Methyl acetate

(CAS No: 79-20-9)

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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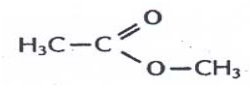
1 Introduction

The present document contains the assessment of the health hazard of methyl acetate 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 AAE Wibowo, Ph.D. (Coronel Institute, Academic Medical Centre, Amsterdam, the Netherlands).

In October 1997, literature was searched in the databases Medline, Toxline, Chemical Abstracts, and Embase, starting from 1966, 1967, 1970, and 1988 respectively, and using the following key words: methyl acetate and 79-20-9. Also the CD-ROMs HSELINE, CISDOC, MHIDAS, and NIOSHTIC were consulted (from 1997 backwards). The final literature search was carried out in Toxline and Medline in October 2003.

In October 2003, the President of the Health Council released a draft of the document for public review. No comments were received.

2 Identity

name	:	methyl acetate
synonyms	:	acetic acid, methylester; methyl acetic ester; methyl ethanoate
molecular formula	:	$C_3H_6O_2$
structural formula	:	
CAS number	:	79-20-9

3 Physical and chemical properties

molecular weight	:	74.08
boiling point	:	56-58°C
melting point	:	-98°C
flash point	:	-10°C (closed cup): -5.6°C (open cup)
vapour pressure	:	22 kPa
solubility in water	:	soluble (at 20°C: 24-25 g/100 mL)
log $P_{octanol/water}$	:	0.18 (experimental); 0.35 (estimated)
conversion factors	:	at 20°C, 101.3 kPa: 1 mg/m^3 = 0.32 ppm 1 ppm = 3.09 mg/m^3

Data from BGC96.

Methyl acetate is a highly volatile, colourless liquid with a rather pleasant odour. The vapour is heavier than air and may travel along the ground.

Olfactory thresholds varying from 0.5 to 610 mg/m^3 (0.16-195 ppm) have been reported. In another experiment with an unknown number of volunteers, the lower (i.e., odour perception by one volunteer) and the upper (i.e., odour perception by all volunteers) were 610 and 915 mg/m^3 (195 and 290 ppm), respectively (BGC96).

4 Uses

Methyl acetate is used in paint removers, as a solvent for cellulose esters in the production of artificial leather and plastics and for lacquers, and as a flavouring agent (perfumes) (BGC96, Lun91).

5 Biotransformation and kinetics

The respiratory uptake defined as ($C_{inhaled\ air} - C_{mixed\ exhaled\ air}$)/$C_{inhaled\ air}$ x 100% for methyl acetate was determined by exposing 4 healthy male volunteers to ca. 300 mg/m^3 (100 ppm) methyl acetate at rest for 10 minutes. The percentage solvent in end-exhaled air and in mixed-exhaled air increased after the start of the exposure and reached a quasi-steady-state level within a few minutes. The mean respiratory uptake for the last 5 minutes of methyl acetate respiration was ca. 60%. Methanol, its metabolite, was detected in exhaled air (concentration: 1.3 ppm) at the first minute reaching a quasi-steady state level of 3 ppm at the 5th minute, and suggesting removal of the solvent by metabolism in the wall tissue of the respiratory tract (Kum99).

In vivo human and experimental animal and *in vitro* data showed that biotransformation of methyl acetate takes place by rapid hydrolysis of the compound into methanol and acetic acid by the non-specific carboxylic esterases in the blood and tissues such as respiratory tract (nasal turbinates), liver, and small intestine (BGC96, Gre99, Gre01, Lun91). In rats (n=2/sex/time point) sacrificed 30, 60, and 120 minutes and 18 hours after the last exposure to 6180 mg/m^3 (2000 ppm), 6 hours/day, 5 days/week, for 28 days, blood methyl acetate concentrations were less than 5 ppm (Hof99) while methyl acetate was detected in the blood of rats sacrificed 10 to 20 minutes after exposure to high, probably saturated, concentrations of methyl acetate (BGC96). Hydrolysis may occur already in the upper respiratory tract: *in vitro* using rat nasal ethmoturbinates, a hydrolysis rate of 15 (± 3) nmol/mg S9-protein/min was estimated (Dah87). Nasal respiratory carboxylesterase activity in rat was demonstrated to be about 3

-fold higher that in man while the olfactory activity was similar (Bog98). Methanol is metabolised into formaldehyde, formic acid, and carbon dioxide, and acetic acid via the citric cycle to carbon dioxide and water, but there are differences between rodents and primates (man and monkeys). In primates, the oxidation of formic acid into carbon dioxide is rapidly saturated leading to accumulation of formate in the blood. Methanol is distributed rapidly and evenly to all tissues of the body in amounts depending on their water content (BGC96, Gre99, Gre01, Lun91). Exposure of 2 male volunteers to methyl acetate vapours with an average concentration of 618 mg/m^3 (200 ppm), 2 hours, twice a day, for 3 days, resulted in increasing urinary methanol concentrations of generally 8 to 23 mg/L. Next morning, concentrations were returned to 'normal' (below 5 mg/L). In the course of repetitive exposures, the normal level seems to be raised slightly day by day in each subject, which indicates some accumulation of methanol. Similar values were observed after exposure to vapour concentrations of methanol of 200 ppm (Tad74).

Since the hydrolysis is catalysed by the rather non-specific carboxylic esterases, interference may occur by other compounds while the metabolism of methanol can be retarded by preceding or concomitant ethanol consumption.

6 Effects

Human data

Methyl acetate (10%) was reported to be neither irritating in 48-hour patch tests nor sensitising in a maximisation test using 25 volunteers (no more data presented; unpublished report submitted to the Research Institute for Fragrance Materials - RIFM -, Inc, Englewood Cliffs NJ, USA, cited by Opd79). Citing a 1933 report, 5-minute exposures to concentrations of methyl acetate of 15,000 or 30,000 mg/m^3 (4800 or 9600 ppm) were stated to cause mild, transient irritation of the throat and trachea in 2 out of 4 volunteers. No such effects occurred at exposure to 1000 mg/m^3 (320 ppm) (BGC96). Tada et al. did not report irritation when exposing 2 volunteers to 618 mg/m^3 (200 ppm), for 2 hours, twice a day, for 3 to 4 days (Tad74). No irritation of the throat was experienced in a respiratory uptake study in which 4 healthy male volunteers were exposed through a mouthpiece to ca. 300 mg/m^3 (100 ppm) methyl acetate for 10 minutes (Kum99).

Apart from an increase in deviations from the 30-second time estimations in the afternoon, Nakaaki did not observe a significant difference in time perception (estimation of length of time intervals of 5, 10, and 30 seconds, carried out every

30 minutes) in 2 male volunteers exposed to methyl acetate concentrations of 503 to 885 mg/m^3 (160-283 ppm; average: 656 mg/m^3 or 210 ppm), for 2 x 2 hours/day, for 4 days, when compared to control values obtained in a similar experiment with other solvents. The experiment was repeated twice (Naa74).

A case describing recurrent dizziness, headaches, fatigues, faintness, staggering, and total blindness during one of the attacks in a 69-year-old worker exposed to unknown levels of methyl acetate vapours has been reported. During the subsequent period, sight returned, deteriorated severely, and improved somewhat, and, eventually, atrophy of the optic nerve and changes in the field of vision were diagnosed. The optic nerve damage was attributed to the metabolites methanol or formic acid (BGC96, Lun91). Other cases of eye irritation, visual disturbances, and central nervous system depression were reported (Koh89, Oga88; see BGC96 for review), but in all these cases there was exposure to - mostly unknown concentrations of - mixtures of solvents among which methyl acetate and methanol. These data suggest that methyl acetate may induce optic nerve atrophy probably via its metabolite methanol for which these effects are well known. However, the data do not indicate at which levels visual disturbances can be expected.

Animal data

Irritation and sensitisation

Instillation of 0.1 mL of neat methyl acetate into the eyes of rabbits (n=4) was concluded to be moderately irritating based on a maximum Draize score of 39 (maximum possible score: 110) determined at 24 hours (Ken89). In separate Draize tests, a comparable score (i.e., 39.5) was found in one test following instillation of 0.1 mL 98% pure methyl acetate (Bag92) while instillation of 100 mg methyl acetate cause moderate irritation after 24 hours in the other test (BGC96). Testing according to the OECD guideline 405 showed methyl acetate (0.1 mL; purity: 99.9%) to be irritating to the eyes of rabbits. Conjunctival swelling with white mucus discharge, half closed eyelids with marked hyperaemia, reddened irises, and diffuse corneal clouding were seen 1 to 72 hours and white-stained and bleeding conjunctiva and detached sections 24 to 72 hours after instillation. Seven days after instillation, all 3 rabbits were free from irritant effects (unpublished study cited in BGC96). Finally, following instillation of 5 µL of undiluted compound, methyl acetate was scored an injury grade of 5 (i.e., causing a ‘severe burn’) on a scale from 1 to 10 (Smy54, Smy62).

When tested for skin irritation according to OECD guideline 404 (4-hour semi-occlusive application), methyl acetate (purity: 99.9%) was concluded to be not irritating. Very mild erythema was observed 30 min to 24 hours after removal of the patch while dry rough skin was seen in 1/3 rabbits 24 to 72 hours after removal. All animals were free of irritant effects 48 hours after removal (unpublished study cited in BGC96). Application of 0.01 mL undiluted ester to the clipped skin of rabbits (n=5) caused an injury grade of 1 (i.e., no irritation*) on a scale from 1 to 10 (Smy62). In 3 other studies in rabbits, application of 2 mL to the clipped skin, 24-hour occlusive application to the intact and scarified skin, and 24-hour application of 20 mg (Draize test) were found to cause erythema, to be mildly irritating, and to be moderately irritating, respectively (BGC96).

The committee did not find data from skin sensitisation studies in experimental animals.

The sensory irritation in the upper part of the respiratory was studied by determining the concentration associated with a 50% decrease in the respiratory rate (RD_{50}). Using (probably ten male Swiss OF1) mice, the RD_{50} for methyl acetate was reported to be 2512mg/m^3 (803 ppm) (Mul84; see also Bos92).

Acute toxicity

Four-hour exposures to nominal concentrations of 49,440 and 98,880 mg/m^3 (16,000 and 32,000 ppm) caused mortality in 0/6 and 6/6 rats, respectively (observation period: 14 days) (Smy62). Data on acute effects following single exposure to methyl acetate vapours in mice and cats are summarised in Table 1.

Table 1 Acute effects in mice and cats following single exposure to methyl acetate vapours (cited in BGC96, Bis94)[a].

species[b]	concentration (g/m^3)	duration	effects
mouse	15	20 min	no effects
	24	ca. 6 h	irritation, dyspnoea, narcosis in 1/2; recovery after 6 h
	34	ca. 3.5-5 h	eye irritation, fatigue, dyspnoea, narcosis; mortality (10 h post-exposure)
	42	ca. 1-1.5 h	eye irritation, dyspnoea, narcosis; recovery
	63	52-61 min	eye irritation, dyspnoea, narcosis; mortality in 2/2 (within 3 h post-exposure)
	80	31-42 min	moderate eye irritation, narcosis; mortality in 2/2 (within 3 h post-exposure)
	105	31-46 min	eye irritation, dyspnoea, narcosis; mortality in 2/2 (within 1.5 h post-exposure)
	126	23-35 min	irritation, dyspnoea, convulsions, narcosis, mortality in 2/2 (within 3 min post-exposure)

* Smyth et al. characterised grade 1 elsewhere as giving rise to ‘the least visible capillary injection’ (Smy54).

	147	25-27 min	irritation, paralysis, convulsions, dyspnoea, pronouncedly slowed breathing, narcosis; recovery
	168	10-20 min	immediate irritation, dyspnoea, narcosis, mortality in 2/2 from pulmonary oedema
cat	15	20 min	eye irritation, salivation; recovery
	30	ca. 10 h	eye irritation, dyspnoea, salivation, somnolence; recovery
	56	ca. 4-5 h	eye irritation, dyspnoea, salivation, vomiting (in 1/2), convulsions (in 1/2), narcosis; recovery
	67	ca. 1-3 h	eye irritation, dyspnoea, salivation, convulsions, narcosis, mortality in 2/2
	95	29- 41 min	eye irritation, salivation, dyspnoea, narcosis; mortality in 2/2 (within 50 min post-exposure)
	106	30 min	eye irritation, salivation, vomiting, dyspnoea, narcosis, mortality in 2/2 (within 5 min post-exposure)
	134	10-20 min	eye irritation, salivation, dyspnoea, convulsions, narcosis, mortality in 1/2 (within 5 min postexposure)
	163	14-28 min	eye irritation, salivation, dyspnoea, convulsions, narcosis, mortality in 2/2 (within 9 min post-exposure)

[a] Results of experiments by Flury and Wirth published in 1933.
[b] 2 animals of unknown sex/group were exposed.

At autopsy of the treatment-related deaths, there were no characteristic findings in mice while slight respiratory tract effects (pulmonary emphysema; mucous membrane reddening) were seen in several cats (BGC96, Bis94).

Dermal application of a single dose of methyl acetate (purity: 99.9%) of 2000 mg/kg bw according to OECD Guideline 402 ('limit test') did not induce mortality, clinical signs, effects on body weight gain, or macroscopic changes in male and female Wistar rats (observation period: 14 days) (unpublished study cited in BGC96). Referring to another unpublished report, the dermal LD_{50} in rabbits was stated to be >5000 mg/kg bw (BGC96).

Following single oral administration, LD_{50} values of 6970 mL/kg bw (ca. 6482 mg/kg) and 3700 mg/kg bw were determined for rats (Smy62) and rabbits (Mun72), respectively. In rabbits, the ND_{50} (narcotic dose; i.e., the dose producing stupor, loss of voluntary movements in half of the animals) was ca. 3260 mg/kg bw (44 mMol/kg) (Mun72).

Repeated-dose toxicity

In a preliminary, range-finding study, rats (Hsd: Sprague Dawley SD; n=3/sex/group) were exposed nose-only to concentrations of methyl acetate (purity: >99.5%) of 100, 500, or 2000 ppm (309, 1545, 6180 mg/m^3), 6 hours/day (4 hours on day 5), for 5 consecutive days. No signs of toxicity were observed.

Toxic effects were limited to the high dose group and included impaired body weight gain and nasal lesions (in 1/3 males and 3/3 females) (Hof99).

In the subsequent study performed according to OECD guideline 412, rats (n=10/sex/group) were exposed nose-only to nominal concentrations of 0, 75, 350, and 2000 ppm, 6 hours/day, 5 days/week, for 28 days. An additional group of 10 animals per sex were exposed to 2000 ppm to characterise the elimination kinetics of methyl acetate by sampling blood immediately to 18 hours after the last exposure (n=2/sex/time point). Actual, measured mean concentrations were 0, 79, 335, and 2018 ppm (0, 244, 1035, and 6236 mg/m^3). No compound-related mortality or clinical signs (including neurological disturbances) were seen in any of the exposed groups. In the high-concentration group, a moderately, statistically significantly decreased body weights (by 10%) were found in the male animals throughout the study while in females, body weights were slightly lower being statistically significant at days 3 and 10 in the 'kinetics' group. Food consumption was decreased for both sexes. Haematology, clinical chemistry, and urinalysis examinations revealed statistically significant increases in erythrocyte count, haemoglobin, and haematocrit values (by 4-6%) and decreases in leukocyte count in males (by 34%) and females (by 25%) of the high-concentration group. Serum cholesterol values were statistically significantly decreased in females of all dose groups (by 7, 9, and 22% in the low-, mid-, and high-concentration group, respectively) and in the males of the high-concentration group (by 19%) while calcium concentrations were statistically significantly increased in the high-concentration group (males: by 3%, females: by 2%). Some other changes were noted in high-concentration animals (males: increased albumin; females: increased ALAT, increased urine volume, decreased specific weight). Post-mortem examinations of the high-concentration animals showed statistically significantly decreased absolute and relative liver weights in males (by 16 and 12%, respectively), increased absolute and relative adrenal weights in males (by 18 and 19%) and females (by 20 and 24%), and decreased absolute and relative thymus weights in females (by 26 and 18%). Other changes observed were decreased absolute and relative spleen in males (by 16%) and females (by 10 and 8%, respectively) reaching statistical significance for male absolute spleen weights only, and decreased absolute and relative thymus weights in males (by 22 and 13%; n.s.). In the mid-concentration animals, absolute and relative adrenal weights (by 15 and 13%; statistically significant) were increased in females but decreased (by 6 and 8%; n.s.) in males while thymus weights were decreased in females (absolute by 14%; n.s.; relative by 9%, statistically significant) but increased in males (by 9 and 5%; n.s.). No organ weight changes were seen in the low-concentration group. Apart from, mostly

moderate, degeneration and necrosis of the olfactory epithelium of the conchae nasales in 19/20 animals of the high-concentration group, no abnormalities were seen in any other organ or organ system in any other group upon macroscopic and microscopic examination. In the mid-concentration group, there were no changes in haematology, clinical chemistry, or urinalysis parameters (Hof99). From this 28-day inhalation rat study, the committee concludes that 335 ppm (1035 mg/m^3) is a NOAEL, based on slight systemic toxicity (decreased body weights, changes in liver, adrenals, thymus weights, haematology, clinical chemistry, and urinalysis parameters) and clear damage to the nasal olfactory epithelium found at the next higher concentration of 2018 ppm (6236) mg/m^3.

Carcinogenicity

The committee did not find data on the (potential) carcinogenicity of methyl acetate.

Mutagenicity and genotoxicity

Methyl acetate (purity: 99%) was negative when tested in a pre-incubation assay in *S. typhimurium* strains TA97, TA98, TA100, TA1535, TA1537, and TA1538 both in the absence and presence of a metabolic activation system obtained from induced rat and Syrian hamster livers (concentrations range: 100-10,000 µg/plate; solvent: water) (Zei92). In an unpublished report, methyl acetate (purity: 99.9%) was found negative as well when tested in a plate incorporation assay in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 and in *E. coli* strain WP2 *UvrA* both with and without induced rat liver S9 (concentration range: 4-5000 µg/plate; solvent: DMSO) (BGC96). Methyl acetate (purity: >97%), tested without metabolic activation only at high concentrations (2.91, 3.38, 3.85%), did not induce mutations or mitotic recombinations in *S. cerevisiae* strain D61.M, but strongly induced aneuploidy (Zim85).

In vivo, methyl acetate did not induce a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes obtained from bone marrow of rats (Hsd:Sprague Dawley SD; n=5/sex/group) exposed to (actual) concentrations of 79, 335, and 2018 ppm (244, 1035, 6236 mg/m^3), 6 hours/day, for 28 days (time of sacrifice: 24 h after last exposure) when compared with controls. Treatment did not affect the ratio of polychromatic cells to normochromatic cells (Sta99).

Reproduction toxicity

The committee did not find data from reproduction toxicity studies with methyl acetate in experimental animals.

In an *in vitro* experiment using developing chicken embryos, no teratogenic effects were found (Ver80).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for methyl acetate in the Netherlands is 610 mg/m^3 (200 ppm), 8-hour TWA.

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

8 Assessment of health hazard

Methyl acetate is rapidly hydrolysed into methanol and acetic acid. This may already occur in the respiratory tract and further in the blood and other tissues. Methanol is metabolised via formaldehyde into formic acid and carbon dioxide. Contrary to rodents, the oxidation of formate into carbon dioxide is rapidly saturated in primates leading to formate accumulation in the blood at high methanol exposure and consequently to metabolic acidosis and ocular toxicity. This is supported by some limited information from human cases but there was mostly combined exposure to unknown levels.

Poorly documented human information indicated that liquid methyl acetate is not irritating or sensitising to the skin while irritation of eyes and respiratory tract from exposure to vapours occurred at relatively high levels (≥15,000 mg/m^3 or 4800 ppm). Experimental animal data showed methyl acetate to be irritating to the eyes but only weakly to the skin. Repeated exposure to vapours caused nasal effects at 6236 mg/m^3 (2018 ppm) but not at 1035 mg/m^3 (335 ppm).

Methyl acetate is of low acute toxicity following single inhalation, dermal, and oral exposure. Repeated exposure of rats to concentrations of 244, 1035, or 6236 mg/m^3 (79, 335, 2018 ppm), 6 hours/day, 5 days/week, for 28 days, caused local effects (olfactory epithelial degeneration and necrosis in 19/20 rats) as well as slight systemic effects (small changes in body weights, liver, adrenals, and thymus weights and in haematology, clinical chemistry, and urinalysis parameters) at 6236 mg/m^3 (2018 ppm), but not at 1035 mg/m^3 (335 ppm) (Hof99).

Methyl acetate was not mutagenic in bacteria (*S. typhimurium*) or yeast (*S. cerevisiae*). In yeast, it caused aneuploidy, but no mitotic recombinations, at high concentrations. *In vivo*, no increase in the incidence of micronuclei and no cytotoxicity were observed in bone marrow of male and female rats repeatedly exposed to 6236 mg/m^3 (2018 ppm).

The committee did not find data from chronic (including carcinogenic) or reproduction toxicity studies with methyl acetate.

The committee takes the 28-day inhalation study in rats with a NOAEL of 1035 mg/m^3 (335 ppm) (Hof99) as a starting point for deriving a health-based recommended occupational exposure limit (HBROEL) for methyl acetate. For the extrapolation to a HBROEL, the committee establishes an overall assessment factor of 12. This factor covers the following aspects: inter- and intraspecies variation and differences between experimental conditions and the exposure pattern of the worker. Thus, applying this factor, a preferred value of 100 mg/m^3 (32 ppm) is recommended for methyl acetate.

The committee recommends a health-based occupational limit for methyl acetate of 100 mg/m^3, as an 8-hour time-weighted average.

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Annex

Occupational exposure limits for methyl acetate in various countries

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	200	610	8 h	administrative		SZW03
Germany						
- AGS	-	610	8 h		[d]	TRG00
	-	2440	15 min			
- DFG MAK-Kommission	200	610	8 h		[d]	DFG03
	800	2440	15 min[c]			
Great-Britain						
- HSE	200	616	8 h	OES		HSE02
	250	770	15 min			
Sweden	150	450	8 h			Swe00
	300	900	15 min			
Denmark	150	455	8 h			Arb02
USA						
- ACGIH	200	-	8 h	TLV		ACG03b
	250	-	15 min	STEL		
- OSHA	200	610	8 h	PEL		ACG03a
- NIOSH	200	610	10 h	REL		ACG03a
	250	760	15 min	STEL		
European Union						
- SCOEL	-	-				EC04

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

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

[c] Maximum number 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) are observed.