Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

ethylene oxide; oxirane

EC Number: 200-849-9
CAS Number: 75-21-8

CLH-O-0000001412-86-164/F

Adopted

22 September 217

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public 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 public 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 public 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.

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Substance name: ethylene oxide
EC number: 200-849-9
CAS number: 75-21-8
Dossier submitter: Austria

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
18.11.2016	Germany		MemberState	1
Comment received				
The German CA generally agrees to the proposed classification of ethylene oxide. The German CA also noted that the current harmonised classification entry is incomplete. According to the adaptation to technical and scientific progress (cf. 4. ATP to the CLP Regulation) the hazard class "Flammable gases (including chemically unstable gases)" in section 2.2 of Annex I to CLP Regulation has been amended and therefore, Ethylene oxide has to be classified as Flam. Gas 1, H220, Chem. Unst. Gas A, H230. The classification of Ethylene oxide as chemically unstable gas refers to Table 35.1 of the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria (Sixth revised ed.), New York and Geneva: United Nations, 2015, ISBN 978-92-1-139155-8, ST/SG/AC.10/11/Rev.6. The German CA also strongly suggests that in all cases when there is an update of the classification of substances which have been classified as STOT SE 3 H335 by translation, this endpoint should be reconsidered as well. Especially in this case where acute toxicity via inhalation and skin corrosivity are addressed the appropriateness of H335 and/or EUH071 should have been examined.				
Dossier Submitter's Response				
Phys-chem. properties of the substance have not been evaluated but we agree that the amendments due to the 4th APT of CLP have to be included. According to Comission Regulation (EU) No 487/2013 (4th ATP of CLP regulation) a flammable gas that is also chemically unstable shall additionally be classified in one of the two categories for chemically unstable gases using the methods described in Part III of the UN Recommendations on the Transport of Dangerous Goods. For Ethylene oxide however no further testing is necessary as it is already included in Table 35 of UN RTDG, 6th revision with the classification Chem.Unst. Gas A.				

Ethylene oxide has to be classified as Flam. Gas 1, H220, Chem. Unst. Gas A, H230.

The classification for respiratory tract irritation has been introduced with 12th ATP (91/325/EEC) and no documentation of the former discussion is available. The former classification in Xi; R36/37/36 (DSD 67/548/EEC) has been translated to Eye Irrit. 2, Skin Irrit. 2, STOT SE 3 (CLP-regulation 1272/2008/EC).

According to CLP guidance (Chapter 3.8.2.5) it is a reasonable assumption that corrosive substances may also cause respiratory tract irritation when inhaled at exposure concentrations below those causing frank respiratory tract corrosion. If there is evidence from animal studies or from human experience to support this then Category 3 may be appropriate. In general, a classification for corrosivity is considered to implicitly cover the potential to cause RTI and so the additional Category 3 is considered to be superfluous, although it can be assigned at the discretion of the classifier. The Category 3 classification would occur only when more severe effects in the respiratory system are not observed.

For completeness a rough presentation of the available data can be done here. Evaluation will be based primarily on human data. There are currently no validated animal tests that deal specifically with RTI, but animal studies (single and repeated inhalation toxicity tests) can be used as a part of weight of evidence evaluation.

Ethylene oxide is a corrosive substance. It is gaseous at room temperature with an odor threshold at 260ppm (US EPA, 2010). Following data are available (detailed data are given in the relevant chapters in the CLH-dossier):
Human data:

- casuistic reports of human intoxication showed……..dyspnoea, irritation of the eyes and upper respiratory mucosa (DFG, 1993)
- Survey (165 workers, mean conc 3.4ppm, peak exposure exceeding 260ppm): The most prevalent symptoms other than the odor of ethylene oxide included headaches, skin and eye irritation, dry mouth and sore throat. Other symptoms included skin rash, runny nose, loss of sense of smell, shortness of breath, nausea, numbness in fingers, and drowsiness. (Bryant, 1989)
- Five hospital workers exposed for 30 min to ethylene oxide; three workers experienced more serious signs of toxicity,which included irritation of the upper respiratory tract, dry mouth and thirst, conjunctival irritation, severe headache, and intense generalized pruritus, along with muscular weakness in one worker and dizziness in another (Deleixhe, 1986)
- Case report (4 h/day for 4 days.): Signs and symptoms after the 4-day exposure included coughing, shortness of breath, and wheezing. Respiratory symptoms persisted and 1 year after the accident, pulmonary function tests showed bronchial obstruction and bronchial hyperreactivity (Deschamps, 1992).
- Case report (n=3, workers accidentally exposed for 2 weeks to 2 months to ethylene oxide vapour). Symptoms they experienced included irritation of the conjunctiva and mucous membranes, decreased sense of smell and taste, headaches, nausea, vomiting, and lethargy (Gross, 1979).
- Case report (n=1, accidential exposure for 2-3min to estimated 500ppm): symptoms of intoxication including repeated episodes of nausea, stomach spasms, paleness, lightheadedness, short periods of unconsciousness, convulsive movements of her arms and legs, and periods of apnea (cessation of breathing), muscle twitching, nausea, and malaise continued for 24 h after exposure (Salinas, 1981).

Animal data (acute inhalation studies):

- 4h acute inhalation study (rats, 850 – 2182ppm): During exposure, signs of eye, nasal and oral irritation (blepharospasm; wetness and encrustation around the eyes, nose, and mouth; swollen eye tissue), hypoactivity, and signs of respiratory distress (audible respiration, mouth breathing, increased or shallow respiration, and gasping) were noted. Alle symptoms were reversible. Lung histopathology showed pulmonary congestion, mild haemorrhage, pulmonary edema, emphysema. (Nachreiner, 1991)
- 1h acute inhalation study (rat, 3609-6161ppm): Findings suggest that ethylene oxide was irritating to the eyes and the respiratory tract and toxic to the nervous system (decreased respire. rate, periocular/perinasal encrustation, perinasal wetness, hypoactivity, ataxia, tremors). Gross examination showed effects in the nose, lungs, and kidneys. Lung weights were elevated in animals that died before the study ended compared with the lungs of animals that survived until study termination, particularly in the male groups (Nachreiner, 1992)
- 4h inhalation study (rat, 100-1600ppm): Lacrimation and dyspnea were observed at 800ppm; severe dyspnea, incoordination, semiconsciousness, and diarrhea were observed in animals exposed to 1600ppm. No clinical signs were described for the 100- and 400ppm groups (NTP, 1987).

The criteria for classifying substances as Category 3 for respiratory tract irritation are:

- respiratory irritant effects (characterized by localized redness, oedema, pruritis and/or pain) that impair function with symptoms such as cough, pain, choking, and breathing difficulties are included – human data (Maybe supported by objective measurements).
- there are currently no validated animal tests that deal specifically with RTI, however, useful information may be obtained from the single and repeated inhalation toxicity tests. For example, animal studies may provide useful information in terms of clinical signs of toxicity (dyspnoea, rhinitis etc) and histopathology (e.g. hyperemia, edema, minimal inflammation, thickened mucous layer) which are reversible and may be reflective of the characteristic clinical symptoms described above (weight of evidence evaluation)

Conclusion: The current classification for STOT SE3, H335 seems appropriate.

RAC's response

Since physico-chemical endpoints were not proposed for classification by the dossier submitter and were not open for comment during public consultation, RAC did not evaluate these endpoints.
An evaluation of the current classification as STOT SE 3; H335 was not considered by the dossier submitter, and no data were included in the dossier. RAC did not evaluate the classification for respiratory irritation.

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2016	Austria	Austrian Workers' Compensation Board	National Authority	2

Comment received

We Support classification into the new hazard classes and / or categories.

Dossier Submitter's Response

Thank you for your support.

RAC's response

Thank you for the comment.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
18.11.2016	Germany		MemberState	3

Comment received

Our comment refers to the dossier submitter's proposal to classify ethylene oxide for Repr. 2 – H361fd.
In chapter 4.11.6, the dossier submitter concludes:
"[…] EO (ethylene oxide) has the potential to affect male reproductive organs and female fertility and a potential for developmental toxicity cannot be excluded. […] However, as there are some uncertainties related to the data base, a classification in Category 1B appears not justified, but Category 2 […] is proposed."
In our opinion, there is room for interpretation regarding the proper sense of "some uncertainties related to the data base". We assume that in this context "some uncer-tainties" refer especially to the species-specific differences in metabolism between humans and experimental animals. If we understand the dossier submitter correctly, he is of the opinion that these mere differences are not sufficient to argue for non-classification. However, he also takes the view that these differences are still relevant in such a way that they alleviate the concern for reproductive toxicity in humans from category 1B to category 2. We have doubts whether this line of reasoning is justified.

There is information on physiologically based pharmacokinetic models for ethylene oxide which is also reported in a IARC monograph (IARC 2008). In this document, they say: "[…] exposure to a given concentration of ethylene oxide in air gives similar pre-dicted blood levels of ethylene oxide and areas under the curve for mice, rats and humans (in the range of exposures used in rodent cancer bioassays, i.e. 100 ppm [183 mg/m³] and below; above these concentrations, the differences in GSH depletion may be expected to lead to significant differences in the levels of eth-ylene oxide in blood with comparable concentrations in the ambient air)".
In the CLH-dossier, two inhalation studies are presented in which ethylene oxide produces adverse effects on reproduction relevant for classification already at 100 ppm and below:
According to Mori et al. (1991), spermatogenesis in Wistar rats was affected after exposure to 50 ppm ethylene oxide in a subchronic study. The number of teratic sperms started to increase at that concentration in a statistically significant manner but not in a concentration-dependant manner. General toxicity was not reported.
According to Snellings et al. (1982), statistically significant reproductive and devel-opmental toxic effects were observed in F344 rats exposed to 100 ppm ethylene ox-ide for one generation. The adverse effects appeared in terms of reduced median number of implantation sites per pregnant rat, reduced median number of pups born per litter and reduced median number of fetuses born per number of implantation sites. Signs for maternal toxicity were not reported.

Considering these two inhalation studies in rats and IARC's statement on blood levels and areas under the curve of ethylene oxide in rodents and humans, we question whether it is justified to alleviate the concern for reproductive toxicity in humans from category 1B to category 2 based on qualitative considerations on metabolism. We acknowledge that there are major qualitative differences between humans and rodents. However, relevant adverse effects on reproduction and prenatal development apparently occur at concentrations (i.e. at 50-100 ppm) where PBPK models do not yet predict significant quantitative differences in internal doses of ethylene oxide.

References:
IARC (2008): 1,3-Butadiene, Ethylene Oxide and Vinyl Halides (Vinyl Fluoride, Vinyl Chloride and Vinyl Bromide). IARC Monographs on the Evaluation of Carcinogenic Risks to

Humans, Vol. 97.
Mori et al. (1991): Dose dependent effects of inhaled ethylene oxide on spermato-genesis in rats. Br J Ind Med 48, 270-274.
Snellings et al. (1982): Effects on reproduction in Fischer 344 rats exposed to eth-ylene oxide by inhalation for one generation. Toxicol Appl Pharmacol 63, 382-388.

Dossier Submitter's Response

In the CLH-dossier the difference in the metabolism between humans and animals is presented in Chapter 4.1: *"In humans the major amount of ethylene oxide is metabolized by hydrolysis, only 20% are converted to glutathione conjugates and there is little change in metabolism with increasing exposure concentration. In mice and rats a higher portion of ethylene oxide is metabolized by GSH conjugation (80% and 60 % respectively) resulting in a depletion of GSH at higher exposure concentrations (100ppm and above) and non-linearity in metabolic elimination of ethylene oxide.* " and Fennell, 2001 wrote *"In the linear range for the exposure and blood concentration (below 200 ppm) for rat, mouse, and human, there are similarities in the blood concentration of ethylene oxide across species…"* and *"This extensive GSH depletion results in a nonlinear relationship between exposure concentration and blood concentration, with the break in linearity occurring between 200 and 300 ppm."* Reproductive toxicity was seen in animals already at 100ppm where the GSH depletion is not a relevant factor to be considered and the effects seen are relevant for classification. Therefore it has been concluded in the CLH dossier that the available knowledge on differences in metabolism among different species, including man, is considered insufficient to exclude the relevance of reproductive toxicity seen in several animal species for humans.

The conclusion on reproductive toxicity say : "….*However, as there are some uncertainties related to the data base, a classification in Category 1B appears not justified, but Category 2 (suspected human reproductive toxicant) is proposed."* These uncertainties do not mean uncertainties in the metabolism but uncertainties due to limited information on parental toxicity in some studies (see table 65/66) and the limited exposure information in the presented human data.

RAC's response

RAC agrees that available knowledge on differences in metabolism among different species, including man, is considered insufficient to exclude the relevance of reproductive toxicity seen in several animal species for humans. Although RAC acknowledges that there are limited information on parental toxicity in some studies, RAC does not consider those critical. In a key study (Snelling et al., 1982c), parental toxicity was monitored and no effects on parental body weights were seen. At a higher dose, Hardin et al (1983) reported effects on fertility at doses showing also some parental toxicity. Only Generoso et al (1987) did not provide information on parental toxicity. Additional support for the fertility effects comes from the studies reporting specific effects on spermatogenesis and sperm morphology. These include the studies by Mori et al. (1989, 1991) and Ribeiro et al. (1987). RAC considers that there is enough evidence for classification in Category 1B for fertility effects.

Date	Country	Organisation	Type of Organisation	Comment number
18.11.2016	France		MemberState	4

Comment received

France agrees to classify ethylene oxide as Repr. 2 H361fd, based essentially on experimental animal data.

Dossier Submitter's Response

Thank you for your support.

RAC's response
The dossier submitter considered classification in cat 2 more appropriate that cat 1B because of the uncertainties due to limited information on parental toxicity in some studies and the limited exposure information in the presented human data. Although RAC acknowledges that there are limited information on parental toxicity in some studies, RAC does not consider those uncertainties critical. In a key study (Snelling et al., 1982c), parental toxicity was monitored and no effects on parental body weights were seen. At a higher dose, Hardin et al. (1983) reported effects on fertility at doses showing also some parental toxicity. Only Generoso et al. (1987) did not provide information on parental toxicity. Additional support for the fertility effects comes from the studies reporting specific effects on spermatogenesis and sperm morphology. These include the studies by Mori et al. (1989, 1991) and Ribeiro et al. (1987). RAC considers that there is enough evidence for classification as Category 1B for fertility effects.

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2016	Germany	BASF SE	Company-Manufacturer	5
Comment received				
Please see the attached document ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment to CLH dossier ethylene oxide_BASF.pdf				
Dossier Submitter's Response				
The evaluation of reproductive toxicity of ethylene oxide was done on the basis of all available information considering the reliability of the studies and general/parental toxicity as cofounding factor. Each individual study is evaluated in the CLH-Dossier and described as detailed as possible. The availability of data on general/parental toxicity is additionally indicated in Table 65 and 66. As some of the studies are rather old the information is limited but not implicitely unreliable. <u>Male fertility:</u> The reliability of the Hollingsworth study (1956) was discussed in the comment and assigned Klinisch 4. However in the registration data the registrant assigned Klimisch 2 for the same study used for evaluation of skin irritation/corrosion property. The sperm head morphology test by Ribeiro (1987) is not a standard test but according to a publication by Wyrobek (1975) - testing 25 chemicals for their effects on sperm morphology – positive results in the sperm head morphology test indicate agents which might prove to be mutagenic, teratogenic or carcinogenic (not only mutagenic as discussed by Ribeiro (1987) and in the comment). This study also has been used for the evaluation of reproductive toxicity by WHO (2003), NEDO (2004) or PSL assessment report (2001). The subchronic inhalation study by Snellings (1984) showed a decline in absolute but not relative testicular weight without histological changes. The NOEAL=100ppm was set based on effects on the testicular weight. In the studies by Mori (1991 and 1989) special care has been taken to avoid influence of food intake on sperm heads. Abnormal sperm heads were increased at 250ppm. Excluding teratic types (no dose dependent increase) the rate of immature types was increased at 250ppm. This substance related effect was discussed by the authors as a result of ethylene oxide effects on sertoli cells and therefore relevant for classification (Mori, 1991). The study by Lynch (1984) was not available for evaluation therefore only limited information is given in the CLH-dossier.				

It has to be noted that not only degeneration of seminiferous tubules (guinea pig, rat) and germ cell degeneration (rat) were observed, but also abnormal sperm heads in rats and mice, reduced sperm numbers and reduced sperm motility in Cynomolgous monkeys. Reversibility of germ cell degenerations was only suspected by Mori (1989) as some seminiferous tubules showed germ cell recovery at 13 weeks.

Female fertility:
The study by Generoso (1987)(cited in US EPA, 2010) show effects at 1200ppm and even "more" effects at 300ppm. However in the evaluation it has to be considered that the exposure duration was shorter (1.5 h/day for 4 consecutive days) at 1200ppm compared to 6 h/day for 10 exposures over a 14-day periode at 300ppm. The "missing" dose response can therefore be explained by the study design, i.e. the longer duration of exposure at 300 ppm as compared to the 1200 ppm group. As exposure duration was longer at the 300 ppm group the actual dose was higher and in addition it could be possible that through the longer exposure duration a vulnerable phase was covered.
Hardin (1983) gives a rough presentation of the study details from the study by Hackett (1982 – not publically available). Hackett (1983) has been provided by industry but due to confidentiality this study could not directly be used for the dossier. Therefore the study details presented by Hardin (1983) and US EPA (2010) have been included in the dossier and rechecked with the original study to give a picture of the effects seen. In consequence the assignment of Klimisch 4 in the comment for the study by Hardin (1983) is not relevant as the original data are available.

Thank you for the remark on the study description of Hardin,1983 in Table 54:
"Resorptions ↑ in group 3" is not correct is should be presented as following: "Resorptions ↑ in group 4". For details also see Table 61.

Developmental toxicity:
The administration via intravenous route of exposure by LaBorde (1980) is not considered to be irrelevant due to the use of ethylene oxide for sterilisation of medicinal products and the resulting exposure of patients.
As explained already above the study by Hardin (1983) gives a rough presentation of the study details from the study by Hackett (1982 – not publically available). Detailed data (e.g. quantified fetal body weight or crown-rump length) can be found in the original study Hackett (1982) and in US EPA (2010) and have been presented as detailed as possible due to confidentiality considerations in the dossier.
The findings in the available studies can be summarised as reduced foetal body weight, reduced crown rump length, reduced ossification of skull and sternabrae in the absence of maternal toxicity, which have to be considered adverse. It can be assumed that decreased birth weight and size are disadvantageous for later development in humans. Reduction of implantation sites and resorptions (as mentioned in the comment) are not discussed here as they are relevant for the assesment of effects on fertility.

In general there are findings in a few studies of sufficient reliability (Mori, 1989; Mori, 1991; Snellings, 1982c; Hardin, 1983; Snellings, 1982b) which are supported by several other studies of lesser reliability. Therefore the weight-of-evidence analysis supports the proposed classification as Repr Cat.2 df.

References:
WYROBEK A.J. BRUCE W.R. (1975) Chemical induction of sperm abnormalities in mice. Proc. Nat. Acad. Sci. USA Vol. 72, No. 11, pp. 4425-4429, 1975.

RAC's response
The main evidence on the effects on fertility comes from the one-generation study by Snellings et al. (1982c), in which significantly decreased number of implantations and born foetuses was observed without any signs of parental toxicity (e.g. decreases in weight gain) at 100 ppm. These findings are supported by the studies by Generoso et al. (1987) and Hardin et al. (1983) which showed increased incidences of resorptions and/or decreased incidences of implantations at 300 and 150 ppm, respectively. Although RAC acknowledges that some studies are old, and in some cases contain limited information e.g. on parental toxicity in some studies, RAC does not consider those uncertainties critical. Although at higher dose levels GSH depletion in rats may have had an impact on the toxicity, fertility effects were seen already at levels at which no GSH depletion had been observed. Additional support for the fertility effects comes from the studies reporting specific effects on spermatogenesis and sperm morphology. These include the studies Mori et al. (1989, 1991) and Ribeiro et al. (1987). Findings in these studies are in line with fertility studies, therefore, in RACs opinion there is enough data to support Category 1B classification for fertility effects. RAC agrees with the conclusions of the DS on developmental toxicity. Small decreases in foetal weights were seen when pregnant females were exposed to 100-150 ppm of ETO. In the case of Snellings et al. (1982b) it is uncertain if these were accompanied by decreased maternal body weights. However, in the study by Hackett et al. (1982) decreased foetal weights and skeletal variations were seen in the absence of changes in maternal body weights. At higher doses more severe findings have been found. Single high dose exposures during the critical periods of organogenesis have resulted in foetal deaths and malformations, especially eye disorders. These have been accompanied with slight to severe maternal toxicity. However, it is not possible to conclude that these malformations would have been in all cases secondary to maternal toxicity. On the other hand, at these higher doses GSH depletion may have played a role in the fetotoxicity and teratogenicity of ETO.

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
18.11.2016	France		MemberState	6
Comment received				
Did you consider the use of QSAR analysis to predict respiratory sensitization of ethylene oxide?				
Dossier Submitter's Response				
Valid QSAR models for respiratory sensitisation are not available jet (see https://echa.europa.eu/documents/10162/13643/ir_csa_r7a_r7-3_caracal_draft_en.pdf), therefore a classification proposal based on or supported by QSAR´s is not possible. Although ethylene oxide is the simplest epoxide and epoxides have a structural alert for sensitisation, corrosion/irritation, carcinogenicity and reproductive toxicity no clear conclusion on the cause of the seen respiratory symptoms (irritation or sensitisation) can be drawn. No classification for resp. sens is proposed. (see https://www.nicnas.gov.au/notify-your-chemical/types-of-assessments/permit-categories/structural-alerts-for-permit-categories/table-1-c-structure-contains-only-c,-h,-o)				
RAC's response				
RAC concurs with the DS response. Valid QSAR models for respiratory sensitisation are not available.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
18.11.2016	France		MemberState	7
Comment received				
Acute oral toxicity p25/26 - Although the very limited information available gives few details on study protocols (including the number of animals tested), although all studies reported for acute oral toxicity date from before the implementation of GLP, although many of the data are derived from assays performed on guinea pigs which relevance for extrapolation to humans is not well-defined for acute oral toxicity, France agrees to classify ethylene oxide as Acute Tox.3 H301 (oral LD50 values between 270 and 365 mg/kg bw), supported by the classification proposed for acute inhalation toxicity as Acute Tox. 3 H331 assuming conservatively an equivalent absorption between oral and pulmonary routes. It should also be noted that, as specified in the CLH report of ethylene oxide that, "… Some of the applied EO might have been lost by evaporation during handling/administration so the actual LD50 values might even be lower than reported" (physical state of ethylene oxide at room temperature is gaseous). - Please, confirm that the Smyth (1941) study was actually performed with ethylene oxide, since it is stated that "Smyth (1941) investigated acute oral toxicity of 60 glycol and glycol derivates in male Wistar rats and guinea pigs (m/f)" Acute inhalation toxicity p25/26: - France agrees to classify ethylene oxide as Acute Tox.3 H331 (inhalation LD50 values between 660 and 1972 ppm in rats, mice or dogs for a 4h chamber exposure)				
Dossier Submitter's Response				
Thank you for agreement on classification for acute oral and inhalative toxicity of ethylene oxide. For clarification: Smyth et al. (1941) have determined the dosage–mortality curves of 60 glycols and glycol derivatives for rats and guinea pigs. Ethylene oxide was one out of these 60 compounds. "*In most cases 10 animals were used to dertermine the toxicity of a particular dosage, and enough dosages were administered to include those at which no animal dies and those at which all died*". The results are presented in a table indicating an LD50 rat = 330 mg/kg bw (m) and LD50 guinea pig = 270 mg/kg bw (m) for ethylene oxide				
RAC's response				
Thank you for the comment and the response.				

Date	Country	Organisation	Type of Organisation	Comment number
18.11.2016	United Kingdom	<confidential>	Industry or trade association	8
Comment received				
Acute Toxicity H301 – Toxic if Swallowed Ethylene Oxide is a gaseous substance which is not considered to have a route of exposure via oral ingestion. The data presented in the CLH dossier includes a study from 1941 where details of how the oral application was performed were not provided. Furthermore, section 1.2.3.2 'Human health hazards' of the Guidance on the Application of the CLP Criteria -Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, Version 4.1, June 2015 confirms that the classification for human health should be evaluated against the substance in the physical state at which it is placed on the market and used: "In general, the assumption is made that the testing conditions of valid animal assays				

reflect the hazards to man and these data must be used for classification. Moreover, it is assumed that classification for human health hazards takes into account all the potential hazards which are likely to be faced for all forms or physical states in which the substance is placed on the market and can reasonably be expected to be used. It is assumed that it comprises putative accidental exposures. This approach generally, but not necessarily comprehensively, covers the whole range of intrinsic properties of a substance or mixture: in some cases, substances or mixtures have to be transformed into specific forms not mirroring 'real-life' exposures in order that an animal test can be performed. As a consequence, the results of such tests may have to be evaluated taking into account any limitations due to the fact that the specific form of the tested substance or mixture does not or not perfectly represent that to which human exposure may occur during intended, known, or reasonably expected use. Such evaluation has to be performed according to the state of the scientific and technical knowledge. The burden of proof is on the person placing a substance or mixture on the market."

Based on the above, we do not believe there is a justification for the classification of ethylene oxide as Acute Toxicity H301 – Toxic if Swallowed.

Dossier Submitter's Response

According to CLP-regulation, Art. 9 for the evaluation of available information for the purposes of classification the forms or physical states in which the substance or mixture is placed on the market and in which it can reasonably be expected to be used shall be considered. Reasonably expected use summarises all physical forms and states of a substance or mixture that may occur during intended use or reasonably foreseeable conditions of misuse (CLP guidance).

The physical state of ethylene oxide at room temperature (20°C) is gaseous. At 10°C ethylene oxide is liquid (boiling point 10.7°C). Ethylene Oxide is stored and/or transported as a liquid under moderate pressure. These data indicate that exposue to liquid ethylene oxide may be possible therefore a classification for acute oral toxicity has been proposed.

RAC's response

Thank you for the comment and response. As ethylene oxide is stored and/or transported in liquid form, RAC considers that a classification for acute oral toxicity is relevant.

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2016	Germany	BASF SE	Company-Manufacturer	9

Comment received

Please see the attached document

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment to CLH dossier ethylene oxide_BASF.pdf

Dossier Submitter's Response

Ethylene oxide has been self-classified by industry for Acute Tox 4, H203 based on animal data in rats. The evaluation for classification purposes showed that guinea pigs and mice are more sensitive than rats, therefore a classification as Acute Tox 3, based on an LD_{50}=270mg/kg bw was proposed.

For the discussion if classification for the oral route is appropriate at all please see comment No 8.

RAC's response

Thank you for the comment and response. Based on the LD_{50} value of 270 mg/kg bw, classification as Acute Tox. 3 is considered justified. As ethylene oxide is stored and/or

transported in liquid form, RAC considers that a classification for acute oral toxicity is relevant.

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2016	Austria	Austrian Workers' Compensation Board	National Authority	10
Comment received				
The Austrian Umweltbundesamt could confirm the so far doubtful minimum classification of Oxirane. We see this as a first step of many to come to correct the false harmonised classifications and labellings.				
Dossier Submitter's Response				
Thank you for your support on the necessity for clarification of minimum classifications.				
RAC's response				
Thank you for the comment and response.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
18.11.2016	France		MemberState	11
Comment received				
- France agrees to classify ethylene oxide as Skin Corr. 1B H314 and Eye Dam. 1 H318, based on experimental animal data supported by human data.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
RAC considers that the available data provides evidence for the corrosive potential of ethylene oxide. The 4h animal study describes outcomes that justify a subclassification as Skin Corr. 1C. The study protocol of the other *in vivo* study, with an exposure time of up to 1 hour, is not reported in detail. It was indicated that effects were observed already after 6 minutes of exposure, but due to the lack of detail, RAC considers that this study cannot be used as a key study to justify a classification as Skin Corr. 1B. RAC also considers, that the fact that the studies were performed using occlusive patches makes a detailed interpretation of the study results complicated. Overall, RAC proposes classification as Skin Corr. 1; H314.				

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2016	Germany	BASF SE	Company-Manufacturer	12
Comment received				
Please see the attached document ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment to CLH dossier ethylene oxide_BASF.pdf				
Dossier Submitter's Response				
Classification is based on the latest available data provided by registrants or publicly available. As indicated in the comment human studies show that EO causes severe (irreversible) effects. This human evidence could not be used for evaluation of this property as it has not been included in the registration dossier. Based on the available studies Skin Corr 1B is proposed.				

RAC's response
Thank you for the comment and response. RAC agrees that the available data do not allow differentiation between the skin corrosion subcategories 1A/1B/1C. RAC also considers, that the fact that the studies were performed using occlusive patches makes a detailed interpretation of the study results complicated.

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2016	Germany	BASF SE	Company-Manufacturer	13
Comment received				
Please see the attached document ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment to CLH dossier ethylene oxide_BASF.pdf				
Dossier Submitter's Response				
Classification is based on the latest available data provided by registrants or publicly available. For the evaluation of eye hazard the provided study was considered to be inadequate for classification. As according to CLP-Guidance for substances classified as Skin Corr. Category 1 the serious damage to eyes is implicit this has been the basis for the proposal. Even if a further discussion on the correct subcategory for skin corrosion (1B, 1C or 1) will be held – as proposed in comment No 12 - it has to be considered that the implicit classification as Eye dam 1 will not be affected.				
RAC's response				
Thank you for the comment and response. As ethylene oxide is proposed to be classified as Skin Corr 1, it shall also be classified as Eye Dam. 1; H318 according to CLP.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
18.11.2016	France		MemberState	14
Comment received				
France agrees to classify ethylene oxide as Skin Sens. 1 H317, based essentially on human hemodialysis patients' data (repeatedly exposed to EO-sterilized materials during dialysis treatment via a direct contact to their blood and then more likely to highlight the sensitizing potential of the substance).				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
The criteria for skin sensitization require evidence on sensitisation by skin contact in a substantial number of individuals. The data presented in the dossier contains only a few case reports, each of them presenting one individual with skin reactions after exposure. Taking into consideration the fact that ethylene oxide has been extensively used for sterilization purposes for decades, the number of case reports is considered very low. The case reports do not clearly identify the observed reactions as outcomes of ethylene oxide sensitisation. As the substance causes skin irritation/corrosivity, it is possible that the reported eczema may also have occurred due to irritation. Severe allergic-type reactions and ethylene oxide IgE antibodies among dialysis patients have been reported in several clinical surveillance studies and case reports. All of these				

reports focus on situations in which individuals were exposed to ethylene oxide parenterally (sterilized medical equipment). As these reports do not include information on sensitisation following skin contact, RAC does not consider them relevant for the evaluation of classification for skin sensitisation.

RAC does not consider classification as skin sensitizer appropriate.

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2016	Germany	BASF SE	Company-Manufacturer	15

Comment received

Please see the attached document

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment to CLH dossier ethylene oxide_BASF.pdf

Dossier Submitter's Response

Ethylene oxide is the simplest epoxide and epoxides have a structural alert for sensitisation(1). It is a direct and potent alkylating agent and reacts with hydroxyl, sulfhydryl, amino and carboxyl groups in human macromolecules. As a hapten it becomes an active allergen after binding to human proteins (e.g. HSA-ethylene oxide conjugates). This is a well accepted key event in the Advers Outcome Pathway concept resulting in a type IV hypersensitivity reaction.

It is correct that exposure to ethylene oxide was parenteral and not dermal in most of the presented studies and sensitisation after parenteral exposure is not considered separately in the CLP regulation, therefore the appropriateness of these data of course has to be discussed. However the development of a sensitization is always a systemic process. Allergic reactions can occur at local sites (exposed skin areas) or systemic (e.g. anaphylaxis after parenteral exposure). In principle the systemic availability of sensitized immune cells circulating throughout the body always has to be kept in mind as they can respond when challenge occurs at sites other than the original site of sensitization (WHO, 2012).

The provided comment concludes that *"the majority of reports (dermal exposure) with EO allergies describe IgE-mediated type I immediate reactions that occure in patients with compromised health status ……Reports in the public literature on allergic symptoms in hospital workers using EO sterilized equipment, gowns etc. mostly describe IgE-mediated type I immediate reactions that are not relevant for IgG-dependent skin sensitisation responses."* But the argument that only IgG-dependent skin sensitization reponses (type IV) are relevant for classification cannot be followed. In CLP regulation the following statement on immunological contact urticaria (type I hypersensitivity reaction) can be found: "*Substances meeting the criteria for classification as respiratory sensitisers may in addition cause immunological contact urticaria. Consideration should be given to classifying these substances also as skin sensitisers. Substances which cause immunological contact urticaria without meeting the criteria for respiratory sensitisers should also be considered for classification as skin sensitisers*." Therefore a in depth discussion on the type of immune reaction does not seem to be relevant for classification.

Classification for this endpoint is based on human data (dermal and parenteral route of exposure) and the known mechanism (alkylating agent). Altogether it can be assumed that a sensitizing property of ethylene oxide cannot be neglected. Therefore a classification as Skin Sens 1 is proposed in the CLH-dossier.

(1) https://www.nicnas.gov.au/notify-your-chemical/types-of-assessments/permit-categories/structural-alerts-for-permit-categories/table-1-c-structure-contains-only-c,-h,-o
RAC's response
Thank you for the comment and response. RAC considers that the case reports related to skin exposure do not clearly identify the observed reactions as outcomes of ethylene oxide sensitisation. Furthermore, RAC does not consider the cases, where sensitisation occurs upon parenteral exposure, as relevant for the evaluation of classification for skin sensitisation. RAC proposes no classification for ethylene oxide for this endpoint due to a lack of evidence for a potential to cause skin sensitisation.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
18.11.2016	France		MemberState	16
Comment received				
Considering the transient effects related to central nervous system reported in humans after single exposure (eg: headaches, nausea and vomiting, dyspnoea, vertigo, loss of consciousness, nystagmus, impaired hearing, cardiac arrhythmia, paleness, lightheadedness, unconsciousness, convulsive movements of arms and legs, periods of apnea, Inability to perform minor motor tasks continued for up to 1 week after exposure, muscular weakness), supported by similar effects observed in the acute inhalation toxicity studies in animals (eg: hypoactivity, severe dyspnea, incoordination, semiconsciousness), a classification for narcotic effects (ie STOT SE 3 / H336: May causes drowsiness or dizziness) should be discussed.			
Dossier Submitter's Response				
Ethylene oxide shows effects on the nervous system. Effects after repeated exposure results in a proposed classification as STOT RE1, H372 (Chapter 4.8). Available data of effects on the nervous system after single exposure are presented in Chapter 4.3. Based on the minor severity of effects and the reversibility no classification for STOT SE (Cat 1 or 2) was proposed. A possible classification for STOT SE3, H336 (Transient target organ effects) was not considered in the dossier. There are no guidance values for Category 3. Therefore, if a study shows clear evidence for narcotic effects at any dose level then this could support classification with Category 3. The studies relevant for discussion of narcotic effects of ethylene oxide are presented in Chapter 4.3. Salinas (1981) reported nausea, stomach spasms, paleness, light headedness, short periods of unconsciousness, convulsive movements of arms and legs, periods of apnea, muscle twitching after single exposure (~500ppm) of an 43year-old nurse. Malaise and an inability to perform minor tasks continued for up to 1 week after exposure. Deleixhe (1986) described the accidential exposure of 5 workers (>260ppm) to a mixture of ethylene oxide and carbon dioxide. As carbon dioxide is a narcotic gase the effects (headache, muscular weakness, dizziness) seen in this study may be biased. Bryant (1989) reported the symptoms of 165 hopital workers with exposure to ethylene oxide (mean 3.4ppm, exceeding 260ppm briefly). Headaches, skin and eye irritation, dry mouth, sore throat, skin rash, runny nose, loss of sense of smell, shortness of breath, nausea, numbness in fingers and drowsiness are described. However no distinction between short-term effects and effects due to repeated exposure is possible. DFG (1993) summarized that casuistic reports of human intoxications showed symptoms like headaches, nausea and generally persistent periodic vomiting. Dyspnoea, irritation of the				

eyes and upper respiratory mucosa, heart damage, excitation, stupor, vertigo and loss of consciousness were also observed.
Acute toxicity studies in rats by Snellings (2011) showed clinical signs of ataxia, tremors, absence of the startle reflex, absence of the tail/toe pinch reflex, and decreased respiration after 1h/4h exposure (1443ppm up to 6161ppm). Mandella (1997a) conducted an acute neurotoxicity study in rats. The symptoms are discribed as slightly impaired locomotion, drooping half-closed eyelids, no reaction to approach, low arousal. An inhalation study by NTP (1987) (100-1600ppm) in mice showed severe dyspnea, incoordination, semiconsciousness, and diarrhea at the highest concentration.

The criteria for classifying substances as Category 3 for narcotic effects are:

(a) central nervous system depression including narcotic effects in humans such as drowsiness, narcosis, reduced alertness, loss of reflexes, lack of coordination, and vertigo are included. These effects can also be manifested as severe headache or nausea, and can lead to reduced judgment, dizziness, irritability, fatigue, impaired memory function, deficits in perception and coordination, reaction time, or sleepiness.

(b) narcotic effects observed in animal studies may include lethargy, lack of coordination, loss of righting reflex, and ataxia. If these effects are not transient in nature, then they shall be considered to support classification for Category 1 or 2 STOT SE.

Clear narcotic effects were seen only in a case study by Salinas (1981) and in an acute inhalation study in mice (NTP, 1987) at 1600ppm. Based on the available data no classification for narcotic effects is proposed.

RAC's response

Thank you for the comment and response. Taking into account the human data on symptoms upon exposure to ethylene oxide, and observations from animal acute inhalation toxicity studies and one acute neurotoxicity study, RAC considers that the criteria for classification for specific target organ toxicity based on transient, narcotic effects, are fulfilled. RAC considers that ethylene oxide should be classified as STOT SE 3; H336.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
18.11.2016	France		MemberState	17

Comment received

Neurotoxicity p 44:
- France agrees to classify ethylene oxide as STOT RE 1 H372 (nervous system) based on consequent neurotoxicity effects reported in humans in addition to the experimental animal data.
Hematotoxicity p62:
- France also agrees that hematotoxicity effects are not sufficient for a STOT RE classification, based on low severity and reversibility of the effects.

Dossier Submitter's Response

Thank you for your support.

RAC's response

Thank you for the comment. RAC concurs with the points made.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON ETHYLENE OXIDE

PUBLIC ATTACHMENTS
1. Comment to CLH dossier ethylene oxide_BASF.pdf [Please refer to comment No. 5, 9, 12, 13, 15]