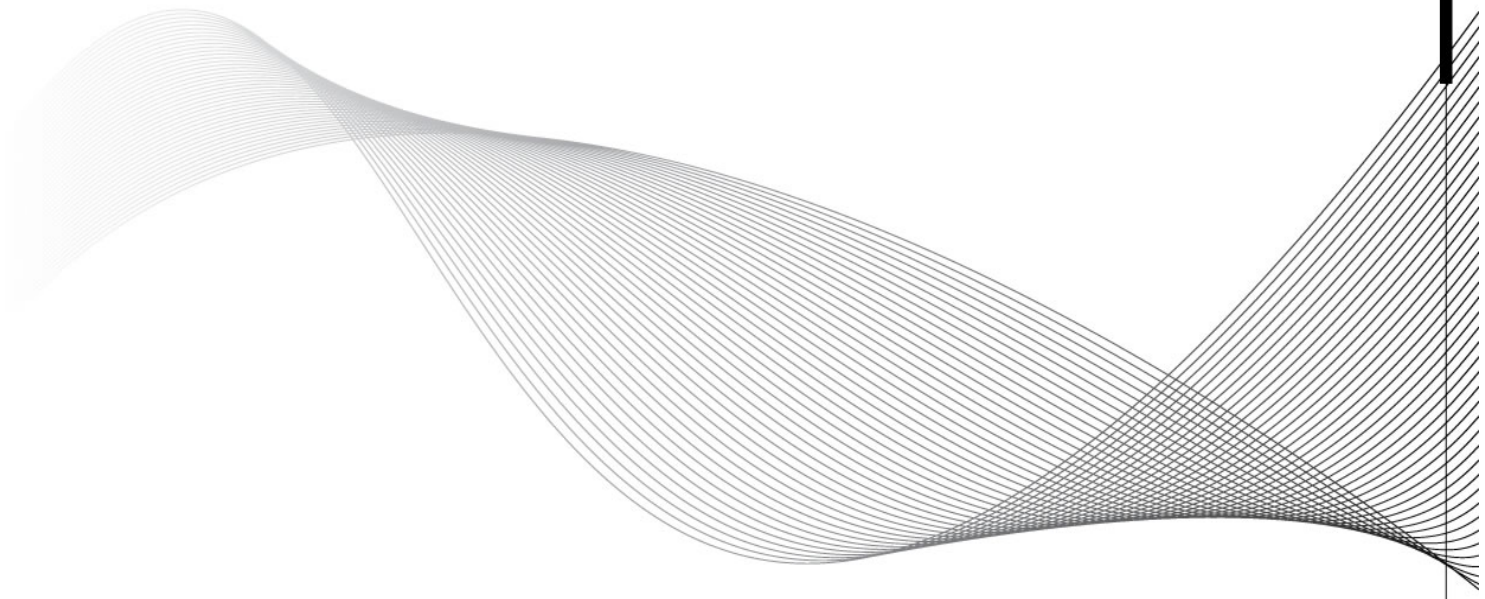
Social Europe



Recommendation from the Scientific Committee on Occupational Exposure Limits for methyl formate

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8 hour TWA	:	50 ppm (125 mg/m^3)
STEL (15 mins)	:	100 ppm (250 mg/m^3)
Notation	:	"skin"

Substance:

Methyl formate H-CO-O-CH_3

Synonyms : Formic acid methyl ester, methanoic acid methyl ester
EINECS N° : 203-481-7
EEC N° : 607-014-00-1
CAS N° : 107-31-3
MWt : 60.05

Conversion factor (20°C, 101 kPa) : 2.50 mg/m^3 = 1 ppm

Classification: F+; R12
Xn; R20/22
Xi; R36/37

1. Occurrence/use

Methyl formate is a colourless liquid with a pleasant ethereal odour. It has a MPt of -99°C, a BPt of 32°C and a vapour pressure of 644 hPa at 20°C. The vapour density is 2.1 times that of air and it is explosive in the range of 5 - 23% in air. Quoted values for the odour threshold range from 600 to 2000 ppm (1500 to 5000 mg/m3).

Methyl formate is used as a solvent and chemical intermediate and as an insecticide and larvicide. It is a component of cigarette smoke and coffee. Production rates in the EC are in excess of 10,000 tonnes per annum.

2. Health Significance

Methyl formate is absorbed through the lungs (Schrenk *et al.*, 1936). The death of a 19-month-old child after occlusive application of a methyl formate insecticide on the scalp for 20 min indicates a good penetration of methyl formate through the skin (Gettler, 1940). Acute intoxications were also reported in sick children after application of alcohol-soaked (methanol or ethanol) cloth on the abdominal area (Giménez et al. 1968).

The metabolism of methyl formate is thought to occur by hydrolysis to methanol and formic acid, either nonenzymatic or by esterases present in plasma, liver and other tissues. Besides hydrolysis, oxidative ester cleavage has been shown to occur and methyl formate is biotransformed to formaldehyde and formic acid by oxidation with cytochrome P450 enzymes (Nihlén and Droz 2000). Methanol is also converted via formaldehyde to formate. The higher sensitivity of man and monkeys to methanol poisoning compared to rats and mice (Johlin *et al.*, 1987) is related to the accumulation of formic acid, leading to acidosis (Sejersted *et al.*, 1983) due to lower ability to metabolize formate to carbon dioxide. The rate of formate oxidation is related to hepatic tetrahydrofolate (T_4folate) content and the activities of folate-dependent enzymes. In human liver, H_4folate levels were only 50 % of those observed for rat liver and similar to those found in monkey liver. Total folate was also lower (60% decreased) in human liver than that found in rat or monkey liver. In addition, 10-formyltetrahydrofolate dehydrogenase activity, the enzyme catalyzing the final step of formate oxidation to carbon dioxide, was markedly reduced in both monkey and human liver (33 and 23 nmol/min/mg protein) compared to rat liver (88.3 nmol/min/mg protein). Thus two mechanisms may be operative in explaining low formate oxidation (detoxification) in species susceptible to methanol toxicity (Johlin *et al.*, 1987).

Acute exposure to methyl formate has been investigated in experimental animals. Schrenk *et al*. (1936) reported the effects of methyl formate vapour on the guinea pig after up to 8h exposure. Nasal irritation occurred after 5 mins at 1500 ppm (3750 mg/m^3). Effects such as eye irritation, lachrymation, etching, slow deep respiration, incoordination, narcosis and uncoordinated scratching occurred with increasing concentrations and exposure times. Death occurred after 150-175 mins exposure to 10,000 ppm (25,000 mg/m^3) and 25-35 min exposure to 50,000 ppm (125,000 mg/m^3). Similar data were reported by Nuckolls (1933).

The oral LD_{50} value in rats was reported to be 1500 mg/kg body weight, the dermal LD_{50} for rats to be more than 4000 mg/kg body weight (ECB, 2000).

Five male and female Wistar rats per group were exposed whole-body to methyl formate vapours in concentrations of 0, 100, 500 or 1500 ppm for 2 weeks (6 h/d, 5 d/week). During the whole study period no clinical signs of toxicity were observed in exposed animals. In test group 1 (100 ppm) no treatment-related findings were observed. In test group 2 (500

ppm) multifocal degeneration of the olfactory epithelium of the nasal cavity (minimal to slight) was evident in one male and two females. Animals of test group 3 (1500 ppm) showed reduced body weight changes in males and females, multifocal degeneration of the olfactory epithelium of the nasal cavity in all animals (a mixture of disarrangement and degeneration of olfactory cells, partly necrotic), multifocal squamoid metaplasia of the olfactory epithelium of the nasal cavity in 2 males and 4 females and multifocal inflammatory cell infiltration in 5 males and 4 females. Under the conditions of this study, the NOAEL for methyl formate is 100 ppm (BASF AG, 2003). A 13-week study with methyl formate is not available. However, 2- and 13-week studies are available with formic acid, which is suspected to be the metabolite responsible for the toxic effects in the olfactory epithelium after methyl formate exposure. The inhalation studies with formic acid have shown that the NOAEL from the 13-week inhalation study is 16 ppm, half of the NOAEL from the 2-week study with 31 ppm (NTP, 1992). Accordingly, a NOAEL for methyl formate after 13-week inhalation may be about 50 ppm, half of the NOAEL from the 2-week study.

Twenty human volunteers (10 males and 10 females) were exposed to 100 ppm methyl formate for 8 h in an exposure chamber. The same number of subjects with the same ages (between 20 and 30 years), gender and educational level (university) were examined by the same procedure as a control group. The subjects did not know if they were exposed or not. Three times (morning, noon, evening) during these 8 h, mood, neurobehavioral performance, vision and postural sway were tested. During an undemanding test and a demanding performance task, pulse electromyography (EMG) of the forehead and of the neck were recorded. In the morning and evening spirometry and the odour perception threshold were measured. In the evening, relative fatigue (measured by the Profile of Mood States) was significantly increased in the exposed group and the EMG at the front muscle of the forehead (not at the left neck muscle) during a demanding task showed a different development during exposure compared to controls (decrease in the morning and evening, increase at noon). The other tests showed no significant solvent effect, but 16 of 43 test parameters showed a significant effect of time. The authors conclude that the results of this study indicate a possible effect of methyl formate exposure on the subjective feeling of fatigue after 8 h exposure at 100 ppm in young and healthy subjects, without measurable impairment of neurobehavioural performance (Sethre *et al*., 1998 a, 2000 a).

Neurobehavioural function was assessed in 23 male foundry workers at the end of a working shift (three shifts per day). Personal exposure to methyl formate (median 68 ppm; range 22 to 136 ppm) and isopropanol (median 28 ppm; range 6 to 73 ppm), as well as urinary excretion of methanol was monitored. As controls 15 unskilled workers from the printing industry (exposed to "aliphatics"; not further specified) were used. They did not differ significantly from foundry workers in age, life time exposure, alcohol consumption or the time of examination, but they went significantly longer to school. There were no significant differences in test performance between unskilled printers and foundry workers. With respect to the foundry workers, personal solvent dose correlated significantly with several neurobehavioural functions: lateral sway in monopedal and bipedal standing correlated significantly with the exposure to isopropanol and isopropanol in combination with methyl formate. Higher personal exposures to isopropanol and methyl formate correlated significantly with poorer short-term memory. The three highest exposed workers reached only half of the score in the short-term memory test and showed nearly twice as much sway in monopedal and bipedal standing (Sethre *et al.*, 1998 b).

Neurobehavioural effects of isopropanol and methyl formate were further monitored in 10 foundry workers for 15 days. Workers were employed in a one-shift system. No controls were examined. Personal exposure to methyl formate (36 ± 21 ppm) and isopropanol (44 ± 16 ppm) was assessed. Maximum values of personal exposure to isopropanol reached barely the maximal allowable concentration (MAC) value (400 ppm); the methyl

formate personal exposure of three workers exceeded the MAC value (100 ppm). Urine concentrations of methanol were high (3.1 ± 2.3 mg/l in the morning, 7.8 ± 4.9 mg/l after exposure) compared with the results of other studies; concentrations of isopropanol were rather low (0.88 +/- 0.73 mg/l after exposure). Linear correlation was found between personal exposure and biomonitoring. With the neurobehavioural tests used (postural balance, simple reaction time, digit span of the Neurobehavioural Evaluation System (NES2), a combined memory and reaction-time test), no solvent effect in relation to the dose could be determined (Sethre *et al*., 2000 b).

The use of formate and methanol as biomarkers for monitoring methyl formate exposure is difficult because of high individual baseline levels and very large interindividual variability ranging from <1 to 33,4 mg methanol/l urine and from 4.4 to 39.0 mg formic acid/g creatinine (Berode *et al.*, 2000; Nihlen and Droz, 2000). In addition, the amount of metabolites excreted after exposure to 50 ppm methyl formate is relatively low compared to the respective background levels. Excretion of methanol in the urine of volunteers after exposure to 100 ppm methyl formate for 8 hours (see above Sethre *et al*., 1998 a, 2000 a) resulted in a very slight increase of about 1.78 mg methanol/l (Berode *et al.*, 2000). The authors concluded that urinary methanol cannot be used for this purpose. Excretion of formic acid was higher in volunteers (8.9 and 19.4 mg/g creatinine). However, the values obtained before exposure were high (21.35±9.87 and 14.69±7.71 mg/g creatinine for women and men, respectively) and showed high variability (Berode *et al.*, 2000). A relevant dietary uptake of formic acid has not been taken into consideration. Data from methyl formate exposed foundry workers have shown, that an increase in formic acid excretion could be detected in workers exposed to more than 100 ppm methyl formate (Berode *et al.*, 2000). Taking into account a TWA of 50 ppm for methyl formate, biological monitoring of methanol and formic acid is not feasible. Information about the possibility to use methyl formate itself as a biomarker is not available.

Methyl formate did not induce mutations in *Salmonella typhimurium* with or without metabolic activation (ECB, 2000; Stahl and Kainer, 1991).

Recommendation

In a 2-week inhalation study with Wistar rats, a NOAEL of 100 ppm was established (BASF AG, 2003). According to experiences with formic acid, the NOAEL for a 13-week inhalation study would be expected to be around 50 ppm. A study with human volunteers exposed to 100 ppm methyl formate for 8 hours indicated a possible effect of methyl formate exposure on the subjective feeling of fatigue without measurable impairment of neurobehavioural performance (Sethre *et al*., 1998 a, 2000 a). Due to only minimal subjective effects in volunteers exposed to 100 ppm methyl formate for 8 hours and no effects in workers exposed to 36 ppm methyl formate and 44 ppm isopropanol, the recommended 8-hour TWA is 50 ppm (120 mg/m^3). A STEL (15 mins) of 100 ppm (240 mg/m^3) is proposed to limit peaks of exposure.
The TWA for methanol is 200 ppm. Based on urinary excretion of formic acid as a critical indicator, the data from a toxicokinetic modelling of methyl formate exposure indicated, that a TWA of 200 ppm for methanol would be equivalent to a TWA for methyl formate of no greater than 50 ppm (Nihlén and Droz 2000).
The TWA for formic acid is 5 ppm and was set up to prevent local irritation; this value cannot be used to evaluate systemic effects of formic acid.

A "skin" notation was recommended in view of the reported absorption through the skin.

At the recommended TWA of methylformate difficulties of measurement are not expected.

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