Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the 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

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON ETHANETHIOL; ETHYL MERCAPTAN

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: ethanethiol; ethyl mercaptan
EC number: 200-837-3
CAS number: 75-08-1
Dossier submitter: Austria

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
11.02.2022	Belgium	Chevron Phillips Chemicals International	Company-Manufacturer	1

Comment received

We appreciate the opportunity to respond to the recommendations from the Austrian authorities on the acute inhalation classification for ethyl mercaptan (CAS 75-08-1). We think the GHS category 4 classification for acute inhalation is most appropriate and the category 3 classification results in an unnecessary over-labeling of this substance. Based on historical workplace experience there is no benefit to workplace safety in classifying ethyl mercaptan as a category 3 acute inhalation substance.

We suggest the final decision on the classification of this substance consider the following:

• Ethyl mercaptan has been in commerce since the 1940 with a demonstrated history of safe use (NIOSH, 1978). It has been classified as category 4 for acute inhalation with an H332: Harmful if inhaled [Warning Acute toxicity, inhalation] since the Globally Harmonized System of Classification and Labelling of Chemicals was introduced and adopted by the United Nations Conference on Environment and Development in 2003 (UNCED, 2003). In addition, ethyl mercaptan is listed on Annex VI as a category 4 acute inhalation toxicant (EU, 2021).

• A search of government databases and the public literature reveal no evidence that the current category 4 classification and warning statement is insufficient. In a survey published in 1978 there were approximately 23,100 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). When we conducted a

recent search we found no reports 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 odor 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 identifies the top 14 chemicals involved in fatal workplace inhalation fatalities (BLS, 2017). This report did not identify ethyl mercaptan as a significant contributor to workplace inhalation fatalities.

• It is not surprising that fatalities by inhalation from ethyl mercaptan are rare across the industry. Because of its strong odor, ethyl mercaptan is easily detected by workers which would prompt them to take precautions to avoid exposure. The odor threshold for ethyl mercaptan is approximately 1.4 x 10-4 ppm (NRC, 2013) while the lowest LC50 reported from animal studies is 2770 ppm for a four-hour exposure in mice (Fairchild and Stokinger, 1958). This is a 27 million-fold difference between odor detection and potentially lethal concentrations in the air. In contrast, hydrogen sulfide, has been shown to cause lethality by inhalation in the workplace (BLS, 2017) and has an odor detection to LC50 ratio of less than 63,000 (The odor-detection threshold for hydrogen sulfide (CAS 7783-06-4) is 8 x 10-3 ppm while the lowest LC50 is 501 ppm for a four-hour exposure to rats (ATSDR, 2016). Between 2011 and 2017 exposures to hydrogen sulfide resulted in 46 workplace fatalities in the United States, second only to the more than 200 fatalities caused by carbon monoxide during this same period (BLS, 2017)).

• During the over eighty years of commercial use, the ethyl mercaptan manufacturing industry and those using ethyl mercaptan have developed practices that have been effective in protecting workplace health and safety. The "Harmful if inhaled" warning, or its historic equivalent, has a specific meaning to those in the industry working with ethyl mercaptan and has effectively guided workplace practices throughout the value chain. Changing to a category 3 classification with its "Toxic if inhaled" warning has the potential to result in changes that may be unevenly applied across the industry. This could undermine the effectiveness of the acute inhalation hazard warning as a risk-mitigation tool.

• As we point out, current workplace practices for ethyl mercaptan have been effective in the manufacturing setting for protecting workplace health. For downstream users of ethyl mercaptan the change in hazard classification could have an unintended impact and could even result in changes that are counter-productive to protection of health. One of the significant downstream uses of ethyl mercaptan is as an odorant to provide warning of exposure to otherwise odorless products such as propane. Ethyl mercaptan is ideal for this use because of its extremely low odor threshold and its low inherent hazard profile. Changes in the inhalation hazard classification could cause downstream users to reconsider their use of ethyl mercaptan and instead, select another, potentially more hazardous substance or one with a higher odor perception threshold thus reducing the risk mitigation potential of this use.

Thus, it is our opinion there would be no benefit to public health or workplace safety in changing the GHS classification from category 4 to category 3 and could have a downside for workplace health.

From a technical perspective, the proposed GHS/CLP category 3 classification is based on results from an inhalation study in mice (Fairchild and Stokinger, 1958). According to all available inhalation study guidelines, and as specified in OECD 403 protocol, the preferred species is the rat (OECD, 2018, 2009; US EPA, 1998). We recognize that the CLP

guidelines advise classification based on the lowest ATE in the most sensitive species tested (ECHA, 2017). However, the same guidelines specify that the use of species other than the preferred species be supported by suitable justification and application of scientific judgement (ECHA, 2017 page 241).

There does not appear to be scientific justification provided by the Austrian review for the use of the mouse dataset for classification of acute inhalation toxicity. We could find no information in the public literature or in available guidelines justifying the selection of the mouse over the rat for the purposes of this classification. Simply selecting the lowest LC50 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 LC50 is 442 ppm (12.5 mg/L) which would justify the historical use of GHS category 4 classification criteria for acute inhalation.

An additional consideration is the susceptibility of mouse colonies to the Sendai virus which can confound interpretation of inhalation studies in mice. The Sendai virus is a highly infectious respiratory virus that compromises pulmonary function in infected mice (Faísca and Desmecht, 2007). Rats can also become infected with Sendai but are less susceptible to the respiratory effects than mice (Parker and Reynolds, 1968; Parker et al., 1978). While the prevalence of mouse colony Sendai infection in the 50s has not been characterized, the possibility does raise an additional level of uncertainty about the interpretation of the mouse inhalation study used as justification for the category 3 classification of ethyl mercaptan.

We trust you will take our concerns into consideration as you reach your decision on the acute inhalation classification of ethyl mercaptan.

References

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

ATSDR, 2016. TOXICOLOGICAL PROFILE FOR HYDROGEN SULFIDE AND CARBONYL SULFIDE. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service, Atlanta, GA.

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

ECHA, 2017. Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7a: Endpoint specific guidance. Helsinki, Finland. https://doi.org/10.2823/337352

EU, 2021. REGULATION (EC) No 1272/2008 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC). European Union 02008R1272 — EN — 01.10.2021.

Fairchild, E., Stokinger, H., 1958. Toxicologic studies on organic sulfur compounds. I. Acute toxicity of some aliphatic and aromatic thiols (mercaptans). Am. Ind. Hyg. Assoc. J.

19, 171–189. https://doi.org/10.1080/00028895809343573

Faísca, P., Desmecht, D., 2007. Sendai virus, the mouse parainfluenza type 1: a longstanding pathogen that remains up-to-date. Res. Vet. Sci. 82, 115–125. https://doi.org/10.1016/j.rvsc.2006.03.009

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.

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

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

OECD, 2018. GUIDANCE DOCUMENT ON INHALATION TOXICITY STUDIES Series on Testing and Assessment - Second edition.

OECD, 2009. Test No. 403: Acute Inhalation Toxicity. OECD Guidel. Test. Chem. 403, 1–11. https://doi.org/https://doi.org/10.1787/20745788

Parker, J., Reynolds, R., 1968. NATURAL HISTORY OF SENDAI VIRUS INFECTION IN MICE. Am. J. Epidemiol. 88, 112–125. https://doi.org/doi.org/10.1093/oxfordjournals.aje.a120859

Parker, J.C., Whiteman, M.D., Richter, C.B., 1978. Susceptibility of inbred and outbred mouse strains to Sendai virus and prevalence of infection in laboratory rodents. Infect. Immun. 19, 123–130. https://doi.org/10.1128/iai.19.1.123-130.1978

UNCED, 2003. Globally Harmonized System of Classification and Labelling of Chemicals (GHS), First. ed. United Nations Conference on Environment and Development (UNCED), New York and Geneva.

US EPA, 1998. Health Effects Test Guidelines OPPTS 870.1300 Acute Inhalation Toxicity. https://doi.org/EPA 712–C–98–193

Dossier Submitter's Response

Thank you for this additional information.
Classification according to CLP is based on intrinsic hazards, evaluation of the downstream consequences of a classification is not part of the dossier.
Ethanethiol currently has a minimum classification for acute toxicity via inhalation and therefore has been reevaluated. The proposal for harmonized 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 taken into account in the derivation of the appropriate hazard classification and should 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 LD50 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. However, expert judgement may allow another ATE value to be used in preference, provided this can be supported by a robust justification. 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 (ECHA guidance, 2017). Based on our knowledge no such information is available, therefore the LC50 value from the most sensitive species has been used for classification. Presented human evidence (Shibata, 1966 cited in NIOSH, 1978) showed that after acute exposure (20min) to ethanethiol at 50-112ppm, some physiological changes occurred (decreased breathing rate) and the olfactory apparatur became fatigued within minutes of exposure (n=3 males). However, this limited data can not be used to omit the proposed classification.
RAC's response
Thank you for your comment. RAC agrees with the DS's respons. CLP classification is based on assessment of intrinsic hazards of substances; therefore, all available data should be taken into account for the purpose of classification.

Date	Country	Organisation	Type of Organisation	Comment number
11.02.2022	France		MemberState	2
Comment received				
Acute oral toxicity: Based on the results of the study available, FR agrees with the classification Acute Tox 4, H302 and the ATE of 680 mg/kg bw. Acute inhalation toxicity: Based on the results of the studies available, FR agrees with the classification Acute Tox 3, H331 and the ATE of 7.14 mg/L.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your comment and support.				