CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

Chemical name:

ethanethiol; ethyl mercaptan

EC Number: 200-837-3

CAS Number: 75-08-1

Index Number: 016-022-00-9

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CONTENTS

ABBREVIATIONS

ATE	Acute Toxicity Estimate
bw	body weight
CAS	Chemical Abstract Service
CL	Confidence Limit
CLH	Harmonised Classification and Labelling
CLP	Classification, Labelling and Packaging Regulation (EC) No 1272/2008
d	day
Dgr	Danger
GLP	Good Laboratory Practice
IPCS	International Programme on Chemical Safety
Kow	Partition coefficient octanol/water
LD_{50}	Lethal dose, 50%
LC_{50}	Lethal concentration, 50%
m/f	male/female
OECD	Organisation for Economic Co-operation and Development
PC	Product Category
WHO	World Health Organization

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	ethanethiol; ethyl mercaptan
Other names (usual name, trade name, abbreviation)	1-mercaptoethane ethyl mercaptan aethanethiol aethylmercaptan thioethanol
ISO common name (if available and appropriate)	-
EC number (if available and appropriate)	200-837-3
EC name (if available and appropriate)	ethanethiol
CAS number (if available)	75-08-1
Other identity code (if available)	-
Molecular formula	C2H6S
Structural formula	 **(source:** European Chemicals Agency, http://echa.europa.eu/**)**
SMILES notation (if available)	CCS
Molecular weight or molecular weight range	62.13 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	-
Description of the manufacturing process and identity of the source (for UVCB substances only)	-
Degree of purity (%) (if relevant for the entry in Annex VI)	-

1.2 Composition of the substance

Ethanethiol is a mono-constituent substance.

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)
Ethanethiol	>98%	Flam. Liq. 2, H225 Acute Tox. 4*, H332 Aquatic Acute 1, H400 Aquatic Chronic 1, H410	Flam. Liq. 1, H224 Acute Tox. 4, H302 Acute Tox. 4, H332 Skin Sens. 1B, H317 Aquatic Acute 1, H400 Aquatic Chronic 1, H410

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
Unknown impurities	<2%	-	-	-

Impurities not relevant for classification.

Information on the test substances (if available) is given in the study descriptions.

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 4: For substance with an existing entry in Annex VI of CLP

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATEs	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	016-022-00-9	ethanethiol; ethyl mercaptan	200-837-3	75-08-1	Flam. Liq. 2 Acute Tox. 4* Aquatic Acute 1 Aquatic Chronic 1	H225 H332 H400 H410	GHS02 GHS09 GHS07 Dgr	H225 H332 H410			
Dossier submitters proposal	016-022-00-9	ethanethiol; ethyl mercaptan	200-837-3	75-08-1	**Add** Acute Tox. 4 **Modify** Flam. Liq. 1 Acute Tox. 3	**Add** H302 **Modify** H224 H331	**Add** GHS06 **Remove** GHS07	**Add** H302 **Modify** H224 H331		**Add** oral: ATE = 680 mg/kg bw inhalation: ATE = 7.14 mg/L (vapours)	
Resulting Annex VI entry if agreed by RAC and COM	016-022-00-9	ethanethiol; ethyl mercaptan	200-837-3	75-08-1	Flam. Liq. 1 Acute Tox. 4 Acute Tox. 3 Aquatic Acute 1 Aquatic Chronic 1	H224 H302 H331 H400 H410	GHS02 GHS06 GHS09 Dgr	H224 H302 H331 H410		oral: ATE = 680 mg/kg bw inhalation: ATE = 7.14 mg/L (vapours)	

Table 5: Reason for not proposing harmonised classification and status under consultation

Hazard class	Reason for no classification	Within the scope of consultation
Explosives	*hazard class not assessed in this dossier*	No
Flammable gases (including chemically unstable gases)	*hazard class not assessed in this dossier*	No
Oxidising gases	*hazard class not assessed in this dossier*	No
Gases under pressure	*hazard class not assessed in this dossier*	No
Flammable liquids	Flam Liq. 1, H224	Yes
Flammable solids	*hazard class not assessed in this dossier*	No
Self-reactive substances	*hazard class not assessed in this dossier*	No
Pyrophoric liquids	*hazard class not assessed in this dossier*	No
Pyrophoric solids	*hazard class not assessed in this dossier*	No
Self-heating substances	*hazard class not assessed in this dossier*	No
Substances which in contact with water emit flammable gases	*hazard class not assessed in this dossier*	No
Oxidising liquids	*hazard class not assessed in this dossier*	No
Oxidising solids	*hazard class not assessed in this dossier*	No
Organic peroxides	*hazard class not assessed in this dossier*	No
Corrosive to metals	*hazard class not assessed in this dossier*	No
Acute toxicity via oral route	Acute Tox. 4, H302	Yes
Acute toxicity via dermal route	*hazard class not assessed in this dossier*	No
Acute toxicity via inhalation route	Acute Tox. 3, H331	Yes
Skin corrosion/irritation	*hazard class not assessed in this dossier*	No
Serious eye damage/eye irritation	*hazard class not assessed in this dossier*	No
Respiratory sensitisation	*hazard class not assessed in this dossier*	No
Skin sensitisation	*hazard class not assessed in this dossier*	No
Germ cell mutagenicity	*hazard class not assessed in this dossier*	No
Carcinogenicity	*hazard class not assessed in this dossier*	No
Reproductive toxicity	*hazard class not assessed in this dossier*	No
Specific target organ toxicity-single exposure	*hazard class not assessed in this dossier*	No
Specific target organ toxicity-repeated exposure	*hazard class not assessed in this dossier*	No
Aspiration hazard	*hazard class not assessed in this dossier*	No
Hazardous to the aquatic environment	*hazard class not assessed in this dossier*	No
Hazardous to the ozone layer	*hazard class not assessed in this dossier*	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

Ethanethiol already has a harmonized classification. It has been discussed by the TC C&L and included into Annex I of Directive 67/548/EEC with the 25th ATP (F; R11 Xn; R20 N; R50-53). No further information is available.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

[B.] Justification that action is needed at Community level is required.

Reason for a need for action at Community level:

- Change in existing entry due to new data
- Change in existing entry due to new interpretation/evaluation of existing data
- Change in existing entry due to changes in the criteria

Further detail on need of action at Community level

Ethanethiol has been harmonized classified based on the criteria of Directive 67/548/EEC and the data available at the time of evaluation.

A proposal from a manufacturer, importer or downstream user which has new information that could lead to a change in the current harmonised classification and labelling (Article 37(6), CLP) has been received by the Austrian CA. For evaluation of flammability more recent data is available indicating the need for a more stringent classification to protect workers. Evaluation of available acute toxicity data shows that an additional classification for oral toxicity is indicated.

For inhalation toxicity minimum classification (*) has been assigned which is reassessed in this dossier.

5 IDENTIFIED USES

Ethanethiol is registered in the EU in the tonnage band of ≥ 1 000 to < 10 000 T. It may be used as odorant for natural gas, intermediate and starting material in manufacture of plastics, insecticides and antioxidants[1].

Table 6: The following uses are indicated at ECHA dissemination site [accessed August 2021]:

Categories	Use(s)	Technical function
Manufacture	Manufacture of ethanethiol	-
Formulation	Formulation into mixture under strictly controlled conditions (PC 28: perfumes, fragrances)	-
Uses at industrial sites	Use as an intermediate under strictly controlled conditions (PC 19: intermediate) Injection in gas under strictly controlled conditions (PC 28: perfumes, fragrances) Use as an anti-coking agent under strictly controlled conditions (PC 20: Products such as pH-regulators, flocculants,	-

[1] Ethanethiol | C2H5SH - PubChem (nih.gov)

	precipitants, neutralisation agents)	
Uses by professional workers	-	-
Consumer Uses	Combustion as gas odorant (PC 13: fuels) Injection of gas odorant-tracer in LPG or natural gas (PC 13: fuel)	-
Article service life	-	-

6 DATA SOURCES

ECHA dissemination site https://echa.europa.eu/de/substance-information/-/substanceinfo/100.103.524

Original study reports provided by the registrant(s) as well as scientific literature served as information sources. Please see section 14 References for details.

7 PHYSICOCHEMICAL PROPERTIES

Table 7: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	liquid	ECHA dissemination site [Feb, 2021]	value taken from regulatory review document
Melting/freezing point	-144.4°C	ECHA dissemination site [Feb, 2021]	value taken from regulatory review document
Boiling point	34°C at 100.9 kPa	ECHA dissemination site [Feb, 2021]	measured OECD 103 (differential scanning calorimetry)
Relative density	0.839 g/cm3	ECHA dissemination site [Feb, 2021]	value taken from regulatory review document
Vapour pressure	58.9 kPa at 20°C	ECHA dissemination site [Feb, 2021]	value taken from regulatory review document
Surface tension	23.1mN/m at 25°C and 1 g/L	ECHA dissemination site [Feb, 2021]	value taken from reliable peer reviewed secondary source.
Water solubility	8.86 g/l at 20°C	ECHA dissemination site [Feb, 2021]	non-guideline test
Partition coefficient n-octanol/water (LogKow)	1.5 at 20 °C and pH 7	ECHA dissemination site [Feb, 2021]	value taken from regulatory review document
Flash point	<-30˚C	ECHA dissemination site [Feb, 2021]	measured EC, A9 (closed cup)
Flammability	extremely flammable liquid	ECHA dissemination site [Feb, 2021]	there is no indication, on the basis of chemical structure or experience in handling and use, that the substance is pyrophoric

Property	Value	Reference	Comment (e.g. measured or estimated)
			(flammable in contact with air) or flammable in contact with water
Explosive properties	non explosive	ECHA dissemination site [Feb, 2021]	substance contains no chemical groups that are associated with explosive properties
Self-ignition temperature	299˚C	ECHA dissemination site [Feb, 2021]	value taken from regulatory review document
Oxidising properties	not oxidising	ECHA dissemination site [Feb, 2021]	substance is incapable of reacting exothermically with combustible materials on the basis of its chemical structure
Granulometry	-	ECHA dissemination site [Feb, 2021]	substance is a liquid
Stability in organic solvents and identity of relevant degradation products	-	-	-
Dissociation constant	pKa 10 at 20˚C	ECHA dissemination site [Feb, 2021]	QSAR, not expected to dissociate in the environment
Viscosity	0.000287 Pa.s at 25˚C	ECHA dissemination site [Feb, 2021]	value taken from reliable peer reviewed secondary source

8 EVALUATION OF PHYSICAL HAZARDS

8.1 Explosives

Not evaluated.

8.2 Flammable gases (including chemically unstable gases)

Not evaluated.

8.3 Oxidising gases

Not evaluated.

8.4 Gases under pressure

Not evaluated.

8.5 Flammable liquids

Table 8: Summary table of studies on flammable liquids

Method	Results	Remarks	Reference
DSC (ASTM E537-86) (EC method A.2 and OECD 103) 1 (reliable without restriction) GLP	boiling point 34.1 °C	ethanethiol, purity 99.84% 2 measurements at 100.9 kPa (34.1 °C and 34.5 °C)	Anonymous, 2012
Closed cup method according to Abel (EN ISO 13736) (EC method A.9) 1 (reliable without restriction) GLP	flash point < -30 °C	ethanethiol, purity 99.97% 2 measurements to 101.325 kPa corrected results: -26.2 °C and -31.8 °C	Anonymous, 2010

8.5.1 Short summary and overall relevance of the provided information on flammable liquids

The boiling point was measured by differential scanning calorimetry. The lowest result of two measurements at 100.9 kPa (34.1 °C and 34.5 °C) was converted to standard atmospheric pressure by applying the Sidney-Young-equation, which can be applied when the pressure difference is less than 5 kPa. The boiling point was determined to be 34.1 °C. The accuracy criteria according to OECD 103 is fulfilled and the study was conducted according to GLP. The Klimisch score is 1.

This is supported by a boiling point of 35 °C, taken from the WHO IPCS International Chemical Safety Cards (ICSC 0470, 2004[2]). No information on the primary source of these data or the method used is available. However, this information is taken from an internationally peer-reviewed chemical safety card and can be considered reliable and suitable for use as a supporting evidence for this endpoint.

The flash point was measured by EN ISO 13736. With -26.2 °C and -31.8 °C both measurements gave values below the CLP criteria (< 23 °C). The lowest result of two determinations is decisive, which lies below the recommended temperature range of -30 to 75 °C for this method. Therefore, the result is stated with < -30 °C. The study was conducted according to GLP. The Klimisch score is 1.

The study is considered reliable and suitable for evaluation of this endpoint. This is supported by a flash point of -48.3 °C, taken from the WHO IPCS International Chemical Safety Cards (ICSC 0470, 2004). Although no information on the primary source of the data or the method used is available, this information is taken from an internationally peer-reviewed chemical safety card and can be considered reliable and suitable for use as a supporting evidence for this endpoint.

8.5.2 Comparison with the CLP criteria

A flammable liquid has to be classified in one of the three categories if:

Category	Criteria
1	Flash point < 23 °C and initial boiling point ≤ 35 °C
2	Flash point < 23 °C and initial boiling point > 35 °C
3	Flash point ≥ 23 °C and ≤ 60 °C

[2] ICSC 0470, 2004: https://www.ilo.org/dyn/icsc/showcard.display?p_lang=en&p_card_id=0470&p_version=2

For ethanethiol the flash point is < -30 °C and the boiling point is 34.1 °C.

8.5.3 Conclusion on classification and labelling for flammable liquids

Based on the presented studies the flash point was determined to be < -30 °C and the boiling point was determined to be 34.1 °C. Comparing the results with CLP regulation, Table 2.6.1, a harmonised classification of ethanethiol as Flammable Liquid, Category 1, H224 (Extremely flammable liquid and vapour) is proposed.

8.6 Flammable solids

Not evaluated.

8.7 Self-reactive substances

Not evaluated.

8.8 Pyrophoric liquids

Not evaluated.

8.9 Pyrophoric solids

Not evaluated.

8.10 Self-heating substances

Not evaluated.

8.11 Substances which in contact with water emit flammable gases

Not evaluated.

8.12 Oxidising liquids

Not evaluated.

8.13 Oxidising solids

Not evaluated.

8.14 Organic peroxides

Not evaluated.

8.15 Corrosive to metals

Not evaluated.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Based on a water solubility of 8860 mg/l and a log Kow of 1.5 (20°C, pH 7) ethanethiol will be absorbed effectively via the dermal and oral route. The dermal penetration rate of a saturated aqueous solution of ethanethiol, calculated from the physico-chemical data, is 0.57 mg/cm^2/hour (Fiserova-Bergerova, 1990, cited in DFG, 2005).

Shibata (1966b, cited in DFG, 2005) showed that 60-80 % of inhaled ethanethiol (based on concentrations of 50 ml/m^3 for 35-60 min) was absorbed by humans.

The metabolism was investigated by Snow (1957) using radiolabeled compounds related to ethanethiol (diethyl disulphide, S-ethyl thiolbenzoate). They have been rapidly absorbed and distributed in the body tissues without any notable local concentration after oral and subcutaneous administration in mice.

In rodents, excretion of compounds related to ethanethiol occurred mainly via the kidney as inorganic sulfate. Organic metabolites, ethyl methyl sulfone, and an unidentified product accounted for 10-20% of the sulfur excreted in the urine. There was little fecal excretion, but approximately 14% of the dose was excreted in the breath. It was hypothesized that oxidation converted the thiol to the sulphide and then to the sulfone (Snow, 1957; National Research Council, 2013).

Metabolism of simple thiols is in general described by JEFCA (2000). Ethanethiol is not explicitly mentioned in this report, however it can be assumed that the principles also apply to this substance: Simple thiols may be metabolized along several pathways. (1) Simple aliphatic and aromatic thiols undergo S-methylation in mammals to produce the corresponding methyl thioether or sulfide. Methylation is catalysed by thiopurine methyltransferase in the cytoplasm and thiol methyltransferase in microsomes, and both reactions require S-adenosyl-l-methionine as a methyl group donor. Thiopurine methyltransferase is present in human liver, kidney, and erythrocytes; preferential substrates for this enzyme include aromatic and heterocyclic thiols. S-Methylation of aliphatic thiols is catalysed by microsomal thiol methyltransferase, and the resulting methyl thioether (sulfide) metabolite would undergo S-oxidation to give the methyl sulfoxide and methyl sulfone analogues as urinary products. (2) Thiols may react with glutathione and other endogenous thiol substances to form mixed disulfides. Both microsomal and cytoplasmic thioltransferases have been reported to catalyse the formation of mixed disulfides. The resulting mixed disulfides can undergo reduction back to thiols, oxidative desulfuration, or oxidation to a sulfonic acid via the intermediate thiosulfinate and sulfinic acids. The principal form in the circulation would probably be a mixed disulfide formed with albumin. (3) *S*-Glucuronidation of aromatic thiols has been reported, and this may be a pathway for the metabolism of aromatic thiols (thiophenols) and simple aromatic disulfides after their reduction. Glucuronyl transferases behave similarly towards hydroxyl and sulfydryl groups, and the two activities have the same subcellular location and optimal pH. (4) Thiols may be oxidized to form sulfenic acids (RSOH), which are unstable and readily undergo further oxidation to sulfinic (RSO2H) and sulfonic (RSO3H) acids or combine with nucleophiles. The sulfonic acid group is a highly polar centre and makes molecules highly soluble in water. In general, sulfonic acids are stable to metabolism. (5) Alkyl thiols of low relative molecular mass undergo oxidative desulfuration *in vivo* to yield CO2 and SO4=. This reaction has been shown, for example, for methanethiol. Whereas the carbon atom from thiols may be used in the biosynthesis of amino acids, the sulfur atom is not used significantly in the synthesis of sulfur-containing amino acids.

Ethanethiol is a metabolite of the human body and is excreted in the breath of normal individuals; patients with advanced liver disease excrete it at higher concentrations (National Research Council, 2013).

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

Table 9: Summary table of animal studies on acute oral toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels, duration of exposure	Value LD_{50}	Reference
similar to OECD 420 non-GLP key study 2 (reliable with restrictions) derivations: no information on age of rats and fasting, body weight development not documented, generalized information on clinical and pathological observations	rats, Wistar derived, males n= 5 m/group	ethanethiol, undiluted	single oral dose, gavage 210, 420, 840, 1680, or 3360 mg/kg bw observation period: 15 d	LD_{50} (15d) = 682 mg/kg bw in males (CL: 517 – 900 mg/kg bw) LD_{50} (24h) = 1034 mg/kg bw in males (CL: 667 – 1603 mg/kg bw)	Fairchild and Stokinger, 1958

10.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

Fairchild and Stokinger (1958) investigated acute oral toxicity of nine organic sulphur compounds, including ethanethiol. Ethanethiol (undiluted) was administered (via gavage) to male Wistar rats (200±20g) (5/dose) at single doses of 210, 420, 840, 1680, or 3360 mg/kg bw. The animals were subsequently observed for a period of 15 days. Mortality data are shown in

Table 10. In the highest dose group, all animals (5/5) died within 7h after administration. In the 1680 mg/kg bw test group all animals died before the end of the study period. High mortality was observed in the 840 mg/kg bw group (4/5) at the end of the study and no mortality (0/5) was observed in the 210 and 420 mg/kg bw dose groups. Clinical signs of toxicity were described generally for the group of thiols[3] as sedative action or deep comatose sleep for 48 hours (at maximal sublethal doses), and diarrhea (at high doses) and have not been allocated to the individual substances. Gross pathology generally did not show significant gross or microscopic tissue changes. Survivors of near lethal doses showed changes, which, although inconsistent, were indicative of liver and kidney damage. Microscopic examinations revealed occasional marked changes in the kidneys of rats (degeneration with sweeling, some necrosis of the tubular epithelium, thickening of Bowman´s capsule, hyaline deposition in glomerular tufts). More often only minor lesions with varying degrees of cloudy swelling of the tubules and hyaline casts in the lumina were seen. In general, liver changes were characterized by lymphocytic infiltration, occasional necrotic foci with small haemorrhages, and varying degrees of fatty degeneration. Only rarely tissue studies showed significant pathologic conditions as the result of relatively small doses of thiols. The oral LD_{50} for ethanethiol was determined to be 682 mg/kg bw (CL: 517 – 900 mg/kg bw) (calculated by the method of Weil, 1954).

[3] In the study report, the testing results for nine sulfur compounds are described (ethanethiol, 1-propanethiol, 2-methyl-1-propanethiol, 2-methyl-2-propanethiol, 1-butanethiol, 1-hexanethiol, methyl heptanethiol, benzenethiol, α-toluenethiol). Mortality data are presented in detail for each substance but the general signs of toxicity are only summarized as common effects of thiols. Therefore, allocation of (severity of) effects to single substances is not possible.

Table 10: Mortality following single oral administration of ethanethiol (Fairchild and Stokinger, 1958).

	Cumulative mortality following single oral administration					
Single oral dose [mg/kg bw]	day 1	day 2	day 3	day 5	day 10	day 15
210	0/5	0/5	0/5	0/5	0/5	0/5
420	0/5	0/5	0/5	0/5	0/5	0/5
840	2/5	2/5	2/5	2/5	3/5 (7^{th} day)	4/5 (11^{th} day)
1680	4/5	4/5	4/5	5/5	-	-
3360	5/5 (from 4 to 7h)	-	-	-	-	-

10.1.2 Comparison with the CLP criteria

According to Table 3.1.1 of Regulation (EC) No. 1272/2008 a substance shall be classified as

- Acute Tox 4 (oral) if the LD_{50}/ATE values are > 300 and ≤ 2000 mg/kg bw.

- Acute Tox 3 (oral) if the LD_{50}/ATE values are > 50 and ≤ 300 mg/kg bw.

For evaluation of acute oral toxicity of ethanethiol one study (Klimisch 2) with male rats is available determining an LD_{50} value of 682 mg/kg bw (CL: 517 – 900 mg/kg bw) (Fairchild and Stokinger, 1958).

10.1.3 Conclusion on classification and labelling for acute oral toxicity

Single oral administration of ethanethiol resulted in a LD_{50} in rats of 682 mg/kg bw (CL: 517 – 900 mg/kg bw) (Fairchild and Stokinger, 1958). Referring to the criteria laid down in Table 3.1.1. of CLP regulation ethanethiol meets the criteria for classification as Acute Tox 4, H302 (Harmful if swallowed).

An ATE value of 680 mg/kg bw (rounded value) has to be assigned based on the study by Fairchild and Stokinger (1958).

10.2 Acute toxicity - dermal route

Not evaluated.

10.3 Acute toxicity - inhalation route

For the evaluation of this endpoint four studies with rats and one with mice are available. A conversion factor of 1ppm = 2.578 mg/m^3 has been applied (DFG, 2019).

Table 11: Summary table of animal studies on acute inhalation toxicity

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance, form and particle size (MMAD)**	**Dose levels, duration of exposure**	**Value** **LC_{50}**	**Reference**
no guideline followed non-GLP	rats, Wistar derived, males	ethanethiol vapour chamber exposure	2600, 3150, 3573, 4438, 4832, 4868, 5100, 5125 ppm (6.61, 8.00, 9.08,	LC_{50} (15d) = 11.39 mg/L (4420 ppm; CL:	Fairchild and Stokinger, 1958

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance, form and particle size (MMAD)**	**Dose levels, duration of exposure**	**Value** **LC_{50}**	**Reference**
key study 2 (reliable with restrictions) remarks: no information on age of rats, body weight development not documented, generalized information on clinical and pathological observations	n= 5m/group		11.28, 12.28, 12.37, 12.98, 13.02 mg/L) exposure duration: 4h observation period: 15 d	4299-4541 ppm) LC_{50} (48h) = 11.77 mg/L (4565 ppm; CL: 4448-4682 ppm) LC_{50} (24h) = 12.55 mg/L (4870 ppm; CL: 4783-4957 ppm)	
no guideline followed non-GLP Key study 2 (reliable with restrictions) remarks: no information on age of rats, body weight development not documented, generalized information on clinical and pathological observations	mice, Swiss-derived, males n=10m/group	ethanethiol vapour chamber exposure	2600, 3150, 3573, 4438, 4832 ppm (6.61, 8.00, 9.08, 11.28, 12.28 mg/L) exposure duration: 4h observation period: 15 d	LC_{50} (48h) = 7.14 mg/L (2770 ppm) (CL: 2661-2879 ppm)	Fairchild and Stokinger, 1958
similar to OECD 403 non-GLP 2 (reliable with restrictions) derivations: acclimatization for 3 d, rats were 6-8 weeks old, temperature and humidity in the animal holding area exceeded the	rat, Sprague Dawley, Crl:CD(SD)BR strain m/f n= 5/sex/dose	ethanethiol vapour head only exposure (dynamic conditions)	0 and 991 ppm (analytic concentration) (nominal atmosphere concentration 1445 ppm) exposure duration: 4h observation period: 14 d	LC_{50} > 2.56 mg/L (991 ppm) No mortality was observed.	Anonymous,1987

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance, form and particle size (MMAD)**	**Dose levels, duration of exposure**	**Value** LC_{50}	**Reference**
OECD guideline range on several occasions.					
similar to OECD 403 non-GLP 2 (reliable with restrictions)	rat, Sprague Dawley m/f n= 5/sex/dose	ethanethiol vapour whole body	0 and 1.93 mg/L (nominal concentration) analytical concentration was 0.11 mg/L or 44.09 ppm ± 12.59 exposure duration: 4h observation period: 16 d	LC_{50} > 0.11 mg/L (44 ppm) No mortality was observed.	Anonymous, 1983
no guideline followed non-GLP 3 (not reliable)	rat, Sprague Dawley m/f n= 5/sex/dose	ethanethiol vapour whole body	m: 28400 ppm f: 15000 ppm 27000 ppm exposure duration: 1h	No LC_{50} can be derived m: no mortality f: 27000 ppm (69.6 mg/L): 3/5 15000 ppm (38.6 mg/L): 0/5	Vernot, 1977

10.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

Fairchild and Stokinger (1958) conducted acute inhalation toxicity studies with nine organic sulphur compounds[4] (single substance administration) in rats (n=5m/group) and mice (n=10m/group). For ethanethiol concentrations up to 5125 ppm were used with an exposure duration of 4h. The generation of thiol vapours was accomplished by either of two methods: (1) bubbling a stream of nitrogen gas (to prevent possible oxidation to sulfide) through a midget fritted-glass bubbler, which contained the liquid thiol, or (2) by passage of nitrogen into a borosilicate glass nebulizer which contained the thiol. Each of the described methods was used interchangeably, but with some of the lower boiling point thiols the bubbler proved more manageable and gave more uniform chamber concentrations than the nebulizer. During exposure the

[4] ethanethiol, 1-propanethiol, 2-methyl-1-propanethiol, 2-methyl-2-propanethiol, 1-butanethiol, 1-hexanethiol, methyl heptanethiol, benzenethiol, α-toluenethiol. For each substance a separate acute toxicity study was made, however method of vapour generation as well as general signs of toxicity were described generally and therefore cannot be allocated to the relevant substance ethanethiol.

concentrations within the chamber were determined routinely. Variations between extremes of vapour concentrations measured during any test was never greater than 15%, usually being about 9%; the minimum variation between concentrations was 0.4% while the mean variation for all exposures was approximately 4%. LC_{50} values were calculated by the method of Miller and Tainter (1944).

In male rats (Wistar derived) (200 ± 20g) mortality was observed at 4438 ppm and above (see Table 12). The LC_{50} was determined to be 12.55 mg/L (4870 ppm) at 24 hours, 11.77 mg/L (4565 ppm) at 48 hours, and 11.39 mg/L (4420 ppm) at 15 days after the exposure period.

Mice were more susceptible than rats. All male mice (Swiss-derived, 25-28g) exposed to concentrations of 4438 and 4832 ppm died. At 3573 ppm 8/10 died during 4-exposure period and 10/10 died within 24h. At 3150 ppm and 2600 ppm 7/10 and 4/10 animals died within 24h, respectively. For more details see Table 12. An LC_{50} = 7.14 mg/L (2770 ppm) has been determined at 48h after exposure.

Signs of intoxication for rats and mice were described as a summary for the tested thiols as increased respiration and hyperactivity, uncoordinated movement and staggering gait, muscular weakness, partial skeletal muscle paralysis beginning in 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, animals exposed to minimal lethal concentrations died while in a semiconscious condition of long duration. Animals exposed to ethanethiol very often remained in a semiconscious condition of sedation and lethargy 4 to 6 h post-exposure before showing signs of recovery. Thiols were irritating to the mucous membranes within approximately 15 min after exposure and animals in high concentrations showed rubbing of the eyes and nose, eye closure, occasional sneezing, watering of the eyes and retracting of the head.

Table 12: Cumulative mortality following acute inhalation exposure to ethanethiol vapour (Fairchild and Stokinger, 1958).

Analysed conc. [ppm and mg/L]	Cumulative Mortality							
	rats				mice			
	0-4h	24h	48	15d	0-4h	24h	48h	15d
2600 (6.7 mg/l)	0/5	0/5	0/5	0/5	1/10	4/10	4/10	4/10
3150 (8.12 mg/L)	0/5	0/5	0/5	0/5	4/10	7/10	7/10	7/10
3573 (9.21 mg/L)	0/5	0/5	0/5	0/5	8/10	10/10	-	-
4438 (11.44 mg/L)	0/5	0/5	1/5	1/5	10/10	-	-	-
4832 (12.46 mg/L)	1/6	3/6	3/6	4/6	10/10	-	-	-
4868 (12.55 mg/L)	1/5	2/5	2/5	2/5	-	-	-	-
5100 (13.15 mg/L)	2/5	5/5	-	-	-	-	-	-
5125	2/6	2/6	2/6	2/6	-	-	-	-

(13.21 mg/L)								

Anonymous (1987) reported an acute inhalation study with male and female Sprague-Dawley rats exposed for 4h to concentrations of 0 and 991 ppm (2.56 mg/L, analytic concentration) (head only). Vapour was generated using a 'J' tube with in-line filter. Air flow rates were monitored continuously at half-hourly intervals. No mortality was observed, therefore no LC_{50} could be derived. Transient signs of exposure included chromodacryorrhea, nasal secretion and respiratory distress shortly after exposure, with a full recovery observed in less than 24 hours. A slight reduction in control and exposed animal's body weights was noted and believed to be caused from the restraint procedure. Body weights recovered by day 7. No gross observations were noted at necropsy.

Anonymous (1983) exposed 5 male and 5 female rats in a glass chamber with a volume of 38L to a nominal concentration of 1.93 mg/L. Vapour was generated using a water-jacketed counter-flow column and monitored. The analytical concentration was 0.11 mg/L or 44.09 ppm ± 12.59 SD. No mortality was observed, no clinical signs were observed and no cross observations were noted at necropsy. A slight reduction in female mean body weight was noted on day 4. No LC_{50} could be derived.

According to Vernot (1977) five male rats (Sprague Dawley, 200-300g) survived 1h inhalation exposure to a concentration of 28400 ppm and five female rats to a concentration of 15000 ppm (concentration measured by standard techniques, very limited reporting). However, 3/5 female rats died after 1h exposure to 27000 ppm (69.6 mg/L). Information on the observation period is not available. Due to very limited information the study was rated as not reliable.

10.3.2 Comparison with the CLP criteria

According to Table 3.1.1 of Regulation (EC) No. 1272/2008 a substance (vapour) shall be classified as

- Acute Tox 4 (inhal) if the LC_{50} values are > 10.0 mg/L and ≤ 20.0 mg/L (4h exposure)
- Acute Tox 3 (inhal) if the LC_{50} values are > 2.0 mg/L and ≤ 10.0 mg/L (4h exposure)
- Acute Tox 2 (inhal) if the LC_{50} values are > 0.5 and ≤ 2 mg/L (4h exposure)
- Acute Tox 1 (inhal) if the LC_{50} values are ≤ 0.5 mg/L (4h exposure)

Based on the available studies it can be summarized that mice are more susceptible with a LC_{50} = 7.14 mg/L (2770 ppm) compared to rats with a LC_{50} = 11.39 mg/L (4420 ppm) (Fairchild and Stockinger, 1958). Due to the applied dosing regimen other studies could not identify LC_{50} values.

10.3.3 Conclusion on classification and labelling for acute inhalation toxicity

In general, classification is based on the lowest ATE value available i.e. the lowest ATE in the most sensitive appropriate species tested. Acute inhalation exposure to ethanethiol vapours resulted in a LC_{50} in mice of 7.14 mg/L (Fairchíld and Stokinger, 1958).

Referring to the criteria laid down in Table 3.1.1. of CLP regulation ethanethiol meets the criteria for classification as Acute Tox 3, H331 (Toxic if inhaled).

An ATE value of 7.14 mg/L has to be assigned based on the study by Fairchild and Stokinger (1958).

10.4 Skin corrosion/irritation

Not evaluated.

10.5 Serious eye damage/eye irritation

Not evaluated.

10.6 Respiratory sensitisation

Not evaluated.

10.7 Skin sensitisation

Not evaluated.

10.8 Germ cell mutagenicity

Not evaluated.

10.9 Carcinogenicity

Not evaluated.

10.10 Reproductive toxicity

Not evaluated.

10.11 Specific target organ toxicity-single exposure

Not evaluated.

10.12 Specific target organ toxicity-repeated exposure

Not evaluated.

10.13 Aspiration hazard

Not evaluated.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not evaluated.

12 EVALUATION OF ADDITIONAL HAZARDS

Not evaluated.

13 ADDITIONAL LABELLING

Not relevant.

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