Ethyl formate

(CAS reg no: 109-94-4)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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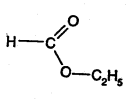
1 Introduction

The present document contains the assessment of the health hazard of ethyl formate by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by KJ van den Berg, Ph.D. (TNO Nutrition and Food Research, Zeist, the Netherlands).

The evaluation of the toxicity of ethyl formate has been based on the review by the American Conference of Governmental Industrial Hygienists (ACG99). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, literature was retrieved from the online data bases Medline, Toxline, and Chemical Abstracts covering the period 1966 to 26 April 1999 (19990426/UP), 1965 to 29 January 1999, and 1967 to 24 April 1999 (19999042/ED), respectively, and using the following key words: ethyl formate, ethyl methanoate, methanoic acid ethyl ester, and 109-94-4. HSDB and RTECS, data bases available from CD-ROM, were consulted as well (NIO99, NLM99). The final literature search has been carried out in April 1999.

In July 2001, the President of the Health Council released a draft of the document for public review. The committee received no comments.

2 Identity

name	:	ethyl formate
synonyms	:	ethyl methanoate; methanoic acid, ethyl ester; formic acid, ethyl ester; formic ether
molecular formula	:	$C_3H_6O_2$
structural formula	:	
CAS reg no	:	109-94-4

Data from ACG99, NLM99.

3 Physical and chemical properties

molecular weight	:	74.08
boiling point	:	54.3°C
melting point	:	-80°C
flash point	:	-20°C (closed cup)
vapour pressure	:	at 20°C: 25.9 kPa
solubility in water	:	soluble (13.6 g/100 mL)
Log $P_{octanol/water}$	:	0.23
conversion factors	:	1 ppm = 3.1 mg/m^3
(20°C, 101.3 kPa)	:	1 mg/m^3 = 0.32 ppm

Data from ACG99, NLM99, Ric94.

Ethyl formate is a colourless to water-white, unstable liquid (ACG99). An odour threshold of 96 mg/m^3 (31 ppm) has been reported (Amo83).

4 Uses

Ethyl formate is used as flavour for lemonade and essences; as a solvent for nitrocellulose; as a fungicide and larvicide for, amongst others, tobacco, cereals, dried fruits; and in organic synthesis (ACG99, Ric94). In the Netherlands, ethyl formate is not registered for use as a pesticide (CTB01).

5 Biotransformation and kinetics

Ethyl formate is readily absorbed into the blood via the alveoli of the respiratory system.

It is also reported to be absorbed from the gastrointestinal tract and slightly through the skin (Bis93).

With moisture, ethyl formate readily hydrolyses into formic acid and ethanol (Gre98). Enzymatic hydrolysis also occurs. Formic acid is metabolised further by the tetrahydrofolate system to CO_2. Ethanol is metabolised further in the liver to acetaldehyde, acetic acid, and, finally, CO_2, by alcohol dehydrogenase, aldehyde dehydrogenase, and the tricarbonic acid cycle, respectively (Gre98).

6 Effects and mechanism of action

Human data

Without presenting details, it was stated that human exposure to 330 ppm ethyl formate (~1000 mg/m^3) resulted in a slight irritation of eyes and nose, persisting for at least 4 hours (Flu31). Exposure to 10,500 ppm (32,500 mg/m^3) is reported to cause moderate, but progressive, irritation of eyes and nose (Gre98).

Dermal application of 4% ethyl formate under occlusion did not result in signs of irritation in human volunteers (Gre98).

It is estimated that occupational exposure to 100 ppm (300 mg/m^3) does not lead to metabolic acidosis caused by accumulation of acidic metabolites (Gre98).

Animal data

Acute toxicity

Exposure of mice and cats to ethyl formate at concentrations of 500 ppm (1600 mg/m^3) and 10,000 ppm (31,000 mg/m^3) for 20 min, caused eye irritation and dyspnea. In dogs, pulmonary oedema was observed after exposure to 10,000 ppm (31,000 mg/m^3) ethyl formate for 4 hours (Flu31). In acute inhalation studies using guinea pigs and frogs, ethyl formate (concentration unknown) was reported to be irritating to mucous membranes (ACG99).

In rabbits, liquid ethyl formate has been found irritating to the eyes (scoring an injury grade of 4 on a scale of 1 to 10, indicating a so-called 'severe burn' from 0.02 mL undiluted material; see also Car46), but not to the skin (scoring an injury grade of 1, indicating 'the least visible capillary injection' from undiluted material) (Smy54).

No studies were found on the sensitising potential of ethyl formate.

Following exposure of rats to 8,000 ppm (24,000 mg/m^3) ethyl formate for 4 hours, 5 out of 6 animals died. When exposed to saturated vapour*, 5 minutes was the maximum exposure duration which did not induce mortality (Smy54). Deaths were reported in cats and in dogs, following exposure to 10,000 ppm (31,000 mg/m^3) ethyl formate for 80 minutes and 4 hours, respectively (Flu31). Citing studies

* The (theoretic) concentration in saturated air can be calculated using the formula: (vapour pressure in Pa x 10^6 ppm)/10^5 Pa. Using a vapour pressure of 25,900 Pa, the committee estimates that these animals could have been exposed to, at most, 259,000 ppm or (roughly) 800,000 mg/m^3.

from the 1930s, it was stated that concentrations of 12,800 to 41,600 ppm (40,000-130,000 mg/m^3) (duration not presented) caused marked nervous system depression and, frequently, development of pneumonia in rabbits and guinea pigs while in guinea pigs, air saturated with ethyl formate vapours resulted in tremors, progressive CNS depression, and death from circulatory and respiratory failure within a few minutes (Oet59).

The dermal LD_{50} of ethyl formate in rabbits is reported to be over 20 mL/kg bw (> 18,000 mg/kg bw) (Smy54).

Oral LD_{50}s of 1850 and 4290 mg/kg bw have been reported in rats (Jen64, Smy54).Toxic signs observed include CNS depression within 5-10 minutes, and laboured respiration, while mortality occurred within a period of 15 minutes to 2 hours (Jen64). In guinea pigs, the oral LD_{50} was 1110 mg/kg bw. CNS depression and irritation of the gastrointestinal tract were observed, and deaths occurred within 10 minutes to 2 hours (Jen64). In rabbits, an oral (gavage) LD_{50} of 2070 mg/kg bw is reported (observation time: 24 h). The ND_{50} (*i.e.*, the narcotic dose or the dose producing stupor, loss of voluntary movements in half of the animals) was estimated to be 2070 mg/kg bw as well (Mun72).

Repeated dose toxicity

In a range-finding experiment preceding testing its carcinogenicity in mice (A/He) (see below), the maximum tolerated dose of ethyl formate following 6 intraperitoneal injections over a 2-week period was found to be 500 mg/kg body weight (Sto73).

Groups of Osborne Mendel rats (n=10/sex/group) were exposed to doses of ethyl formate of 1000, 2500, and 10,000 mg/kg diet (approximately equivalent to 0, 50, 150, and 500 mg/kg bw) for 17 weeks. At the termination of the study, there were no changes in body weight gain, organ weights, or histology of major organs. No further details were reported. Considering the volatility of ethyl formate, administration through feed will not be an appropriate way of administration. No details were given on the stability on ethyl formate in the feed although for other componds tested losses of up to 30 (or incidentally up to 58) percent over a 7-day period occurred (Hag67).

A/He mice (n=15/sex/dose) received intraperitoneal injections thrice weekly, for 8 weeks, followed by a 16-week follow up, resulting in total doses of ethyl formate of 2400 or 12,000 mg/kg bw. From preceding experiments, the latter dose was calculated to be the maximum tolerated dose (see above). Emphasis was on

the occurrence of pulmonary tumours (expressed as number of mice with lung tumours and number of lung tumours per mouse), but other organs and tissues, such as liver, kidney, spleen, thymus, intestine, and salivary and endocrine glands, were also examined. No increase in tumour incidence was observed in the lungs or any of the other.organs examined However, no further details were given (Sto73). The committee judges the study as insufficient to draw any conclusion on the carcinogenic potential of ethyl formate.

Mutagenicity and genotoxicity

No mutagenic activity of ethyl formate was observed in the bacterial strains *S. typhimurium* TA1535, TA1537, TA1538 and in the yeast *S. cerevisiae* (Lit76).

Ethyl formate is not reported to give mitotic chromosomal loss and duplication ('malsegregation') in the yeast *S. cerevisiae* (Liu97, Zim85).

Reported in an abstract, there was an increase in the rate of lethal mutations (4.7% ± 1.6% *vs* 0.5% ± 0.3% in controls) in the second pair of autosomes of males, following treatment of fertilised eggs from *D. melanogaster* with an unknown concentration of ethyl formate vapour, for 5 to 20 minutes in a moist sealed chamber. A very high mortality (only 7.5% developed into fertile males) was observed in the treated eggs (Alt56).

Reproduction toxicity

No teratogenicity was found in the developing chicken embryo test at a concentration of ethyl formate of 25 mg per egg (Ver80).

No other data from animal studies were found on the reproduction toxicity potential of ethyl formate.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for ethyl formate in the Netherlands is 100 ppm (300 mg/m^3), 8-hour TWA.

Existing occupational exposure limits for ethyl formate in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

In man, it was stated that exposure to concentrations of ethyl formate of 330 ppm (1000 mg/m^3) and higher were slightly irritating to the eyes and nose, but the significance of this finding could not be assessed due to limited reporting. Ethyl formate is not irritating to the human skin.

In experimental animals, ethyl formate was found to be irritating to the eyes and the lungs, but not to the skin. No studies on potential sensitisation were found.

In acute inhalation studies, ethyl formate caused lethality in 5 out of 6 rats at a concentration of 8,000 ppm (24,000 mg/m^3). No LC_{50} values were found. Signs of toxicity included depression of the central nervous system (CNS) and respiratory and circulatory effects. The dermal LD_{50} in rabbits is greater than 20 mL/kg bw (or 18,000 mg/kg bw). Oral LD_{50} values of 1110, 1850, and 2070 mg/kg bw were reported for guinea pigs, rats, and rabbits, respectively. CNS depression, laboured respiration, and irritation of the gastrointestinal tract were observed.

Ethyl formate did not induce mutations in bacteria or yeast or chromosome damage in yeast, but caused a positive response in an old, not standardised mutation assay in *Drosophila*.

The committee did not find adequate data on repeated dose toxicity (including those on carcinogenicity and reproduction toxicity) or on genotoxicity tests in mammalian cell systems *in vitro* or in mammals *in vivo*.

The committee concludes that there are no adequate data to derive a health-based occupational exposure limit. However, following and in line with the approach by the German MAK-Kommission (Gre98)*, the risk of effects due to accumulation of metabolites and of metabolic acidosis due to exposure to the current MAC value of 300 mg/m^3 can be assessed. Assuming a 70-kg worker inhales 1.25 m^3 during one working hour and retention is 100%, exposure to 300 mg/m^3 of ethyl formate will result in an hourly uptake of 375 mg (5.06 mmol) or 5.4 mg (0.072 mmol)/kg bw. Assuming hydrolysis is complete, this implies the uptake of equimolar amounts of ethanol and formic acid. For the conversion of formic acid into carbon dioxide, the metabolic rate in primates is reported to be 0.75 mmol/kg bw/hour. For ethanol, the elimination rates are 1.15 and 1.35 mmol/kg bw/hour in women and men, respectively. From these figures, it can be seen that

* Figures presented in the following lines are reproduced from Gre98.

accumulation of metabolites will not occur. Assuming a human blood volume of 4.5 L, the aforementioned hourly uptake of 375 mg or 5.06 mmol of ethyl formate will result in blood levels of formic or acetic acid of 1.12 mmol/L or of 2.24 mmol H^+-ions/L, assuming a complete dissociation of these acids. This leads to a decrease in the blood bicarbonate level from 24 to 21.76 mmol/L. Using the Henderson-Hasselbalch equation and taking a pK value for bicarbonate of 6.1 and a concentration of nondissociated acid in open systems of 1.2 mmol/L, it can be calculated that this will cause a blood pH value of 7.38 which is at the low end of the normal physiological blood pH-range of 7.37-7.46. In these calculations, the extracellular space and other physiological buffering systems are not taken into consideration, and a one-hour bolus intake is assumed. Therefore, overloading of the buffer capacity of the body and, subsequently, a metabolic acidosis is not expected.

The committee considers the toxicological data base on ethyl formate too poor to justify recommendation of a health-based occupational exposure limit.

The committee concludes that no accumulation of metabolites or metabolic acidosis are expected to occur at the present MAC-value, and hence that the current MAC value is about right with respect to systemic effects.

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Annex

Occupational exposure limits for ethyl formate in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	lit ref[b]
	ppm	mg/m^3				
The Netherlands						
- Ministry of Social Affairs and Employment	100	300	8 h	administrative		SZW01
Germany						
- AGS	100	300	8 h			TRG00
	100	300	15 min			
- DFG MAK-Kommission	100	310	8 h	MAK	S; [d]	DFG01
	100	310	15 min[c]			
Great Britain						
- HSE	100	308	8 h	OES		HSE01
	150	402	15 min			
Sweden	-	-				Arb00b
Denmark	100	300	8 h			Arb00a
USA						
- ACGIH	100	303	8 h	TLV		ACG01
- OSHA	100	300	8 h	PEL		ACG00
- NIOSH	100	300	10 h	REL		ACG00
European Union						
- SCOEL	-	-				CEC00

[a] S = skin notation; which means that skin absorption may contribute considerably to the body burden; sens = substance can cause sensitisation

[b] Reference to the most recent official publication of occupational exposure limits

[c] Maximum frequency per shift: 4, with a minimum interval between peaks of 1 hour

[d] Classified in pregnancy risk group C, *i.e.*, there is no reason to fear a risk of damage to the embryo or fetus when MAK and BAT (Biological Tolerance Value for Working Materials) values are observed