4-Ethylmorpholine

(CAS reg no: 100-74-3)

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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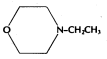
1 Introduction

The present document contains the assessment of the health hazard of 4-ethylmorpholine 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 of the Academic Medical Center, Amsterdam, the Netherlands).

Literature was retrieved from the data bases Medline, Toxline, Embase, and Chemical Abstracts starting from 1966, 1967, 1988, and 1970, respectively, and using the following key words: ethylmorpholine and 100-74-3. HSEline, Cisdoc, Mhidas, and NIOSHtic (covering the period 1985/87 until 1997), data bases available from CD-ROM, were consulted as well. Data considered to be critical were evaluated by reviewing the original publications. The final literature search was carried out in October 1997, followed by an additional search in June 2001.

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	:	4-ethylmorpholine
synonyms	:	*N*-ethylmorpholine
molecular formula	:	$C_6H_{13}NO$
structural formula	:	
CAS no	:	100-74-3

3 Physical and chemical properties

molecular weight	:	115.2
boiling point	:	139°C
melting point	:	-62.8°C
flash point	:	32.2°C (closed cup)
vapour pressure	:	at 20°C: 0.81 kPa
solubility in water	:	soluble
Log $P_{octanol/water}$	:	0.14 (estimated)
conversion factors (20°C; 101.3 kPa)	:	1 mg/m^3 = 0.21 ppm 1 ppm = 4.79 mg/m^3

Data from ACG99, http://esc.syres.com.

4-Ethylmorpholine is a colourless liquid with an ammonia-like odour. It is flammable and a dangerous fire hazard (ACG99). An odour threshold of 6.7 mg/m^3 (1.4 ppm) has been reported (Amo83).

4 Uses

4-Ethylmorpholine is used as a catalyst in the manufacture of urethane foam, as an intermediate for dyestuffs, pharmaceuticals, rubber accelerators and emulsifying agents, as a solvent for dyes, resins, and oils, and as a substrate for enzyme reactions (NLM01).

5 Biotransformation and kinetics

There is no primary data available on the kinetics of this compound. Secondary information reported that the substance can be absorbed by inhalation and through skin contact (Hat91).

6 Effects and mechanism of action

Human data

In an unpublished study cited by ACGIH, irritation to the eyes, nose, and throat, and olfactory fatigue was reported in 10 volunteers when exposed to 479 mg/m^3

(100 ppm) for 2.5 minutes. There were slight and no irritation at 2.5-minute exposures to 240 and 120 mg/m^3 (50 and 25 ppm), respectively (ACG99).

In polyurethane foam workers occupationally exposed to a variety of aliphatic amine catalysts among which 4-ethylmorpholine, (transient) corneal oedema and vision abnormalities have been reported (Der66, Mas65). However, the committee is of the opinion that no conclusions concerning dosis-effect relationships can be drawn. Exposure was to several amines and it was not clear at which levels these effects occurred. In one report (Der66), it was stated that incomplete studies showed that lesions occurrred at "substituted morpholine" levels of 40 ppm or higher, while in another paper (Mas65) it was said that vision distortion was experienced at (not specified) conentrations below those producing eye or respiratory irritation. Furthermore, in unpublished information cited by ACGIH workers exposed to 4-ethylmorpholine levels of generally 3-4 ppm, but never higher than 11 ppm, were reported to complain of drowsiness and visual abnormalities (optical halos, foggy vision) may occur at (ACG99).

Animal data

Smyth *et al*. reported an injury grade of 7 on a scale from 1 to 10 following instillation of 4-ethylmorpholine into the eyes of rabbits (Smy54). Following instillation of one drop of pure 4-ethylmorpholine into the eye of an anaesthetised rabbit, Mellerio and Weale reported blinking reactions, and, after 5 minutes, reddening of the inner surfaces of the lids and the nictating membrane, and further "haziness" of the cornea, irregularities and sloughing of the surface, and general appearance associated with violent desiccation (Mel66).

When tested for its potential skin irritating properties, Smyth *et al*. reported an injury grade of 1 (*i.e.*, giving rise to 'the least visible capillary injection') on a scale from 1 to 10 when 0.01 mL of undiluted 4-ethylmorpholine was applied to the clipped skin of 5 albino rabbits for 24 hours (Smy54).

The committee did not find data on the sensitising potential of 4-ethylmorpholine.

Following exposure of rats to 9580 mg/m^3 (2000 ppm) 4-ethylmorpholine for 4 hours, 1 out of 6 animals died. When exposed to saturated vapour*, 2 hours was the maximum exposure duration which did not induce mortality (Smy54).

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* 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 810 Pa, the committee estimates that these animals could have been exposed to, at most, 8,100 ppm or (roughly) 39,000 mg/m^3.

An oral LD_{50} of 1780 mg/kg bw (range: 1490 - 2120 mg/kg bw) has been reported in rats (observation period: 14 days) (Smy54).

4-Ethylmorpholine was positive when tested in the presence of metabolic activation systems from induced rat or hamster livers in a preincubation assay using *S. typhimurium* strain TA1535 at concentrations of 100-10,000 µg/plate. A negative result was obtained when tested without adding such metabolic activation systems. When tested with and without metabolic activation in strains TA98, TA100, and TA1537, results were negative as well (Zei87). Hedenstedt found 4-ethylmorpholine to be mutagenic upon testing in *S. typhimurium* strains TA100 and TA1535 both in the absence and the presence of a microsomal system obtained from induced rat livers. No other strains were tested. Since the compound itself was not an alkylating agent, an alkylating impurity might have been responsible for the mutagenic effect. This possibility was investigated by testing 4-ethylmorpholine for alkylating properties by means of the reaction with 4-(*p*-nitrobenzyl)pyridine. Since a positive response was obtained with 4-ethylmorpholine in this latter test, an alkylating impurity, possibly ethyleneimine or some derivative of this highly potent mutagenic agent, might have been responsible for the positive response in the former test (no more details presented; only abstract available) (Hed76). Presented in an abstract without further details, 4-ethylmorpholine was stated to be negative when tested at 5 dose levels with and without metabolic activation in the L5178Y mouse lymphoma assay (Con82).

In the same abstract, it was stated that 4-ethylmorpholine was negative as well in the BALB/3T3 transformation assay (Con82).

The committee did not find data on the toxicity, including carcinogenicity and reproduction toxicity, of 4-ethylmorpholine following repeated exposure.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for 4-ethylmorpholine in the Netherlands is 25 mg/m^3 (5 ppm), 8-hour TWA, with a skin notation.

Existing occupational exposure limits for 4-ethylmorpholine in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

The committee did not find adequate human data.

From experimental animal data that are old and not from tests performed according to current guidelines, the committee concludes that 4-ethylmorpholine is severely irritating to the eyes, but not irritating to the skin.

In acute inhalation studies, 4-ethylmorpholine caused lethality in 1 out of 6 rats at a 4-hour exposure to 9580 mg/m^3 (2000 ppm). The oral LD_{50} was 1780 mg/kg bw in rats.

4-Ethylmorpholine induced mutations *in vitro* in *S. typhimurium* but not in mouse lymphoma cells. 4-Ethylmorpholine was negative in the BALB/3T3 transformation assay.

The committee did not find data on the toxicity, including carcinogenicity and reproduction toxicity, of 4-ethylmorpholine following repeated exposure.

The committee considers the toxicological data base on 4-ethylmorpholine too poor to justify recommendation of a health-based occupational exposure limit.

The committee concludes that there is insufficient information to comment on the level of the present MAC value.

References

ACG99 American Conference of Governmental Industrial Hygienists (ACGIH). N-Ethylmorpholine. In: ACGIH. TLVs® and other occupational exposure values - 1999. [CD-ROM]. Cincinnati OH, USA: ACGIH®, Inc, 1999.

ACG00 American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values - 2000. Cincinnati OH, USA: ACGIH®, Inc, 2000: 56.

ACG01 American Conference of Governmental Industrial Hygienists (ACGIH). 2001 TLVs® and BEIs®. Threshold Limit Values for chemical substances and physical agents. Biological Exposure Indices. Cincinnati OH, USA: ACGIH®, Inc, 2001: 32.

Amo83 Amoore JE, Hautala E. Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxicol 1983; 3: 272-90.

Arb00a Arbejdstilsynet. Grænseværdier for stoffer og materialer. Copenhagen, Denmark: Arbejdstilsynet, 2000; (At-vejledning C.0.1).

Arb00b Arbetarskyddstyrelsen. Hygieniska gränsvärden och åtgärder mot luftföroreningar. Solna, Sweden: National Board of Occupational Safety and Health, 2000: 36; (Ordinance AFS 2000/3).

CEC00 Commission of the European Communities (CEC). Commission Directive 2000/39/EC of 8 June 2000 establishing a first list of indicative occupational exposure limit values in implementation ofCouncil Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work. Official Journal of the European Communities 2000; L142 (16/06/2000): 47-50.

Con82 Conaway CC, Myhr BC, Rundell JO, *et al.* Evaluation of morpholine, piperazine and analogues in the L5178Y mouse lymphoma assay and BALB/3T3 transformation assay. Environ Mutagen 1982; 4: 390.

Der66 Dernehl CU. Health hazards associated with polyurethane foam. J Occup Med 1966; 8: 59-62.

DFG01 Deutsche Forschungsgemeinschaft (DFG): Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area. List of MAK and BAT values 2001. Maximum concentrations and biological tolerance values at the workplace. Weinheim, FRG: Wiley-VCH, 2001: 60; (rep no 37).

Hat91 Hathaway GJ, Proctor NH, Hughes JP, *et al.*, eds. In: Proctor and Hughes's chemical hazards of the workplace. 3rd ed. New York, USA: Van Nostrand Reinhold, 1991: 299-300.

Hed76 Hedenstedt A. Mutagenicity screening of industrial chemicals: seven aliphatic amines and one amide tested in the Salmonella/microsomal assay. Mutat Res 1976; 53: 198-9.

HSE01 Health and Safety Executive (HSE). EH40/2001. Occupational Exposure Limits 2001. Sudbury (Suffolk), England: HSE Books, 2001: 18.

Mas65 Mastromatteo E. Recent occupational health experiences in Ontario. J Occup Med 1965; 7: 502-11

Mel66 Mellerio J, Weale RA. Hazy vision in amine plant operatives. Br J Ind Med 1966; 23: 153-4.

NLM01 US National Library of Medicine (NLM). N-Ethylmorpholine. In: Hazardous Substances Data Bank (HSDB) (last revision date N-ethylmorpholine file: 2 February 2000); http://toxnet.nlm.nih.gov.

Smy54 Smyth HF Jr, Carpenter CP, Weil CS, *et al.* Range finding toxicity data. List V. AMA Arch Ind Hyg Occup Med 1954; 10: 61-8.

SZW01 Ministerie van Sociale Zaken en Werkgelegenheid (SZW). Nationale MAC-lijst 2001. The Hague, the Netherlands: Sdu, Servicecentrum Uitgevers, 2001: 27.

TRG00 TRGS 900. Grenzwerte in der Luft am Arbeitsplatz; Technische Regeln für Gefahrstoffe. BArbBl 2000; 2.

Zei87 Zeiger E, Anderson B, Haworth S, *et al.* Salmonella mutagenicity tests: III. Results from testing of 255 chemicals. Environ Mol Mutagen 1987; 9 (suppl 9): 1-110.

Annex

Occupational exposure limits for 4-ethylmorpholine 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	5	23	8 h	administrative	S	SZW01
Germany						
-AGS	-	23			S	TRG00
-DFG MAK-Kommission	-[c]	-[c]				DFG01
Great-Britain						
-HSE	5	24	8 h	OES	S	HSE01
	20	96	15 min			
Sweden	5	25	8 h		S	Arb00b
	10	50	15 min			
Denmark	5	23.5	8 h		S	Arb00a
USA						
-ACGIH	5	24	8 h	TLV	S	ACG01
-OSHA	20	94	8 h	PEL	S	ACG00
-NIOSH	5	23	10 h	REL	S	ACG00
European Union						
-SCOEL	-	-				CEC00

[a] S = skin notation; this means 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] Listed among substances for which studies of the effects in man or in experimental animals have yielded insufficient information for the establishment of MAK values