The MAK-Collection for Occupational Health and Safety

GMS PUBLISSO ZB MED-Publikationsportal Lebenswissenschaften

Ethanethiol

MAK Value Documentation, supplement – Translation of the German version from 2019

A. Hartwig[1,*] MAK Commission[2,*]

1 *Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Institute of Applied Biosciences, Department of Food Chemistry and Toxicology, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Building 50.41, 76131 Karlsruhe, Germany*

2 *Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany*

* *E-Mail: A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)*

Keywords:

ethanethiol, odour nuisance, maximum workplace concentration, MAK value, peak limitation, skin absorption

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the maximum concentration at the work place (MAK value) of ethanethiol [75-08-1]. No new studies are available for ethanethiol itself. Therefore, the MAK value is derived by read-across with the structurally similar methyl mercaptan for which the MAK value of 0.5 ml/m³ is based on slight behavioural changes at 2 ml/m³ in a 90-day inhalation study in rats. The MAK value of 0.5 ml/m³ for ethanethiol is supported by a limited inhalation study with 3 volunteers, showing irritation and other symptoms after repeated exposure to ethanethiol in a concentration of 3.9 ml/m³, but not after 0.39 ml/m³. The behavioural changes in rats exposed to methyl mercaptan are presumably not neurotoxic effects but a result of the odour nuisance or the local irritation. Therefore, ethanethiol is classified in Peak Limitation Category I with an excursion factor of 1 by analogy with methyl mercaptan. There are no developmental toxicity studies and ethanethiol remains assigned to Pregnancy Risk Group D. According to skin absorption models, percutaneous absorption is expected to contribute significantly to systemic toxicity. Therefore, ethanethiol is designated with an "H". There are no data on sensitization.

Citation Note:
Hartwig A, MAK Commission. Ethanethiol. MAK Value Documentation, supplement – Translation of the German version from 2019. MAK Collect Occup Health Saf. 2020 Dec;5(4):Doc081.
DOI: 10.34865/mb7508e5_4ad

Manuscript completed:
26 Apr 2018

Publication date:
21 Dec 2020

MAK value (1969)	**0.5 ml/m³ (ppm) ≙ 1.3 mg/m³**
Peak limitation (2018)	**Category I, excursion factor 1**
Absorption through the skin (2018)	**H**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2000)	**Pregnancy Risk Group D**
Germ cell mutagenicity	**–**
BAT value	**–**
CAS number	75-08-1
Molar mass	62.13 g/mol
Vapour pressure at 20 °C	589 hPa (ECHA 2018)
log K_{OW}	1.5 (calculated; ECHA 2018)
Solubility at 20 °C	8.86 g/l water (ECHA 2018)
1 ml/m³ (ppm) ≙ 2.578 mg/m³	**1 mg/m³ ≙ 0.388 ml/m³ (ppm)**

For ethanethiol, documentation from 2000 and a supplement on peak limitation from 2002 are available (Greim 2005, combined in one translation).

The previously valid, provisional MAK value for ethanethiol was derived in analogy to that for methyl mercaptan. The MAK value for methyl mercaptan has now been re-evaluated and confirmed (see Hartwig and MAK Commission 2020 a). Therefore, the MAK value for ethanethiol has also been re-evaluated.

Mechanism of Action

As already described in the documentation of 2000 (Greim 2005), in the presence of suitable metal ions thiols can contribute to the formation of reactive oxygen species by autoxidation. The resulting disulfides can again be reduced to thiols. This redox cycling can lead to oxidative stress. Aliphatic thiols have a haemolytic effect, recognizable by the presence of Heinz bodies in the erythrocytes, which are formed by irreversibly denatured haemoglobin. As a result, the number of erythrocytes decreases as they lose their deformability and are destroyed in the reticulohistiocytic system. Erythroclasia occurs predominantly in the spleen, recognizable by enlargement and dark discoloration. A decrease in circulating erythrocytes stimulates compensatory erythropoiesis, but if too few new erythrocytes are formed this can lead to anaemia (Munday 1989).

Toxicokinetics and Metabolism

Ethanethiol is absorbed by the respiratory and gastrointestinal tract and exhaled in partially unchanged form (Greim 2005).

There are no studies available for the dermal absorption of ethanethiol. Using the mathematical models of Fiserova-Bergerova et al. (1990), Guy and Potts (1993) and Wilschut et al. (1995), dermal fluxes of 1.07, 0.08 and 0.13 mg/cm^2 and hour, respectively, can be calculated for a saturated aqueous solution. Under standard conditions (skin area 2000 cm^2, exposure time 1 hour), the total amount of substance absorbed through the skin is 2140 mg, 160 mg and 260 mg, respectively.

Effects in Humans

As already described in the documentation of 2000 (Greim 2005), a poorly documented study from Russia reported that 3-hour daily exposure (5 or 10 days) of volunteers (5 days: n = 2; 10 days: n = 1) to 3.9 ml ethanethiol/m^3 led to adverse effects such as irritation of the oral and nasal mucosa, nausea and decreased odour perception, whereas 0.39 ml/m^3 did not (Blinova 1965; Greim 2005).

More recent studies of the effects of ethanethiol on humans are not available.

Animal Experiments and in vitro Studies

Acute toxicity

Inhalation

The 4-hour LC_{50} of ethanethiol is 4420 ml/m^3 for rats and 2770 ml/m^3 for mice, and is thus in the same order of magnitude as the 4-hour LC_{50} values of 1-butanethiol of 4020 and 6060 ml/m^3 for rats and 2500 ml/m^3 for mice. Increased respiration rate, initial restlessness (hyperactivity in mice), later sedation, uncoordinated movements, prone position, staggering gait, muscular weakness, cyanosis, but also irritation of the mucous membranes (rubbing of eyes and nose, eye closure, watering of the eyes, corneal opacity) and retracting of the head were observed (Greim 2005; OECD 2010).

Rabbits were exposed to ethanethiol concentrations of 10, 100 or 1000 ml/m^3 for 20 minutes. The respiration rate and expiratory volume decreased at 1000 ml/m^3 (no other details; Farr and Kirwin 1994).

Oral administration

The oral LD_{50} of ethanethiol for the rat is 682 mg/kg body weight. The value for 1-butanethiol is higher at 1500 mg/kg body weight (OECD 2010).

Dermal application

The dermal LD_{50} value for ethanethiol is greater than 2000 mg/kg body weight, as is that for 1-butanethiol, 1-propanethiol and 2-methyl-2-propanethiol. Ethanethiol and 1-butanethiol were tested in rats, the last two thiols in rabbits. Apart from skin reactions, no effects were observed (OECD 2010).

Subacute, subchronic and chronic toxicity

There are no valid animal studies after subchronic or chronic exposure. After subcutaneous injections of 10 or 90 mg ethanethiol/kg body weight daily or every second day for one year in rats and rabbits, necrosis at the injection site and clear signs of haemolysis in the blood and spleen were observed (no other details; Farr and Kirwin 1994; Greim 2005).

Local effects on skin and mucous membranes

After occlusive application of 0.5 ml ethanethiol to the intact shaved skin of 6 rabbits for 4 hours, moderate erythema was observed; this was reversible within 24 hours (Farr and Kirwin 1994; OECD 2010).

The instillation of 0.1 ml ethanethiol into the conjunctival sac of one rabbit caused slight irritation (no other details; Fairchild and Stokinger 1958).

In mice exposed twice to a concentration of 1930 mg/m³ (about 750 ml/m³) for one minute, irritation of the upper respiratory tract was not observed (no other details; ECHA 2018).

Allergenic effects

There are no data available.

Reproductive and developmental toxicity

There are no data available.

Manifesto (MAK value/classification)

The critical effects are those on the erythrocytes, the central nervous system and possibly irritation of the mucous membranes and the odour nuisance.

MAK value. Data in humans or valid animal studies after subchronic or chronic exposure that are suitable for the derivation of a threshold limit value are not available to date. As with all thiols, ethanethiol is a substance with a strong, unpleasant odour. In view of the low perception threshold of between 2.6×10^{-10} and 0.002 ml ethanethiol/m³ (Greim 2005), the odour effect is likely to be the main effect. However, there is no reliable information on the concentration at which excessive nuisance occurs.

A poorly documented study from Russia reported that daily exposure (5 or 10 days) of volunteers (5 days: n = 2; 10 days: n = 1) to 3.9 ml ethanethiol/m³ led to adverse effects such as irritation, nausea and decreased odour perception, whereas 0.39 ml/m³ did not (Blinova 1965; Greim 2005).

The previously valid, provisional MAK value for ethanethiol of 0.5 ml/m³ was derived in analogy to that for methyl mercaptan. The MAK value of methyl mercaptan has now been re-evaluated and confirmed (see Hartwig and MAK Commission 2020 a).

Based on the results of the above-mentioned study in volunteers together with the behavioural changes observed in rats in a 90-day inhalation study with **methyl mercaptan** at concentrations of 2 ml/m³ and above, the MAK value for ethanethiol of 0.5 ml/m³ has been retained, despite the uncertainties in the evaluation.

For the assessment of systemic effects, studies with butanethiols are used. Similar systemic effects have been observed in several studies with inhalation exposure of rats to different **butanethiols**. The threshold values calculated in these studies are of the same order of magnitude and show that the MAK value of 1 ml/m³ protects against the systemic effects of 1-butanethiol (see Hartwig and MAK Commission 2020 b). The same is assumed for the structurally similar ethanethiol.

Peak limitation. The behavioural changes in rats exposed to 2 ml methyl mercaptan/m³ in a 90-day inhalation study is interpreted as a consequence of the unpleasant odour or irritant effect. Therefore, ethanethiol is now assigned to Peak Limitation Category I in analogy to methyl mercaptan. Since no sufficiently valid data are available for humans, the excursion factor is 1.

Prenatal toxicity. There are no developmental toxicity studies available for ethanethiol. Therefore, ethanethiol remains classified in Pregnancy Risk Group D.

Absorption through the skin. Experimental studies of the dermal absorption of ethanethiol are not available. The estimation of dermal absorption under standard conditions using the mathematical models of Fiserova-Bergerova et al. (1990), Guy and Potts (1993) and Wilschut et al. (1995) yields absorbed amounts of between 160 mg and 2140 mg. As in the case of 1-butanethiol (see Hartwig and MAK Commission 2020 b), it is assumed that the systemically tolerable concentration is about 1 ml/m³. Assuming complete pulmonary absorption (100%) and a respiratory volume of 10 m³ per working day, the inhaled amount of ethanethiol after exposure at the level of the MAK value is 13 mg. Since the amount estimated to be dermally absorbed is significantly higher than this value, ethanethiol is designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are no findings of skin sensitization caused by ethanethiol in humans and no studies in animals. There are also no findings of respiratory sensitization. Ethanethiol is therefore not designated with either "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

References

Blinova EA (1965) [Setting standards for the concentration of substances having a strong odour in the ambient air of industrial plants]. Gig Sanit 30: 18–22

ECHA (European Chemicals Agency) (2018) Information on registered substances. Dataset on ethanethiol (CAS Number 75-08-1), joint submission, first publication 03 Mar 2011, last modification 23 Mar 2018. https://echa.europa.eu/de/registration-dossier/-/registered-dossier/2123, accessed 02 May 2018

Fairchild EJ, Stokinger HE (1958) Toxicologic studies on organic sulfur compounds. 1. Acute toxicity of some aliphatic and aromatic thiols (mercaptans). Am Ind Hyg Assoc J 19: 171–189. DOI: 10.1080/00028895809343573

Farr CH, Kirwin CJ (1994) Organic sulfur compounds. In: Clayton CD, Clayton FE (eds) Patty's industrial hygiene and toxicology, vol 2F, 4th ed. John Wiley & Sons, New York, NY, 4311–4372

Fiserova-Bergerova V, Pierce JT, Droz PO (1990) Dermal absorption potential of industrial chemicals: criteria for skin notation. Am J Ind Med 17: 617–635. DOI: 10.1002/ajim.4700170507

Greim H (ed) (2005) Ethanethiol. MAK Value Documentation, 2000. In: The MAK-Collection for Occupational Health and Safety, Part I: MAK Value Documentations, vol 21. Wiley-VCH, Weinheim, 195–203. Also available from DOI: 10.1002/3527600418.mb7508e0021

Guy RH, Potts RO (1993) Penetration of industrial chemicals across the skin: a predictive model. Am J Ind Med 23: 711–719. DOI: 10.1002/ajim.4700230505

Hartwig A, MAK Commission (2020 a) Methyl mercaptan. MAK Value Documentation, supplement – Translation of the German version from 2019. MAK Collect Occup Health Saf 5: Doc82. DOI: 10.34865/mb7493e5_4ad

Hartwig A, MAK Commission (2020 b) 1-Butanethiol. MAK Value Documentation, supplement – Translation of the German version from 2019. MAK Collect Occup Health Saf 5: Doc79. DOI: 10.34865/mb10979e5_4ad

Munday R (1989) Toxicity of thiols and disulphides: involvement of free-radical species. Free Radic Biol Med 7: 659–673. DOI: 10.1016/0891-5849(89)90147-0

OECD (Organisation of Economic Co-operation and Development) (2010) C2-C4 aliphatic thiols category, 1-ethanethiol (CAS No. 75-08-1), 1-propanethiol (CAS No.107-03-9), 1-butanethiol (CAS No.109-79-5), 2-propanethiol, 2-methyl (CAS No. 75-66-1). SIDS Initial Assessment Report. OECD, Geneva. https://hpvchemicals.oecd.org/UI/handler.axd?id=236e6893-6b1b-48d3-895c-e31db1f9f55d, accessed 31 May 2016

Wilschut A, ten Berge WF, Robinson PJ, McKone TE (1995) Estimating skin permeation. The validation of five mathematical skin permeation models. Chemosphere 30: 1275–1296. DOI: 10.1016/0045-6535(95)00023-2