Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

ethanethiol; ethyl mercaptan

EC Number: 200-837-3
CAS Number: 75-08-1

CLH-O-0000007153-80-01/F

Adopted

15 September 2022

15 September 2022

CLH-O-0000007153-80-01/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **ethanethiol; ethyl mercaptan**

EC Number: **200-837-3**

CAS Number: **75-08-1**

The proposal was submitted by **Austria** and received by RAC on **25 November 2021.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Austria has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **13 December 2021**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **11 February 2022**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Beata Pęczkowska**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **15 September 2022** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	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** inhalation: ATE = 7.14 mg/L (vapours) oral: ATE = 680 mg/kg	
RAC opinion	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** inhalation: ATE = 7.1 mg/L (vapours) oral: ATE = 680 mg/kg	
Resulting entry in Annex VI if adopted by RAC and agreed by Commission	016-022-00-9	ethanethiol; ethyl mercaptan	200-837-3	75-08-1	Flam. Liq. 1 Acute Tox. 3 Acute Tox. 4 Aquatic Acute 1 Aquatic Chronic 1	H224 H331 H302 H400 H410	GHS02 GHS06 GHS09 Dgr	H224 H331 H302 H410		inhalation: ATE = 7.1 mg/L (vapours) oral: ATE = 680 mg/kg	

GROUNDS FOR ADOPTION OF THE OPINION

RAC evaluation of physical hazards

Summary of the Dossier Submitter's proposal

Flammable liquids

The dossier submitter (DS) presented a study for determination of the flash point using the Abel closed cup method according to EC A.9 with ethanethiol (purity 99.97 %), reporting a flash point of < -30 °C (Anonymous, 2010). This is supported by a flash point of -48.3 °C, taken from the WHO IPCS International Chemical Safety Cards (ICSC 0470, 2004).

The boiling point was measured by differential scanning calorimetry (DSC) according to EN ISO 537-86 and EC method A.2 (Anonymous, 2012). The lowest result of two measurements at 100.9 kPa (34.1 °C and 34.5 °C) was converted to standard atmospheric pressure (101.3 kPa) 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. This is supported by a boiling point of 35 °C, taken from the WHO IPCS International Chemical Safety Cards (ICSC 0470, 20042).

The DS proposed classification as Flam. Liq. 1, H224 (Extremely flammable liquid and vapour).

Comments received during public consultation

No comments were received.

Assessment and comparison with the classification criteria

Based on presented measurements, the flash point was determined to be < -30 °C and the boiling point was determined to be 34.1 °C. RAC agrees with the DS that ethanethiol meets the classification criteria of the CLP Regulation, Table 2.6.1, (Flash point < 23 °C and initial boiling point ≤ 35 °C) for **Flam. Liq. 1, H224 (Extremely flammable liquid and vapour).**

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Acute oral toxicity

In one acute oral toxicity study in rats (Fairchild and Stokinger, 1958). Ethanethiol (undiluted) was administered (via gavage) to male Wistar rats (5/dose) at five single doses from 210 to 3360 mg/kg bw. The animals were subsequently observed for a period of 15 days. Mortality is summarised in the table below.

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

Dose (mg/kg bw)	Mortality in males
210	0/5
420	0/5
840	4/5 (mortality within 11d after administration)
1680	5/5 (mortality within 5d after administration)
3360	5/5 (mortality within 7h after administration)

The oral LD_{50} for ethanethiol was determined to be 682 mg/kg bw (calculated by the method of Weil, 1954). The DS proposed classification as Acute Tox. 4; H302 with an ATE of 680 mg/kg bw based on an acute oral toxicity study in rats.

Acute inhalation toxicity

There are four acute inhalation toxicity studies with rats and one with mice available.

In a study by Fairchild and Stokinger (1958), ethanethiol concentrations up to 13.21 mg/L (5125 ppm) and 12.46 (4832 ppm) were used with an exposure duration of 4h in rats and mice, respectively. The generation of ethanethiol vapours was accomplished by methods appropriate to prevent possible oxidation to sulfide. During exposure the concentrations within the chamber were determined routinely. Variations between extremes of vapour concentrations measured during any test was never greater than 15 %, while the mean variation for all exposures was approximately 4 %. The animals were subsequently observed for a period of 15 days. Mortality is summarised in the table below.

***Table**: Mortality following acute inhalation exposure to ethanethiol vapour for 4h (Fairchild and Stokinger, 1958).*

Analysed Concentration		Mortality	
mg/L	ppm	Rats (Wistar) males	Mice (Swiss) males
6.7	2600	0/5	4/10 (within 24h after exp.)
8.12	3150	0/5	7/10 (within 24h after exp.)
9.21	3573	0/5	10/10(within 24h after exp.)
11.44	4438	1/5 (within 48h after exp.)	10/10 (within 4h after exp.)
12.46	4832	4/6 (within 15d after exp.)	10/10 (within 4h after exp.)
12.55	4868	2/5 (within 24h after exp.)	-
13.15	5100	5/5 (within 24h after exp.)	-
13.21	5125	2/6 (within 4h after exp.)	-

LC_{50} values were calculated by the method of Miller and Tainter (1944).

In male rats (Wistar) the LC_{50} was determined to be 11.39 mg/L (4420 ppm) at 15 days after the exposure period. In male mice (Swiss) the LC_{50} = 7.14 mg/L (2770 ppm) has been determined. Mice were more susceptible than rats.

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). No mortality was observed, therefore no LC_{50} could be derived. Transient effects of exposure included chromo-dacryorrhea, nasal secretion and respiratory distress shortly after exposure, with a full recovery observed in less than 24h.

Anonymous (1983) exposed five male and five female rats in a glass chamber with a volume of 38 L to a nominal concentration of 1.93 mg/L. The analytical concentration was 0.11 mg/L or

44.09 ppm ± 12.59 SD. No mortality and no clinical signs were observed. No LC_{50} could be derived.

According to Vernot (1977), five male rats (Sprague Dawley) survived 1h inhalation exposure to a concentration of 28400 ppm (73.22 mg/L) and five female rats to a concentration of 15000 ppm (38.67 mg/L) (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.

The DS proposed Acute Tox. 3; H331 (Toxic if inhaled) with an ATE of 7.14 mg/L (vapours) based on an acute inhalation study in mice as the most sensitive species (Fairchild and Stokinger, 1958).

Comments received during public consultation

One MSCA supported the DS's proposal for classification and ATE values for both acute oral and inhalation toxicity based on the results of the studies available.

One Company/Manufacturer did not agree with the change in classification for acute inhalation toxicity from category 4 to 3, as proposed by DS, based on the following arguments:

- in a survey published in 1978 there were approximately 23100 workers in the US engaged in activities involving potential exposure to ethyl mercaptan with no reported fatalities caused by inhalation of ethyl mercaptan alone (NIOSH, 1978);

- in a recent search no reports were found of direct fatalities reported from acute inhalation of ethyl mercaptan and no evidence of serious injury. There are reports of fatalities, either accidental or intentional (suicide), from exposure to propane containing ethyl mercaptan as an odour signal but the cause of death was determined to be asphyxiation from propane (Aquila *et al.*, 2020; Lowry *et al.*, 1991). A report by the US Bureau of Labor Statistics identifying the top 14 chemicals involved in workplace inhalation fatalities (BLS, 2017) did not identify ethyl mercaptan as a significant contributor to workplace inhalation fatalities;

- the lowest LC_{50} reported from animal studies is 2770 ppm for a 4-h exposure in mice (Fairchild and Stokinger, 1958), while the odour detection threshold for ethyl mercaptan is approximately 1.4×10^{-4} ppm (NRC, 2013), thus 27 million-fold lower than potentially lethal concentrations in the air;

- current workplace practices for ethyl mercaptan have been effective in the manufacturing setting for protecting workplace health;

- according to all available inhalation study guidelines, and as specified in OECD TG 403 protocol, the preferred species is the rat (OECD, 2018, 2009; US EPA, 1998), although the CLP guidelines advise classification based on the lowest ATE in the most sensitive species tested (ECHA, 2017) and the use of species other than the preferred species be supported by suitable justification and application of scientific judgement (ECHA, 2017, page 241);

- selecting the lowest LC_{50} value does not constitute scientific justification for the selection of an alternative species over the preferred species; the Fairchild and Stokinger 1958 publication includes a study in rats, the preferred species; in this study the reported LC_{50} is 442 ppm (12.5 mg/L) which would justify the historical use of GHS category 4 classification criteria for acute inhalation toxicity.

The DS responded to the above comments by stating that classification according to the CLP Regulation should be based on intrinsic hazards, and the proposal for harmonised classification has been prepared based on the information and studies reported in the registration dossier and original studies provided by registrant(s). All available relevant data needs to be included in the CLH report and considered in the derivation of the appropriate hazard classification to allow an independent assessment by RAC. Omission of relevant information needs to be explicitly justified which is not applicable for the data on mice based on the information given in the reference (Fairchild, 1958). When experimental data for acute toxicity are available in several animal species, scientific judgement shall be used in selecting the most appropriate LC_{50} value from among valid, well-performed tests. As mentioned above, in general, classification is based on the lowest ATE value available i.e., the lowest ATE in the most sensitive appropriate species tested. If there is information available to inform on species relevance, then the studies conducted in the species most relevant for humans should normally be given precedence over the studies in other species (CLP guidance, 2017). No such information is available; therefore, the LC_{50} value from the most sensitive species has been used for classification.

Assessment and comparison with the classification criteria

Acute oral toxicity

The key data consists of the acute oral toxicity study in rats (similar to OECD 420 test guideline, not GLP compliant; Fairchild and Stokinger, 1958). The LD_{50} was > 420 and < 840 mg/kg bw for male rats; LD_{50} calculated by the method of Weil[1] was 682 mg/kg bw (95 % confidence limit 517-900 mg/kg bw).

The disadvantage of the above study is that only male rats were tested. Considering that an inhalation study by Vernot (1977) indicates that female rats are more sensitive than males, and the LD_{50} for female rats would be lower than that obtained for male rats. However, a lower LD_{50} for females is not expected to be below the criteria for Acute Tox. 4 (< 300 mg/kg bw).

Based on results of one acute oral toxicity study available, RAC agrees with the DS that ethanethiol meets the classification criteria of the CLP Regulation, Table 3.3.1, (the LD_{50} values > 300 and ≤ 2000 mg/kg bw.) for **Acute Tox. 4; H302** (Harmful if swallowed), with an **ATE** of **680 mg/kg bw** (rounded-off).

Acute inhalation toxicity

In the key study on acute inhalation toxicity in rats and mice (Fairchild and Stokinger, 1958) lethal concentrations were in the range between 11.44 and 13.15 mg/L (> 4438 and < 4832 ppm) for male rats and in a range between 6.7 and 9.21 mg/L (> 2600 and < 3150 ppm) air for male mice. The LC_{50} calculated by the method of Miller and Tainter (1944) was 11.39 mg/L (4420 ppm) for male rats and 7.14 mg/L (2770 ppm) for male mice. Mice were more susceptible than rats.

It is noted that the saturated vapour concentration is 1500 mg/L (581846 ppm) calculated from the ideal gas law equation for vapour pressure of ethanethiol of 58.9kPa at 20 °C. Therefore, the concentrations of the tested ethanethiol are much lower than the saturated vapour concentration at 20 °C. Therefore, a test atmosphere consisting of mist of ethanethiol is not expected. The generation of the ethanethiol atmosphere in the above study was accomplished with a bubbler

[1] Weil, C.S.: Tables for Convenient Calculation of Median-Effective Dose (LD_{50} or ED_{50}) and Instruction in Their Use. Biometrics, 8: 249-304 (1954)

or nebulizer and thus the test material was inhaled in a form of vapour as reported in the study description. Due to the fact that the temperature in the chamber is below the boiling point and the vapour pressure at 20 °C is below 101.3 kPa, ethanethiol is not considered as a gas.

The DS further presented two non-standard acute inhalation toxicity studies in rats (Anonymous, 1987; Anonymous, 1983), where no mortality was observed and an LC_{50} could not be derived, and one poorly reported acute inhalation study (Vernot, 1977) in rats (1 h exposure) which was considered as not reliable.

Both studies in rats and mice by Fairchild and Stokinger, 1958, were conducted following the same procedure. The generation of ethanethiol vapours and measurements of its concentration were carried out by the same methods in both mice and rat tests. More reliable data was obtained in the mice study, as there were more animals per group than in the rat study. According to Guidance on IR&CSA, Section R.7.4.5.1 *"when equally reliable data from several species are available, priority should be given to the data relating to the most sensitive species, unless there are reasons to believe that this species is not an appropriate model for humans"*. Taking all available data into account there is no evidence indicating which a species of animals is more relevant to humans taking into account the mode of action of ethanethiol. Thus, the LC_{50} obtained in the most sensitive species should be used for classification of acute inhalation toxicity of ethanethiol. It should be noted that only male rodents were tested in the key acute inhalation toxicity study by Fairchild and Stokinger (1958), but female rats were known to be more susceptible than male rats, as shown by the Vernot (1977) study. Therefore, it can be assumed that the (actual) LC_{50} for male and female rats combined would be lower than the LC_{50} obtained for male rats only.

Based on results of the key acute inhalation toxicity study and LC_{50} value from the most sensitive species, mice (Fairchild and Stokinger, 1958), RAC agrees with the DS that ethanethiol meets the classification criteria of the CLP Regulation, Table 3.3.1, (LC_{50} > 2.0 and ≤ 10.0 mg/L, 4h exposure to vapours) for **Acute Tox. 3; H331 (Toxic if inhaled), with an ATE value of 7.1 mg/L (vapours).**

Additional references

NIOSH, 1978. Criteria for a Recommended Standard: Occupational Exposure to n-Alkane Mono Thiols, Cyclohexanethiol, and Benzenethiol. Centers for DiseaseControl, National Institute for Occupational Safety and Health, Atlanta, GA. https://doi.org/DHHS (NIOSH) Publication Number 78-213;

Aquila, I., Ricci, C., Sacco, M.A., Gratteri, S., De Aloe, L., De Pasquale, C.C., Ricci, P., 2020. The role of ethanethiol in deaths from acute poisoning by gas mixtures: A suicide case involving a decomposed corpse and a review of the literature. Med. Leg. J. 88, 199–204. https://doi.org/10.1177/0025817219891948;

Lowry, W.T., Gamse, B., Armstrong, A.T., Corn, J.M., Juarez, L., McDowell, J.L., Owens, R., 1991. Toxicological investigation of liquid petroleum gas explosion: human model for propane/ethyl mercaptan exposures. J. Forensic Sci. 36, 386–396;

BLS, 2017. Fatal chemical inhalations in the workplace up in 2017, The Economics Daily. Washington, DC;

NRC, 2013. Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 15, 15th ed. National Academies Press, Washington, DC, USA. https://doi.org/10.17226/18449;

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).