Ethanethiol

(CAS No: 75-08-1)

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 ethanethiol 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 A Spooren, Ph.D., A Wientjes, M.Sc., and H Stouten, M.Sc. (TNO Nutrition and Food Research, Zeist, the Netherlands).

The evaluation of the toxicity of ethanethiol has been based on the review by the American Conference of Governmental Industrial Hygienists (ACGIH) (ACG91). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in January 1998, literature was searched in the on-line databases Medline, Toxline, and Chemical Abstracts, starting from 1966, 1965, and 1967, respectively, and using the following key words: ethanethiol, ethyl mercaptan, mercaptoethane, thioethanol, thioethyl alcohol, ethyl thioalcohol, ethyl hydrosulfide, and 75-08-1.

In July 2000, the President of the Health Council released a draft of the document for public review. No comments were received.

An additional search in Toxline and Medline in November 2003 did not result in information changing the committee's conclusions.

2 Identity

name	:	ethanethiol
synonyms	:	ethyl mercaptan; mercaptoethane; ethyl hydrosulfide; ethyl sulfhydrate; ethyl thioalcohol; thioethanol; thioethyl alcohol
molecular formula	:	C_2H_6S
structural formula	:	$H_3C\text{-}CH_2SH$
CAS number	:	75-08-1

3 Physical and chemical properties

molecular weight	:	62.13
boiling point	:	35°C
melting point	:	-144°C
flash point	:	-48°C (closed cup)
vapour pressure	:	at 20°C: 59 kPa
solubility in water	:	poorly soluble (at 20°C: 0.7 g/100 mL)
log $P_{octanol/water}$	:	1.27 (estimated)
conversion factors	:	at 20°C, 101.3 kPa: 1 ppm = 2.6 mg/m^3 1 mg/m^3 = 0.39 ppm

Data from ACG91, NLM03, http://esc.syrres.com.

Ethanethiol is a colourless liquid with one of the most penetrating and persistent, leek-like (mephitic) odours known. It is flammable and has a dangerous fire risk (ACG91). Odour thresholds in air ranging between 0.03 and 90 µg/m^3 (0.01-35 ppb) (Amo83, Rut86) have been reported.

4 Uses

Ethanethiol is used as an intermediate and starting material in the manufacture of plastic, insecticides, and antioxidants, and as an odourant for natural gas (ACG91).

5 Biotransformation and kinetics

Ethanethiol is an endogenous human metabolite. It is excreted in the breath of 'normal' subjects and in higher concentrations in the breath as well as the urine of cirrhotic patients (NIO78).

From inhalation experiments with 1 or 2 human volunteers, it was concluded that 60-80% of the inhaled ethanethiol was absorbed from the lungs into the blood at a constant rate (no more details presented) (NIO78).

The committee did not find other human data.

In rabbits exposed to about 78 mg/m^3 (30 ppm) for 25 minutes, trace amounts of ethanethiol were found in the blood. Exposure to about 26,000 mg/m^3 (10,000 ppm) resulted in significant ethanethiol levels in the blood. After ending exposure, amounts were very small and decreased very rapidly. Ethylmethyl

sulphide and diethyl sulphide were detected in exhaled air and the blood (no more details presented) (Far94).

The committee did not find other animal experimental data on ethanethiol.

From experiments with other thiols including ethanethiol derivatives such as diethyl sulphide and ethyl thiobenzoate, NIOSH proposed two metabolic pathways. In the one way, the sulphur atom of ethanethiol is metabolised by oxidation and is excreted for the major part in the urine as inorganic sulphate. The carbon moiety enters the carbon metabolic pool and is excreted ultimately as CO_2. In the other way, ethanethiol is methylated into ethylmethyl sulphide that is converted into ethylmethyl sulphoxide and ethylmethyl sulphone by subsequent oxidations (NIO78).

6 Effects and mechanism of action

Human data

Available human studies are essentially short-term exposures designed to measure odour threshold or accidental exposures.

Katz and Talbert performed a series of experiments to study odour thresholds of amongst others certain thiols including ethanethiol by exposing subjects at vapour concentrations ranging from ‘1 part in 10 to 1 part in 1013’ for various periods. In addition to the determination of odour intensities, nasal and eye irritation were noted. The 6 volunteers involved described the odour of ethanethiol as that of decayed cabbage but did not experience significant irritation of eyes, nose, or throat (Kat30). Exposure of human volunteers (n=3) to 10 mg/m^3 (4 ppm) ethanethiol, 3 hours/day, for 5 (2 volunteers) or 10 (1 volunteer) days, produced an increase in the odour perception threshold, mild fatigue (measured by an unexplained method), and a reduction of the rheobase* of the visual apparatus**, as well as in subjective symptoms such as periodic nausea, irritation of the mucous membranes of the mouth, lips, and nose, and a feeling of head heaviness and fatigue. The intensity of odour decreased after 1.5

* Rheobase is the minimal strength of an electrical stimulus of indefinite duration that is able to cause excitation of a tissue, e.g., muscle or nerve; chronaxie is the shortest duration of an effective electrical stimulus having a strength equal to twice the minimum strength required for excitation (rheobase) (from: http://cancerweb.ncl.ac.uk/omd). Optical chronaximetry dates from the 1950s and is considered unimportant and obsolete.

** According to NIO78, the chronaxie of the visual apparatus of the eye was measured by use of an electronic pulsed stimulator that applied weak electric discharges to the eyeball.

to 2 hours. The effects were not noted at exposure of 1 mg/m^3 (0.4 ppm) in the same volunteers exposed 1 month later (Bli65). However, in view of the very small number of volunteers exposed and the lack of details concerning the way vapours were generated and monitored, the committee cannot draw conclusions from this study regarding a dose-effect relation.

In another study, exposure of 3 volunteers for 20 minutes to approximately 130 and 290 mg/m^3 (50, 112 ppm) caused decreases in breathing rate (in 2/3) and increases in minute volume of expiration and tidal volume. Odour fatigue set in within minutes of exposure (Far94).

Citing a report from 1918, it was stated that an accidental exposure of high-school students to an estimated concentration of about 10 mg/m^3 (4 ppm) for 1 hour had caused headache, discomfort, abdominal pain, vomiting, and diarrhoea. NIOSH suggested that these complaints could have been the result of mass hysteria and anxiety rather than of specific effects of ethanethiol (NIO78).

Animal data

Irritation and sensitisation

Instillation of 0.1 mL of undiluted ethanethiol into the conjunctival sac of rabbits caused slight irritation (Fai58).

Referring to an unpublished study (dated 1977), it was stated that dermal application in rats and rabbits had caused pain and skin discolouration in rats but that there had been no persistent irritation. Moderate erythema lasting less than 24 hours was noted in rabbits after a 4-hour contact period (Far94). The committee did not find information on the potential sensitising effects of ethanethiol.

Referring to an unpublished report (dated 1983), it was mentioned that no sensory irritation was measured by whole-body plethysmography in mice exposed to about 90 mg/m^3 (35 ppm) for two 1-minute periods (Far94). In 4-hour inhalation experiments in which rats and mice were exposed to concentrations ranging from about 6750 (2600 ppm) to about 12,560 (mice) or 13,330 (rats) mg/m^3 (4832, 5125 ppm), irritation of the eye and nose mucous membranes was observed within approximately 15 minutes after exposure to the higher (not specified) concentrations (Fai58).

Acute toxicity

In rats and mice, 4-hour LC_{50} values were about 11,500 and 7200 mg/m^3 (4420, 2770 ppm), respectively. Characteristic toxic signs observed in these species when exposed to maximal sublethal and lethal concentrations of ethanethiol (and of many other thiols investigated in this experiment) included increased respiration and restlessness (hyperactivity in mice), uncoordinated movement and staggering gait, muscular weakness, partial skeletal muscle paralysis beginning in the hind limbs, light to severe cyanosis, tolerance of prone position, and mild to heavy sedation. Animals exposed to maximal lethal concentrations died from respiratory arrest while those exposed to minimal lethal concentrations died being in a long-lasting semiconscious condition (Fai58). Female and male rats (n=5/sex) survived a 1-hour exposure to 39,000 and 73,800 mg/m^3 (15,000, 28,400 ppm), respectively, while exposure to about 72,000 mg/m^3 (27,700 ppm) was lethal to 3/5 females (Ver77). No mortality was found in rats (head-only) exposed to about 2580 mg/m^3 (991 ppm) for 4 hours (unpublished study dated 1987) (Far94). In male rats (number not indicated), 85,800 mg/m^3 (33,000 ppm) was determined to be the concentration causing coma (defined as complete loss of the righting reflex) in 50% of the animals. No information on exposure duration or mortality was given. Blood levels of ethanethiol greater than 200 nmoles/mL (±12 mg/L) would induce coma (Zie72, Zie74).

The acute dermal LD_{50} (24-hour occlusion) in rabbits was greater than 2000 mg/kg bw (unpublished report dated 1977) (Far94).

Following oral or intraperitioneal administration to rats, acute LD_{50}s (15-day observation periods) were 682 and 226 mg/kg bw, respectively. The sedative action was the most characteristic effect of ethanethiol. Other signs were similar to those found in animals exposed by inhalation (see above, Fai58).

Repeated-dose toxicity

In an in Russian reported study (published in 1964), mice exposed to approximately 5125 mg/m^3 (1972 ppm), daily for 4 hours, died after 4 to 9 days, apparently from severe CNS depression. At necropsy, inflammatory changes in the lung, degenerative changes in the liver, and an increased heart weight were observed. In mice exposed to approximately 1025 mg/m^3 (394 ppm), daily for 4 hours, there was a decreased body weight. At necropsy, no pathological changes were seen. Following exposure of rats, rabbits, and mice to approximately 100 mg/m^3 (40 ppm), 4 hours/day, for 5 months (see also Bli65), there were minor cardiovascular regulatory disorders in rabbits and a mild increase in nervous

excitability in rats. At necropsy, no morphological organ changes were found (Far94). Since no more details were presented, such as strain, sex, and number of animals exposed, exposure conditions (such as hours a day, days a week), quantification and statistical analysis of effects, the committee considers this study not suitable for deriving a health-based occupational exposure limit.

In a study, reported in Japanese (published in 1959), subcutaneous administration of 10 and 90 mg/kg* to rats and rabbits daily or every other day for 1 year caused localised necrosis at the site of injection and reductions in red blood cells and haemoglobin and increases in leukocytes and reticulocytes. The most marked changes were noted in the spleen and include hyperaemia, dilation of the sinusoids, haemosiderin deposits, fibrosis, erythrocyte destruction, and increased haematopoiesis. This haemolysis may have been due to thiol-disulphide redox cycling with free-radical formation and specific toxicity to the haemoglobin in erythrocytes (Far94, NIO78).

The committee did not find studies on the reproduction toxicity or carcinogenic potential of ethanethiol.

Mutagenicity and genotoxicity

Ethanethiol was negative in *S. typhimurium* (unpublished study dated 1983) (Far94).

Ethanethiol was tested in the mouse lymphoma forward mutation assay at concentrations of 60.6-1000 µg/mL both in the presence and the absence of a metabolic activating system. Doses ≥201.5 µg/mL were toxic or resulted in less than 10% survival. No increases in mutation frequency were observed in the presence of an S9 mix. When tested without metabolic activation, increases in mutation frequency were 1.6, 3.7, and 1.8 at doses of 60.6, 90.5, and 135 µg/mL, respectively. The results of this test were considered to be equivocal and additional testing using duplicate doses was recommended in order to obtain definitive results (Pen85).

When tested in Chinese hamster ovary cells, it produced statistically significant increases in the total number of SCEs and in the number of SCEs per chromosome (in both cases 1.2-fold) at 840 µg/mL in the absence of a metabolic system. When tested in the presence of a metabolic activation system, this dose caused a 1.2-fold increase in both end points as well, but this increase was

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* According to NIO78, doses were 0.01 and 0.09 mL/kg, which would imply that they should have been approximately 8 and 75 mg/kg.

statistically significant as to the total number of SCEs only. At the next higher dose level of 2500 µg/mL, all cells recovered were first division metaphases which could not be evaluated for SCEs. In a second trial performed with one dose level of 2500 µg/mL only - the chromosomes were recovered 43 hours after exposure in order to allow for 2 cell divisions - , there were statistically significant, 2.4-2.5-fold increases in the total number of SCEs and the number of SCEs per chromosomes both in the presence and absence of a metabolic system (Pen84).

In vitro studies

In *in vitro* experiments, ethanethiol inhibited both gluconeogenesis and ureogenesis in rat hepatocytes, depressed cellular ATP content, and caused an increased reduction of the mitochondria. Ethanethiol also affected the oxidative metabolism of rat liver and rat brain mitochondria. In ox-heart submitochondrial particles, ethanethiol inhibited electron transfer between cytochrome c and oxygen. Purified cytochrome c oxidase was inhibited by ethanethiol in a non-competitive manner. It is suggested that inhibition of the terminal part of the mitochondrial electron transfer chain by ethanethiol was related to the mechanism by which energy production in brain is depressed during hepatic failure. A suggestion is made that inhibition of mitochondrial electron transfer by ethanethiol may be relevant in the mechanism by which energy production in brain is depressed during hepatic coma (Vah79, Wil80).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for ethanethiol in the Netherlands is 1 mg/m^3 (0.5 ppm), 8-hour TWA.

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

8 Assessment of health hazard

Ethanethiol is an endogenous human metabolite, which can be excreted in breath. In 2 volunteers, 60-80% of the inhaled ethanethiol was absorbed from the lungs into the blood at a constant rate. Experiments with other thiols and ethanethiol derivatives indicate that ethanethiol may be 1) metabolised by oxidation of its sulphur atom followed by urinary excretion as inorganic sulphate while the carbon moiety may enter the carbon metabolic pool resulting in

ultimate excretion as CO_2, or 2) methylated into ethylmethyl sulphide followed by oxidation into ethylmethyl sulphoxide and ethylmethyl sulphone.

Limited human experimental data suggest that ethanethiol may cause periodic nausea, feeling of head heaviness and fatigue, and irritation to the mucous membranes of mouth, lips, and nose at exposure to 10 mg/m^3 (4 ppm), for 3 hours. No such effects may occur at 1 mg/m^3 (0.4 ppm).

Ethanethiol was slightly irritating to the eyes and skin of rabbits. Four-hour inhalation LC_{50} values were about 7200 and 11,500 mg/m^3 (2770 and 4420 ppm) in mice and rats, respectively, animals showing CNS depression and cyanosis. The dermal LD_{50} in rabbits was >2000 mg/kg bw; the oral LD_{50} in rats 682 mg/kg bw. Ethanethiol was negative in *S. typhimurium*, produced equivocal results in the mouse lymphoma forward mutation assay, and elicited a positive response in the Chinese hamster ovary SCE assay.

The committee did not find data from relevant repeated-dose toxicity studies including those on the potential reproduction toxicity and carcinogenicity.

The committee considers the toxicological database on ethanethiol too poor to justify recommendation of a health-based occupational exposure limit.

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

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Annex

Occupational exposure limits for ethanethiol 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	0.5	1	8 h	administrative		SZW04
Germany						
- AGS	0.5	1.3	8 h		[d]	TRG03
	0.5	1.3	15 min			
- DFG MAK-Kommission	0.5	1.3	8 h			DFG03
	1	2.6	10 min[c]			
Great-Britain						
- HSE	0.5	1.3	8 h	OES		HSE02
	2	5.2	15 min			
Sweden	-	-				Swe00
Denmark	0.5	1	8 h			Arb02
USA						
- ACGIH	0.5	-	8 h	TLV		ACG04
- OSHA	10	25	ceiling	PEL		ACG03
- NIOSH	0.5	1.3	15 min, ceiling	REL		ACG03
European Union						
- SCOEL	-	-				EC04

[a] S = skin notation; which 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] Maximum number per shift: 4, with a minimum interval between peaks of 1 hour.

[d] Listed among compounds with MAK values but no pregnancy risk group classification.