Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

2-phenoxyethanol

EC Number: 204-589-7
CAS Number: 122-99-6

CLH-O-0000001412-86-283/F

Adopted

13 June 2019

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: 2-phenoxyethanol
EC number: 204-589-7
CAS number: 122-99-6
Dossier submitter: The United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
06.11.2018	France		MemberState	1
Comment received				
To be noted that 2-phenoxyethanol is used in dyeing and finishing of leather and textile. In January 2018, Sweden and France notified ECHA their intention to jointly prepare an Annex XV restriction dossier according to article 69 of REACH Regulation No 1907/2006. https://echa.europa.eu/sv/registry-of-restriction-intentions/-/dislist/details/0b0236e182446136 The substance is listed in the scope of substances submitted to restriction for sensitizing, irritating and corrosive substances found in textile articles, leather, skin and fur.				
Dossier Submitter's Response				
Noted, thank you.				
RAC's response				
Thank you for this information.				

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2018	Germany		MemberState	2
Comment received				
Table 3 of chapter 2.1 Proposed harmonised classification and labelling according to the CLP criteria: Under "Classification/ Hazard Class and Category Code(s)" in the columns of "Dossier submitters proposal "respectively "Resulting Annex VI entry if agreed by RAC and COM" the note "(respiratory tract irritation)" to the STOT-SE 3 is mentioned. This note should be deleted because it will not be reflected in the future Annex VI Part 3				

Table 3. This note is redundant because the differentiation of the Hazard Category STOT SE 3 by the hazard phrase H335 or H336 is fully sufficient. In this case H335 is assigned to the hazard category STOT SE 3 in order to ensure, that it concerns an irritant effect of the respiratory tract.
Dossier Submitter's Response
Thank you. Unfortunately we cannot make any changes to the dossier at this point but we agree this note should not be present when the opinion is developed by RAC.
RAC's response
Agreed. H335 is sufficient to communicate a hazard of respiratory tract irritation.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
12.11.2018	Germany	BASF SE	Company-Manufacturer	3
Comment received				
see attached document ECHA note – An attachment was submitted with the comment above. Refer to public attachment 122-99-6_PE_response to CLH dossier_public consultation_20181109.pdf				
Dossier Submitter's Response				
Thank you for your attached comment specifically agreeing with the proposal for classification and labelling for Acute Tox. 4 (oral) and no classification (inhalation).				
RAC's response				
Than you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2018	Sweden		MemberState	4
Comment received				
Acute toxicity (oral): The Swedish CA support the proposed classification Acute Tox. 4 with an ATE of 1394 mg/kg bw. Acute toxicity (inhalation): Based on the information available in the CLH report, the Swedish CA support the proposed no classification for acute inhalation toxicity, but also notes that 2-phenoxyethanol was not tested up to the limit dose for classification.				
Dossier Submitter's Response				
Thank you for your support. It is acknowledged that 2-phenoxyethanol was tested only up to a maximum of 1.07 mg/l in a 14 day study in rats. There were no clinical signs of toxicity and no deaths occurred at or below this dose level.				
RAC's response				
Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2018	Sweden		MemberState	5
Comment received				
The Swedish CA support the proposed classification Eye Dam. 1 based on the observed irreversibility of corneal effects in one animal after 21 days, supported by similar data from the 15d-study.				
Dossier Submitter's Response				
Thank you for your supporting comment. Please note that additional information is provided by Industry regarding one of the eye irritation studies (Anon. 1983) (details provided in comment 7). Industry note that in the single animal which was observed to have persisting corneal effects at the end of the observation period of 15 days, the untreated eye was also affected. It is inclear as to whether both eyes were treated by accident or whether the effect was unrelated to treatment.				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2018	Switzerland	Dow Europe GmbH	Company-Manufacturer	6
Comment received				
The classification for eye irritation should be based upon a weight of evidence approach, considering all available data. The RMS has proposed classification of 2-phenoxyethanol (EPh) as eye irritant category 1. This proposal is based upon a lack of full recovery of eye irritation, rather than based upon the severity of response as grading of irritation severity supports classification as eye irritant category 2. In the first study summarized by the RMS, 1/6 animals failed to show full recovery at the end of the 21 day study period. However, based upon the reduction in area affected from greater than or equal to ¾ of the eye at 48 hours to less than ¼ of the eye by the end of the observation period and in consideration of the similar pattern of recovery of other animals, expert judgement can be used to consider that this animal is similarly likely to recover. In the second study, available in the REACh registration dossier, 1/3 animals did not fully recover from eye irritation in 14 days. Again, based upon the pattern of recovery in all animals, and reduction in area affected in this particular animal from greater than or equal to ¾ of the eye at 72 hours to less than ¼ of the eye at 15 days, eventual full recovery is expected. Further, the RMS points out an additional 3 studies in the REACh registration dossier providing information on reversibility, all of which show eye irritation resolving within 14 days. Thus, using expert judgement and a weight of evidence approach, it clear that EPh produces a reversible irritation and that classification as eye irritant category 2 is appropriate.				
Dossier Submitter's Response				
Whilst we agree that the scoring alone merits classification with Category 2, the Guidance on the Application of the CLP criteria make it clear that classification for local effects on the eye is not only evaluated on the severity of the damage but also on the reversibility. The criteria say that a substance should be classified for irreversible eye effects (Category 1) if, when applied to the eye of an animal, it produces in at least one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days. Two studies meet this criterion, although it is acknowledged that in one of these studies, the observation period was shorter at only 15 days (Anon. 1983).				

In light of the additional information provided by Industry (see comment 7), it appears that the study by Anon. 1983 had a considerable shortcoming in that the animals affected at the end of the observation period was also found to have similar findings in the untreated eye. This brings into question the reliability of this study, but does not negate the findings of the other study made available in the REACH Registration dossier (unknown study author, study year 1983).

As you note, 3 additional (poorly reported) studies indicate the effects caused by 2-phenoxyethanol were reversible, however a further 5 studies provide no information on this. Therefore it is not clear whether the effects of 2-phenoxyethanol were reversible or not in these studies. It is also acknowledged that it is possible for there to be a variable response in animals.

RAC's response

Thank you for your comment.
RAC agree with DS's respons.
The classification criterion of CLP regulation (Table 3.3.1 of Annex I) for serious eye damage is met on the basis that at least one animal had effects to the cornea that were not fully reversed within an observation period of 21 days (study 1983 in 6 rabbits) and no clear evidence on full reversibility of eye effects from other available studies.

Date	Country	Organisation	Type of Organisation	Comment number
12.11.2018	Germany	BASF SE	Company-Manufacturer	7

Comment received

see attached document

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 122-99-6_PE_response to CLH dossier_public consultation_20181109.pdf

Dossier Submitter's Response

Thank you for your attached comments and for providing additional information relating to the second eye irritation study (Anon. 1983).

Two animal studies were included in the dossier (REACH 1983 and Anon. 1983). The DS agrees that in both studies, the individual animal scores taken as an average over 24 – 72 h meet the criteria for classification with catergory 2. However, as mentioned above, classification in category 1 is not only based on severity of effects but also reversibility.

The first study was a guideline study, taken from the REACH Registration, and had an observation period of 21 days. As you note in your comment, the scoring for the effects relating to the cornea were not particularly high but one animal continued to show corneal opacity at the end of the observation period of 21 days (score 1). Although you state that this could be expected to be reversible, this was not the case under the conditions of the study. The guidance on the application of the CLP criteria states: classification as serious damage – category 1 should occur if "at least one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days…".

In the second study (Anon. 1983) corneal effects were also noted at the end of the observation period (score 1). As you note, the observation period was shorter than the standard and was only 15 days. In the CLH report it is acknowledged that this shorter observation period does offer some doubt about the proposed classification.

In addition to these two studies, 9 other studies were found in the REACH Registration. None of these studies were performed according to test guidelines and all were limited in their reporting. Eight of these studies indicated that 2-phenoxyethanol was irritating to the eyes. One of the studies (carried out in 1949) showed serious irritation with signs of corneal necrosis (it is noted that the vehicle used in this study was propylene glycol which is notified in the C&L inventory as being an eye irritant). As you note, three studies indicated that the irritation observed was reversible within the observation period (14 days or less) but five of these studies did not provide information on reversibility.

In your attached comment you have provided additional information on the Anon. 1983 study that brings into question the validity of the results obtained. You note that the study author observed that for the rabbit with corneal opacity at the end of the 15 day observation period, both the treated and untreated eye was affected (score 1 for each eye). This brings into question whether the finding was treatment-related and indeed, whether the study can be considered reliable.

RAC's response

Thank you for your comment.
RAC agree with DS's respons.
The classification criterion of CLP regulation (Table 3.3.1 of Annex I) for serious eye damage is met on the basis that at least one animal had effects to the cornea that were not fully reversed within an observation period of 21 days (study 1983 in 6 rabbits) and no clear evidence on full reversibility of eye effects from other available studies.

Date	Country	Organisation	Type of Organisation	Comment number
06.11.2018	France		MemberState	8

Comment received

FR agrees with the proposal.

Dossier Submitter's Response

Thank you for your support. Please note the additional information provided by Industry regarding one of the eye irritation studies (Anon. 1983) (details provided in comment 7). Industry note that in this study in which persistant corneal effects were observed at the end of the observation period of 15 days, the untreated eye was also affected. It is inclear as to whether both eyes were treated by accident or whether the the affect was unrelated to treatment. Therefore the reliability of this study is uncertain.

RAC's response

Thank you for your comment.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2018	Sweden		MemberState	9

Comment received

In the 14d inhalation study in rats, degeneration and squamous metaplasia of the respiratory epithelium occurred in the nasal cavity of 10/10 animals at 1.07 mg/l and in 4/10 animals at 0.246 mg/l. Was the olfactory epithelium also affected? At RAC 45, the proposed STOT-SE 3 classification for butanone oxime was changed to STOT-SE 1 based on degeneration/metaplasia of olfactory epithelium, as this is an irreversible effect (loss of smell) and should be considered adverse. This could also be the case for 2-phenoxyethanol. Since this finding for 2-phenoxyethanol was observed in a 14d-study, a

STOT RE 2 classification could also be considered based on the onset of the observed effects.

Dossier Submitter's Response

There was no mention of involvement of the olfactory epithelium in the study report. In the case of butanone oxime, STOT-SE 1 was awarded, in part, because the olfactory epithelium appeared to be specifically targeted (the respiratory epithelium remained unaffected, therefore it did not appear to be a local effect caused by irritation). In addition to this, the effects to the olfactory epithelium were also noted after administration of butanone oxime in the drinking water. It was therefore deduced that the effects to the olfactory epithelium were targeted as a result of systemic exposure.

During the preparation of the CLH proposal, the DS considered whether these findings supported classification with STOT-RE; however, it is our opinion that the effects observed in the 14-day inhalation study are indicative of reversible signs of respiratory irritatation. The study report does not provide information about the effects observed after a single exposure, but it is noted that the study period was short, only 14 days (10 exposures), and the exposure levels used were relatively low. Therefore, the minimal to mild metaplasia observed in the nasal cavity and larynx of rats are considered indicative of short-term adaptive changes to the irritant potential of 2-phenoxyethanol.

Respiratory effects were not observed in studies carried out by the oral or dermal routes.

Supporting this perspective is the ability of this substance to cause irritation to the eyes (mucous membrances).

RAC's response

Thank you for opinion. RAC supports the DS' opinion.

Date	Country	Organisation	Type of Organisation	Comment number
15.11.2018	Switzerland	Dow Europe GmbH	Company-Manufacturer	10

Comment received

The RMS has proposed that EPh be labeled STOT-SE 3 for respiratory tract irritation. According to the criteria in Annex 1: 3.8.1.1 of the CLP guidance, STOT-SE is to be designated for specific, non-lethal target organ toxicity arising from a single exposure to a substance or mixture. According to the guidance, the studies that provide useful information for STOT-SE classification are acute toxicity studies. An available acute inhalation toxicity study showed no mortality and no clinical signs indicative of respiratory irritation in rats exposed to a saturated vapor of EPh for 8 hours, thus demonstrating that STOT-SE classification is not warranted for EPh. The proposal for respiratory irritation by the RMS is based upon a 2 week inhalation toxicity study wherein rats received 10 exposures to concentrations of up to 1 mg/L EPh. The low concentration of 48.3 mg/m3 was predominantly EPh vapor, while the mid- and high concentrations of 246 and 1070 mg/m3 were predominantly EPh aerosol. No clinical signs of respiratory irritation were observed at any concentration level. No morphological changes indicative of respiratory irritation were observed at the low concentration. Morphological changes were observed at the mid and high concentrations and were characterized by metaplasia, hyperplasia, and inflammation of the nasal cavity, metaplasia at the base of the epiglottis, and an increased thickness of small bronchi and increase in mucous cells in larger bronchi. Metaplasia is considered an adaptive, reversible effect due to repeat exposure to an irritant, as discussed at the 1st International ESTP Expert Workshop on larynx squamous

metaplasia (Kauffman et al., 2009). The observed point-of-contact irritant effects occurred after 10 exposures and there is no indication that similar effects would be expected after a single exposure to EPh, thus STOT-SE classification is not appropriate based upon this study. Considering the observance of slight, adaptive effects, STOT-RE would similarly not be warranted, as "STOT-RE is assigned on the basis of finding of 'significant' or 'severe' toxicity", according to Section 3.9.2.2 of the guidance. Additionally, although durations differ, it should also be noted that the concentrations used were in excess of those warranting a classification for STOT-RE, again demonstrating that STOT-RE classification would not be appropriate based upon the available 2 week inhalation toxicity study. Overall, no respiratory tract effects consistent with STOT-SE or STOT-RE classification were observed.

Dossier Submitter's Response

According to the guidance on the Application of the CLP criteria "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…".

Whilst no effects to the respiratory system were observed in the acute inhalation study, it is noted that theconcentration used was very low (0.057 mg/l). Indeed, in the 14-day inhalation study in which respiratory effects were noted, no such effects were observed following repeated dosing at the lowest concentration of 0.048 mg/l. Further to this, whilst the 14-day study report does not provide information about the effects observed after a single exposure, it is noted that the study period was relatively short, only 14 days (10 exposures). As such, it is our opinion that the 14-day study provides useful information regarding the respiratory irritation potential of 2-phenoxyethanol.

The DS agrees that the effects observed in the 14-day study are not severe enough to warrant classification with STOT-RE and believes that the findings are indicative of an irritation effect to the resipiratory tract. However, it is noted that when applying Haber's rule, the guidance value for classification in a 14-day study would be ≤ 1.2 mg/l and effects to the respiratory epithelium occurred from 0.246 mg/l.

Overall, the DS believes classification with STOT-SE 3; H335, most appropriately covers the effects observed following inhalation exposure of 2-phenoxyethanol in the rat.

RAC's response

Thank you for comment. RAC is of the opinion that 2-phenoxyethanol warrants classification as STOT SE 3

Date	Country	Organisation	Type of Organisation	Comment number
12.11.2018	Germany	BASF SE	Company-Manufacturer	11

Comment received

see attached document

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 122-99-6_PE_response to CLH dossier_public consultation_20181109.pdf

Dossier Submitter's Response

Regarding your attached comments relating to respiratory tract irritation. You highlight that the evaluation of STOT-SE 3; H335 is particularly based on human data and that animal studies may provide useful information, particularly acute toxicity studies in rats and mice. We agree with you but as noted above (comment 10), the guidance also says that useful information can also be obtained from repeated inhalation toxicity studies.

As you mention, we are not aware of any occupational case reports in humans from which a causal relationship between 2-phenoxyethanol exposure and respiratory tract irritation could be deduced. However, consideration should be given to the findings in the available animal (rat) studies. This includes the non-guideline acute inhalationstudy and the 14-day repeated dose inhalation study conducted according to OECD 412. In the acute inhalation study, the concentration used was the saturated vapour concentration of 0.057 mg/l – which is extremely low. No clinical signs of toxicity and no signs of irritation were observed in this study. Similarly, at a the lowest concentration level of 0.048 mg/l (which was also mainly vapour) in the 14-day study, no signs of irritation were noted. At higher dose levels (≥ 0.246 mg/l) signs of irritation to the respiratory tract were noted. Exposure at these concentrations was mainly as an aerosol.

The DS is in agreement that the study used to determine the proposed classification of STOT-SE 3 involved 10 exposures rather than just 1. However, we believe that classification with this hazard class is appropriate, not as a precautionary measure but because the effects observed in the 14-day study are signs of reversible respiratory tract irritation which occur after a relatively low number of exposures and at moderately low exposure concentrations. This is supported by the fact that 2-phenoxyethanol is a known eye irritant and thus might be expected to cause irritation of mucous membranes. Classification with STOT-RE 2 was also considered, however the DS does not believe that the effects observed were severe enough to meet the criteria of this hazard class.

In your attached comments you highlight that exposure with highly concentrated 2-phenoxyethanol is unlikely to occur in reasonably expected uses. Unfortunately, as classification is solely hazard based and not risk-based this argumentation cannot be supported.

You propose to establish a specific concentration limit (SCL) of 10 % for mixtures containing 2-phenoxyethanol. It is noted that the classification criteria consider a generic concentration limit (GCL) of 20 % to be appropriate for this hazard class (although recognising that this may need to be higher or lower depending on the ingredients and the effects). It is our opinion that insufficient information is available to establish a (lower) SCL for 2-phenoxyethanol and consider the GCL to be appropriate.

RAC's response

Thank you for opinion.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
06.11.2018	France		MemberState	12

Comment received

Page 18 and 19 section 10.10.2
Metaplastic lesions of the larynx observed in rats should be considered as adverse effect which due to its severity and extension potentially affect the organ function (as reported by Kaufmann et al. 2009). One 14-day inhalation study showed metaplasia in the nasal cavity and in the larynx, described as minimal to mild effect, at mid and top dosed rats. No other inhalation data are available following repeated dose toxicity to irritating compound. It cannot be excluded that other more severe effects could be observed. Therefore a classification STOT RE in regard to the 14-day study could be foreseen and discussed.

Dossier Submitter's Response
Classification in accordance with CLP should be based on the available data. In this case, the available data show that the degeneration and metaplasia observed in rats following exposure to 2-phenoxyethanol at a dose of 0.246 mg/l were minimal to mild. As the dose was increased to 1.07 mg/l the severity of the effects remained the same (minimal to mild) but more animals were affected. Therefore, the DS considered these effects to be indicative of short-term adaptive changes to the irritant potential of 2-phenoxyethanol. We do not believe they are severe enough for classification with STOT-RE 2.
RAC's response
Thank you for opinion. RAC supports the DS' opinion.

Date	Country	Organisation	Type of Organisation	Comment number
12.11.2018	Germany	BASF SE	Company-Manufacturer	13
Comment received				
see attached document ECHA note – An attachment was submitted with the comment above. Refer to public attachment 122-99-6_PE_response to CLH dossier_public consultation_20181109.pdf				
Dossier Submitter's Response				
We note in your attached comments that you agree with the proposal not to classify for STOT RE. We thank you for your support.				
RAC's response				
Agreed. Thank you for opinion.				

PUBLIC ATTACHMENTS
1. 122-99-6_PE_response to CLH dossier_public consultation_20181109.pdf [Please refer to comment No. 3, 7, 11, 13]