungs; in view of the data regarding its metabolism and in analogy to other substances, oral absorption of formic acid methyl ester is assumed.

The lethal intoxication of a 19-month-old child, whose head was covered with a cream containing formic acid methyl ester under an airtight bathing cap, is described in the documentation from 2003 (Hartwig 2013). It is evident from this that formic acid methyl ester is absorbed well dermally.

For a saturated aqueous solution, fluxes of 1185, 188 and 469 µg/cm^2 and hour are calculated using the models of Fiserova-Bergerova et al. (1990), Guy and Potts (1993) and Wilschut et al. (1995). Assuming the exposure of 2000 cm^2 of skin for one hour, this would correspond to absorbed amounts of 2370, 376 and 938 mg.

A toxicokinetic model was developed for the excretion of methanol and formic acid with the urine from the data from volunteer studies and the workplace studies with inhalation and probable dermal exposure (Hartwig 2013). The data show that after exposure to a formic acid methyl ester concentration of 50 ml/m^3 for 8 hours at an increased rate of respiration, the amount of methanol excreted with the urine is about 4.5 mg/l. The amount of formic acid excreted is about three times the background level; here, the model probably overestimates the workplace values, as the figures in the publication of the workplace studies demonstrate (Nihlén and Droz 2000).

As described in the documentation from 2003 (Hartwig 2013), formic acid methyl ester is cleaved by esterases to form methanol and formic acid. Methanol is oxidized via formaldehyde during metabolism to form formic acid (formate). Thus, two moles of formic acid are formed from one mole of formic acid methyl ester.

The hydrolysis of formic acid methyl ester (no other details) is practically complete (97%) (Nihlén and Droz 2000).

Effects in Humans

There are no data in humans available for the end points sensitization, reproductive toxicity, genotoxicity and carcinogenicity.

Single exposures

The odour threshold for formic acid methyl ester is 600 ml/m^3 (Amoore and Hautala 1983). Exposure for one minute to 1500 ml/m^3 did not lead to irritation in volunteers (Hartwig 2013).

In a volunteer study already described in the documentation from 2003 (Hartwig 2013), 20 persons were exposed at rest to a formic acid methyl ester concentration of 100 ml/m^3 for 8 hours and the results of neuropsychological and sensory investigations were compared with those for 20 persons not exposed. Of the 20 parameters investigated, the results differed in two cases (subjective fatigue and electromyography in one muscle of the forehead); multi-variance analysis showed that the influence of time on fatigue was much greater than that of exposure. The electromyography finding was conspicuous only in the forehead muscle, but not in the left neck muscle. The changes in the electromyography of the forehead muscle were attributed by the authors to the increased fatigue of the volunteers. The authors concluded from the results of this study that 8-hour exposure to 100 ml/m^3 increases subjective fatigue to a small extent, but without influencing the results of the neuropsychological tests (Sethre et al. 1998 a, 2000 a). As, however, no details were given regarding the investigated muscle, frequency or amplitude and the changes detected by electromyography shown in the figure were only marginal, these are regarded as not biologically relevant.

The study was carried out blind, as the concentration used was below the odour threshold of formic acid methyl ester. It can be indirectly concluded from this that no irritant effects occurred, as it would otherwise not have been a blind study.

Repeated exposure

There are no new studies available of repeated exposure in workers. The documentation from 2003 (Hartwig 2013) already described in detail the workplace studies; these investigated foundry workers and determined the exposure levels at the workplace by ambient and personal air monitoring. The exposure data and the effects are given in Table 1. In 21 workers, who were exposed to median concentrations of 47 ml formic acid methyl ester/m^3 (Berode et al. 2000; no data for isopropyl alcohol) or 68 ml formic acid methyl ester/m^3 and 28 ml isopropyl alcohol/m^3 (Sethre et al. 1998 b) determined by personal air sampling, no neuropsychological effects caused by the exposure to formic acid methyl

ester alone were found. The fact that the three workers with the highest levels of exposure (maximum levels of 136 ml formic acid methyl ester/m³ and 73 ml isopropyl alcohol/m³) performed worse in 3 of 15 behavioural psychological tests (pattern memory test, digit span test and impaired balance while standing on one leg and on two legs) was, in the authors' opinion, due to the exposure to isopropyl alcohol (Sethre et al. 1998 b). In a follow-up study in the same foundry by the same research group with nine workers, the observations could not be reproduced, although the investigations were more specific. The concentrations determined by personal air monitoring were 58 ml formic acid methyl ester/m³ as median (Berode et al. 2000) or were between 0 and a maximum of 375 ml isopropyl alcohol/m³ (Sethre et al. 2000 b). Also sensory parameters (odour threshold of butanol) were unaffected (Sethre et al. 2000 b). The observed effects on balance are probably the result of group differences which could not be corrected statistically because of the small number of cases. They are therefore not regarded as substance-related and are not taken into consideration for the derivation of the MAK value.

Tab. 1 Overview of the exposure data and the effects in the workplace studies of formic acid methyl ester

Exposed persons	Type of determination	Range [ml/m³]	AM ± SD/Median [ml/m³]	Effects	References
n = 21, foundry controls: n = 23 (8 qualified, 15 unqualified workers, printing industry)	ambient air, 1 working week	F: 0–531 I: 0–183 CO: 0–76	median: F: 28 I: 39 CO: 10		Sethre et al. 1998 b
	personal air monitoring (n = 21)		median: F: 68 I: 28	in 3/15 neuropsychological tests worse than controls (n = 23): comparison of 3 workers with high-level and 3 with low-level exposure: highly exposed attained half as many points as those with low-level exposure in the pattern memory test and digit span test, when standing upright on one and two legs swaying of the body was almost twice as strong, correlation analysis: influence of I also without F; influence of F (alone/in combination with I/taking into consideration age etc.) inconsistent	
	day 1 (Thursday)	F: 22–136	AM: F: 390 ± 130 ml/m³ × hour (assumption: for 8-hour exposure: 48 ± 16) I: 175 ± 120 ml/m³ × hour (assumption: for 8-hour exposure: 22 ± 15)		
	day 2 (Friday)	no data	AM: F: 386 ± 129 ml/m³ × hour (assumption: for 8-hour exposure: 48 ± 16) I: 115 ± 79 ml/m³ × hour (assumption: for 8-hour exposure: 14 ± 9)		

Tab. 1 *(continued)*

Exposed persons	Type of determination	Range [ml/m³]	AM ± SD/Median [ml/m³]	Effects	References
n = 19 (same collective as in Sethre et al. 1998 b)	personal air monitoring day 1 (Thursday), 8 hours	F: 2–155	median: F: 47	not investigated	Berode et al. 2000
n = 9 (same collective as in Sethre et al. 2000 b)	personal air monitoring determination 1 day during the working week	F: 34–135	median: F: 58		
n = 28 (Σ)		F: 2–155	AM: F: 57.2 ± 45.7		
n = 9 (same company as in Sethre et al. 1998 b)	ambient air (9 hours), 3 weeks		AM: F: 36 ± 21 I: 44 ± 16		Sethre et al. 2000 b
	personal air monitoring	n = 9: F: 0–1200 ml/m³ × hour (assumption: for 8-hour exposure: 0–150 ml/m³; maximum values: 25, 38, 50, 63, 75, 88, 106, 125, 150 ml/m³) I: 0–3000 ml/m³ × hour (assumption: for 8-hour exposure: 0–375 ml/m³; maximum values: 175, 200, 200, 225, 238, 250, 275, 313, 375 ml/m³)		3 workers with high-level exposure: balance while standing on two legs impaired (eyes covered), authors: person-specific and not exposure-related, subjective fatigue lower with higher exposure to I and higher methanol concentration in urine, sensory parameters (odour threshold of butanol) unaffected	

AM: arithmetic mean; CO: carbon monoxide; F: formic acid methyl ester; I: isopropyl alcohol; SD: standard deviation

Summary: In the two workplace studies similarly high formic acid methyl ester concentrations were determined by personal air monitoring (median: 47 and 58 ml/m³, respectively; Berode et al. 2000). The median isopropyl alcohol concentration from personal air monitoring is available for only one workplace study (Sethre et al. 1998 b). In the second study, the data is given as the maximum cumulative exposure (assumption: for an 8-hour shift 0 to a maximum 375 ml isopropyl alcohol/m³; Sethre et al. 2000 b). In the opinion of the authors, above all isopropyl alcohol was responsible for the neuropsychological effects observed in the first study with 21 employees. In the study with 9 employees, however, no substance-related effects were observed despite higher levels of exposure to isopropyl alcohol (Sethre et al. 2000 b); the findings of the first study were therefore not confirmed.

Animal Experiments and in vitro Studies

There are no data available for sensitization, reproductive toxicity and carcinogenicity.

Acute toxicity

Inhalation

Groups of 5 to 10 male BALB/c mice were exposed to formic acid methyl ester concentrations of 202 to 1168 ml/m^3 in a plethysmograph for 30 minutes. The RD_{50} for irritation of the upper airways was 1109 ml/m^3; the extrapolated RD_0 was 184 ml/m^3. The RD_{50} is used to calculate the concentration which leads to a reduction in the respiratory rate of the animals by 50%. Pulmonary irritation did not occur. Using the RD_0, a threshold limit value for local irritation of 30 to 100 ml/m^3 was estimated for humans. In the concentration range of 200 to 400 ml/m^3 the concentration–effect curve was very steep, at higher concentrations it was flatter, which could indicate saturation of the metabolism, if a metabolite is responsible for the irritation. Pre-treatment with the esterase inhibitor tri-ortho-cresyl phosphate led to a reduction of the irritant effect, which demonstrates that the hydrolysis products (above all formic acid) are co-responsible for the irritant effect. The concentration–effect curve of formic acid was not as steep as that for formic acid methyl ester. The slow reduction of the respiratory frequency at the beginning of the 30-minute exposure period could be explained either by the slow reaction of formic acid methyl ester with trigeminus receptors or by the metabolism of formic acid methyl ester by the esterases of the nasal mucosa to form the potent irritants formic acid and formaldehyde (Larsen and Nielsen 2012).

Subacute, subchronic and chronic toxicity

Inhalation

In a 14-day inhalation study, groups of 5 male and 5 female Wistar rats were exposed whole-body to formic acid methyl ester concentrations of 0, 100, 500 or 1500 ml/m^3 for 6 hours a day, on 5 days a week. The histopathological examination focused mainly on the respiratory tract. No blood or urine analyses were carried out. No clinical signs were observed during the entire study. Histopathological changes in the olfactory epithelium of the nasal cavity occurred at 500 ml/m^3 and above; these increased in a concentration-dependent manner and were characterized by disorder and degeneration and in some cases necrosis of the olfactory cells. In addition, multifocal squamous cell metaplasia of the olfactory epithelium of the nasal cavity and multifocal inflammatory cell infiltration were diagnosed. At 500 ml/m^3 1 male and 2 female animals were affected. The changes in the nasal cavity are shown in Table 2. In addition, reduced terminal body weights were determined in the 1500 ml/m^3 group (males –14.3%, females –9.3% compared with the weights of the controls). In this study the NOAEC (no observed adverse effect concentration) for local effects was 100 ml/m^3 and the LOAEC (lowest observed adverse effect concentration) was 500 ml/m^3. For systemic effects, a NOAEC of 500 ml/m^3 was found, and a LOAEC of 1500 ml/m^3 resulting from delayed body weight gains and changes in organ weights (liver, lungs, kidneys and spleen) was obtained (BASF AG 2003). As only few animals in the 500 ml/m^3 group showed local effects in the nose, the results of this study do not contradict those of the 13-week study (see below), in which the NOAEC for local effects was 400 ml/m^3.

It can be assumed that the delayed body weight gains and the resulting changes in organ weights are caused by the irritant effect of the substance. The highest concentration used in this study of 1500 ml/m^3 led to considerable irritation in the respiratory tract of rats, as demonstrated, for example, by the development of necrosis. This concentration is above the RD_{50} for irritation of the upper airways in the mouse of 1109 ml/m^3 (Larsen and Nielsen 2012).

Tab. 2 Changes in the nasal cavity of rats after inhalation exposure to formic acid methyl ester for two weeks (BASF AG 2003)

Sex	♂				♀			
Concentration (ml/m³)	**0**	**100**	**500**	**1500**	**0**	**100**	**500**	**1500**
Number of animals investigated	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**
Section level I								
degeneration, olfactory epithelium	0	0	0	4	0	0	1	5
Section level II								
degeneration, olfactory epithelium	0	0	1	5	0	1[a)]	1	5
squamous cell metaplasia	0	0	0	2	0	0	0	4
Section level III								
degeneration, olfactory epithelium	0	0	0	5	0	0	2	5
squamous cell metaplasia	0	0	0	2	0	0	0	2
Section level IV								
degeneration, olfactory epithelium	0	0	0	4	0	0	0	2
infiltration of inflammatory cells	0	0	0	5	0	0	0	4

[a)] not treatment-related

In a 13-week study published in Korean with an English abstract, which, according to the authors, was carried out in conformity with OECD Test Guideline 413, male and female Sprague Dawley rats (number of animals per sex and group not given) were exposed to formic acid methyl ester concentrations of 0, 100, 400 or 1600 ml/m³ for 6 hours a day, on 5 days a week. At 400 ml/m³ and above, concentration-dependent delays in body weight development (400, 1600 ml/m³: ♂ –7.5%, –26% compared with the weights of the controls; ♀ –7%, –21%), reduced feed consumption (no other details) and in the females increased relative weights of the ovaries, adrenal glands and brain, which is interpreted to be the result of the reduction in body weight, were observed. In both sexes of the high concentration group, the increase in the relative weights of almost all organs investigated was statistically significant. There were changes also in haematological and blood parameters. Among other effects, atrophy of the respiratory epithelium in the nose, and degeneration, regeneration and shrinking of olfactory cells were observed. In this study the NOAEC for local effects was 400 ml/m³ and the LOAEC 1600 ml/m³. For systemic effects a NOAEC of 100 ml/m³ and a LOAEC of 400 ml/m³ were obtained as a result of the delayed body weight gains and changes in organ weights (Kim et al. 2010 a). The NOAEC for local effects from the 13-week study does not contradict the results from the 14-day study as only few animals were affected at 500 ml/m³ in this study. The reduced body weight development probably correlates with the reduced feed consumption, and is therefore to be regarded as a secondary effect.

Local effects on skin and mucous membranes

Skin

Occlusive application for 24 hours led to slight irritation of the skin of 3 rabbits (OECD 2008).

Eyes

Formic acid methyl ester is irritating to the eyes in rabbits (OECD 2008).

Genotoxicity

In vitro

Formic acid methyl ester was found not to be mutagenic in three different mutagenicity tests with Salmonella typhimurium strains. The tests were carried out in accordance with OECD Test Guideline 471 in both the presence and absence of a metabolic activation system (OECD 2008).

The exposure of Salmonella typhimurium strains TA100 and TA1535 for 24 hours to formic acid methyl ester concentrations in the air of between 0.1% and 50% (1000 to 500 000 ml/m^3) did not lead to an increase in the mutation frequency in either the presence or absence of a metabolic activation system. Cytotoxicity occurred at concentrations of 5% and above. The positive controls yielded the expected results (OECD 2008).

In vivo

The oral administration of formic acid methyl ester doses of 0, 250, 500 or 1000 mg/kg body weight did not induce micronuclei in the bone marrow of male ICR mice. The ratio of polychromatic to normochromatic erythrocytes was not affected, and no clinical signs were observed. Each dose group consisted of 6 mice. The vehicle was olive oil. The animals were sacrificed 24 hours after the treatment and 2000 polychromatic erythrocytes were counted per dose group (Kim et al. 2010 b).

Manifesto (MAK value/classification)

The critical effects are central nervous effects and damage to the olfactory and respiratory epithelium of rats.

MAK value. The previously valid MAK value for formic acid methyl ester of 50 ml/m^3 was provisionally established in analogy to the MAK value for methanol at that time of 200 ml/m^3 because of its metabolism to formic acid (see Section "Toxicokinetics and Metabolism") and the assumed more rapid formation of formic acid than is the case with methanol. In addition, it was based on a volunteer study (Sethre et al. 1998 a, 2000 a) and workplace studies of limited meaningfulness with exposure to a mixture of substances (Sethre et al. 1998 b, 2000 b) in which no neuropsychological changes were observed at exposure concentrations of up to 50 ml/m^3 (Hartwig 2013).

These studies with humans have been re-evaluated in detail: in volunteers who were exposed once to a formic acid methyl ester concentration of 100 ml/m^3 for 8 hours, their subjective feeling of fatigue was increased, although no effects were evident in the neuropsychological tests.

In 21 workers, who were exposed to median concentrations of formic acid methyl ester, as determined by personal air sampling, of 47 ml/m^3 (Berode et al. 2000; no data for isopropyl alcohol) or to 68 ml/m^3 and 28 ml isopropyl alcohol/m^3 (Sethre et al. 1998 b), no neuropsychological effects caused by the exposure to formic acid methyl ester alone were found. The fact that the three workers with the highest levels of exposure (maximum levels of 136 ml formic acid methyl ester/m^3 and 73 ml isopropyl alcohol/m^3) performed worse in 3 of 15 behavioural psychological tests was, in the authors' opinion, due to the exposure to isopropyl alcohol (Sethre et al. 1998 b). In a follow-up study in the same plant with nine workers, no significant impairments in neuropsychological tests as a result of formic acid methyl ester or isopropyl alcohol were found although the investigations were more specific (Sethre et al. 2000 b). The median concentration determined by personal air sampling was 58 ml formic acid methyl ester/m^3 (Berode et al. 2000) and the maximum concentrations were 150 ml formic acid methyl ester/m^3 and 375 ml isopropyl alcohol/m^3 (Sethre et al. 2000 b). Also sensory parameters (odour threshold of butanol) were unaffected (Sethre et al. 2000 b). In these workplace studies, therefore, formic acid methyl ester was not found to cause clear behavioural toxicity up to 150 ml/m^3. The concentration of 100 ml/m^3 from the volunteer study is therefore now regarded to be the NOAEC for central nervous effects.

Exposure of test persons to formic acid methyl ester vapour for 1 minute at a concentration of 1500 ml/m³ led neither to irritation of the mucous membranes nor to signs of other toxic effects (see Hartwig 2013; Schrenk et al. 1936). The RD_{50} for irritation of the upper airways of the mouse is 1109 ml/m³; the extrapolated RD_0 is 184 ml/m³. Pulmonary irritation did not occur. It was estimated from the RD_0 that sensory irritation does not occur in humans between 30 and 100 ml/m³ (Larsen and Nielsen 2012). These concentrations are below the odour threshold.

In view of the NOAEC for neuropsychological changes of 100 ml/m³ from the volunteer study and taking into consideration the increased respiratory volume of persons at the workplace compared with that of the volunteers at rest (1:2), the MAK value of 50 ml/m³ has been retained. At this concentration also sensory irritation is not to be expected. The exposure to formic acid methyl ester of the workers in the two workplace studies was of a similar level (median: 47 and 58 ml/m³) and the studies support the MAK value.

The limit value for local toxicity, which was obtained from the 90-day inhalation study in rats (Kim et al. 2010 a), is likewise 50 ml/m³, assuming a NOAEC of 400 ml/m³ for effects on the respiratory epithelium of rats and extrapolation to humans (1:3) and taking into consideration a possible intensification of the effects with chronic exposure, as in the 2-week study atrophy of the respiratory epithelium did not occur, and using the preferred value approach. The limit value which could be derived on the basis of systemic effects, which are interpreted to be secondary, is 10 ml/m³, assuming a NOAEC of 100 ml/m³ after extrapolation of the results from an animal study to humans (1:2) and taking into consideration a possible intensification of the effects with chronic exposure (1:2) and the increased respiratory volume. This derived concentration is much lower than that determined in the workplace studies at which no effects occurred. As values extrapolated from animal studies are based on worst case assumptions, the values derived from a valid volunteer study with the support of two workplace studies and the value from a 90-day inhalation study in rats do not contradict each other. The MAK value is in agreement with that for methanol (Hartwig and MAK Commission 2021) of 100 ml/m³.

Peak limitation. The critical effect for the derivation of the MAK value is probably of systemic nature; Peak Limitation Category II has therefore been retained. As it is unclear whether the systemic findings are the result of formic acid methyl ester itself or its metabolites, and there are no exact data for the short-term exposure of the workers, the default excursion factor of 2 for substances with systemic effects has been set.

Prenatal toxicity. After the absorption of formic acid methyl ester, it is hydrolysed almost completely to formic acid and methanol. Methanol in turn is likewise converted to formic acid. Thus, from one mole of formic acid methyl ester two moles of formic acid are formed. As there are no data for the toxic effects on development of formic acid methyl ester itself, both metabolites must be taken into consideration for the evaluation of the substance.

In 2018, after the MAK value for **methanol** was lowered from 200 ml/m³ to 100 ml/m³, classification in Pregnancy Risk Group C was confirmed (Hartwig and MAK Commission 2021). This took into account the developmental toxicity, developmental neurotoxicity and the estimated formation of formic acid. In volunteers, the **formic acid** concentration in the serum was not increased after exposure for 6 hours to 200 ml methanol/m³. The formic acid concentration in humans increases slightly only after exposure to 400 ml/m³ and above for 8 hours. Thus, as long as the MAK value for methanol of 100 ml/m³ and that for formic acid methyl ester of 50 ml/m³ is not exceeded, even in the case of folate deficiency resulting from the increased requirement for folic acid during pregnancy, methanol or formic acid methyl ester are unlikely to cause prenatal toxicity. Formic acid methyl ester therefore remains classified in Pregnancy Risk Group C.

Germ cell mutagenicity. Studies in germ cells are not available. Formic acid methyl ester is not mutagenic in bacteria. In a study with mice, micronuclei were not induced after oral administration up to the highest dose tested of 1000 mg/kg body weight. Formic acid methyl ester is therefore not classified in one of the categories for germ cell mutagenicity.

Absorption through the skin. In view of the high vapour pressure and low boiling point of 32.3 °C, contact with the skin for a longer period is unlikely. The dermal LD_{50} in rats is above 4000 mg/kg body weight. The oral LD_{50} in rats, however, is 1500 mg/kg body weight (Hartwig 2013).

On the basis of a model calculation (see Section "Toxicokinetics and Metabolism"), a maximum dermally absorbed amount of 2370 mg can be estimated for humans after exposure to a saturated aqueous solution under standard conditions (skin area of 2000 cm^2, exposure for 1 hour). The two other models yield absorbed amounts of 376 and 9381 mg, respectively. The fluxes calculated for formic acid methyl ester were between 188 and 1185 µg/cm^2 and hour, and thus in a range like that determined experimentally for the homologue ethyl acetate of 500 µg/cm^2 and hour (Hartwig and MAK Commission 2019).

After exposure at the level of the MAK value, 1200 mg is absorbed. Thus, absorption through the skin represents more than 25% of the systemically tolerable amount, and the substance is therefore designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are no data available for sensitization. The substance is therefore not designated with either "Sh" (for substances which cause sensitization of the skin) or "Sa" (for substances which cause sensitization of the airways).

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (https://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/conflicts_interest/index.html) ensure that the content and conclusions of the publication are strictly science-based.

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