# Committee for Risk Assessment

# RAC

## 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

13 June 2019

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# 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:** **2-phenoxyethanol**

**EC Number:** **204-589-7**

**CAS Number:** **122-99-6**

The proposal was submitted by **the United Kingdom** and received by RAC on **7 August 2018.**

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

# PROCESS FOR ADOPTION OF THE OPINION

**The United Kingdom** 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 **17 September 2018**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **16 November 2018**.

## ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Bogusław Barański**

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 **13 June 2019** by **consensus**.

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

| | **Index No** | **International Chemical Identification** | **EC No** | **CAS No** | **Classification** | | **Labelling** | | | **Specific Conc. Limits, M-factors and ATE** | **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 | 603-098-00-9 | 2-phenoxyethanol | 204-589-7 | 122-99-6 | Acute Tox. 4*<br>Eye Irrit. 2 | H302<br>H319 | GHS07<br>Wng | H302<br>H319 | | | |
| Dossier submitters proposal | 603-098-00-9 | 2-phenoxyethanol | 204-589-7 | 122-99-6 | **Modify**<br>Acute Tox. 4<br>Eye Dam. 1<br><br>**Add**<br>STOT SE 3 | **Retain**<br>H302<br><br>**Modify**<br>H318<br><br>**Add**<br>H335 | **Retain**<br>GHS07<br><br>**Add**<br>GHS05 | **Retain**<br>H302<br><br>**Modify**<br>H318<br><br>**Add**<br>H335 | | **Add**<br>oral: ATE = 1394 mg/kg bw | |
| RAC opinion | 603-098-00-9 | 2-phenoxyethanol | 204-589-7 | 122-99-6 | Acute Tox. 4<br>STOT SE 3<br>Eye Dam. 1 | H302<br>H335<br>H318 | GHS05<br>GHS07<br>Dgr | H302<br>H335<br>H318 | | oral: ATE = 1394 mg/kg bw | |
| Resulting Annex VI entry if agreed by COM | 603-098-00-9 | 2-phenoxyethanol | 204-589-7 | 122-99-6 | Acute Tox. 4<br>STOT SE 3<br>Eye Dam. 1 | H302<br>H335<br>H318 | GHS05<br>GHS07<br>Dgr | H302<br>H335<br>H318 | | oral: ATE = 1394 mg/kg bw | |

# GROUNDS FOR ADOPTION OF THE OPINION

## HUMAN HEALTH HAZARD EVALUATION

## RAC evaluation of acute toxicity

### Summary of the Dossier Submitter's proposal

#### *Oral route*

Four oral acute toxicity studies were considered by the dossier submitter (DS). Three of these studies were included in the draft Competent Authority Report – CAR – UK (December 2016), Document IIA, Section 3 (hereby referred to as the dCAR). The fourth study was chosen out of 11 provided in the REACH registration dossier (2013) for 2-phenoxyethanol. It was carried out according to OECD guidelines, reported adequately and is considered below.

In a 1982 study, carried out according to OECD TG 401 guidelines (non-GLP), Wistar rats (5/sex/dose) were administered orally doses of 0, 681, 1470, 3160 or 5000 mg/kg bw phenoxyethanol in carboxymethyl cellulose. Mortality occurred at doses ≥ 1470 mg/kg bw and deaths occurred within 24h of dosing. Clinical signs included dyspnoea, apathy, staggering, atony, deficiency in pain and cornea reflexes, exsiccosis and exophthalmos. At necropsy, dead animals had congestion, slightly inflated lungs and sporadically reddened glandular stomachs. No gross pathological abnormalities were noted at necropsy of survivors. The $LD_{50}$s obtained in this study were 1472 mg/kg in females and 3256 mg/kg in males.

In a 1983 study, also following OECD guidelines and pre-dating GLP requirements, Wistar rats (5/sex/dose) received orally 2-phenoxyethanol by gavage at doses of 0, 794, 1000, 1250, 1580, 1990 or 2510 mg/kg bw. Clinical signs occurred within 15 min of administration and included agitation, tremor, ataxia, staggering, lateral and ventral body position, sedation, piloerection, fast breathing and lowered body temperature. Post mortem examination of the deceased animals revealed reddened mucosa of the stomach and small intestine and red spots on the lung surface. Surviving animals recovered completely after 7 days, but found to have some red spots on the lung surface. The $LD_{50}$ for both males and females was 1850 mg/kg bw.

In a study carried out in 1980 (non-guideline and non-GLP), Sprague Dawley rats (5/sex/dose) received orally 2-phenoxyethanol equivalent to 0, 514, 1107, 2380, 5136 or 11070 mg/kg bw. Clinical signs included slight to severe reduction of activity, decreased reflexes and laboured respiration. Rats treated with high doses appeared comatose prior to death or recovery. No lesions were found in survivors. The $LD_{50}$ in males was 1394 mg/kg bw and in females, 2579 mg/kg bw.

In a 1970 acute range-finding study carried out in rats (strain not specified, not guideline or GLP compliant) males and females (5/sex/dose) received orally 2-phenoxyethanol at doses equivalent to 1107, 1328, 3542, 5535 or 11070 mg/kg bw. Animals were then observed for a 14 day post-exposure period. Lethargy, ataxia, hyperpnoea and coma were noted. The $LD_{50}$ value of 1439 mg/kg bw reported in the study was for males and females combined.

The results of the four well-reported studies available gave a range of $LD_{50}$ values in rats between 1394 and 3256 mg/kg bw. These values were supported by a number of lower quality studies (in the REACH registration dossier) carried out in rats, where $LD_{50}$ ranged between 1260 mg/kg bw and 3400 mg/kg bw.

Therefore, classification of 2-phenoxyethanol for acute oral toxicity as Acute Tox. 4; H302 – harmful if swallowed, with an Acute Toxicity Estimate (ATE) of 1394 mg/kg bw was proposed by DS.

***Inhalation route***

There is one acute inhalation study (1963) available in rats. The study was not carried out according to guidelines nor was it performed according to GLP standards. Very little details were provided, including the strain of rat used, the sex or the purity of the substance tested. Dose levels were not given, but it was reported that 2-phenoxyethanol was administered to rats as a saturated vapour for 8 h. Taking into account the vapour pressure of 2-phenoxyethanol (0.01 – 0.014 hPa at 20°C), the corresponding inhalation exposure was 57 mg/m$^3$ (0.057 mg/L, calculation made following Section 3.1.2.3.2 of the Guidance of the Application of the CLP Criteria). The exposure did not result in any deaths or any clinical signs, therefore the $LC_{50}$ was > 0.057 mg/L.

Further information was provided in a sub-acute inhalation toxicity study carried out according to OECD guidelines and GLP. During this study, male and female Wistar rats were exposed to 2-phenoxyethanol (nose-only) at doses of 0, 0.0482, 0.246 or 1.070 mg/L for 6 h/day, 5 days/week for 14 days. No deaths were recorded throughout the study, therefore the $LC_{50}$ from this study was > 1.07 mg/Ll.

No classification of 2-phenoxyethanol was proposed by DS for acute inhalation toxicity.

***Dermal route***

This endpoint was not considered in the CLH dossier.

## Comments received during public consultation

One Member State Competent Authority (MSCA) and one company-manufacturer supported the proposed classification for oral acute toxicity category 4 with an ATE of 1394 mg/kg bw and no classification for acute inhalation toxicity.

## Assessment and comparison with the classification criteria

In the four acute oral toxicity studies described in more detail, the $LD_{50}$ values ranged between 1394 mg/kg bw and 3256 mg/kg bw. It is noted that 2-phenoxyethanol meets the criteria of CLP regulation for classification in acute oral toxicity category 4 (300 < ATE ≤ 2000), with an oral ATE of 1394 mg/kg bw. Therefore, RAC supports the DS' proposal for classification of 2-phenoxyethanol for oral acute toxicity as **Acute Tox. 4; H302 – harmful if swallowed, with ATE=1394 mg/kg bw**.

The results of an acute inhalation toxicity study indicate that the $LC_{50}$ for rats is above 0.057 mg/L (vapour). This is supported by an $LC_{50}$ > 1.07 mg/L (dusts/mists) derived from a subacute inhalation toxicity study, also carried out in rats. As 2-phenoxyethanol has not been tested in higher concentrations, still below those indicated by classification criteria for category 4, its toxicity at these higher concentrations is not known. Taking into account this lack of knowledge, RAC supports the DS' proposal for **no classification for acute inhalation toxicity due to lack of data**.

## RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

### Summary of the Dossier Submitter's proposal

For the assessment of specific target organ toxicity single exposure, the DS` considered the results of a 14-day repeated inhalation toxicity study (6h/day, 5 days/week, 10 daily exposure in two weeks) (2007c). Due to low vapour pressure of 2-phenoxyethanol (leading to concentration of 0.057 mg/L at room temperature), 5 rats/sex/dose were exposed to a mixture of vapour and aerosol, with high proportion of aerosol at top and mid concentrations amounting to 1.07 mg/L and 0.246 mg/L. No clinical signs of toxicity and no adverse effects in blood (haematological and clinical chemistry parameters) and in internal organs were observed, except the respiratory tract, in which respiratory irritation was noted.

At the highest and mid concentration of 1.07 mg/L and 0.246 mg/L, an increase in lung weight was observed and microscopically a degeneration/squamous metaplasia and hyperplasia of respiratory epithelium in the nasal cavity (in all 5 males and females) was observed. The minimal to mild degeneration of the nasal respiratory epithelium was characterised by a decreased thickness of the epithelium with areas of squamous metaplasia (in all males and females at 1.07 mg/L and 1/5 males and 3/5 females at 0.246 mg/L). The minimal to mild hypertrophy of the respiratory epithelium and minimal to mild hyperplasia (in all males and females at 1.07 and 0.246 mg/L) was characterised by an increase in the thickness of the epithelium with occasionally increased numbers of epithelial cells, mainly affecting the nasal septum of the posterior nasal cavity. In addition, inflammatory cell infiltrates in the submucosa of the nasal cavity were found (in all males at 1.07 and 0.246 mg/L and in 4/5 females at both doses). In 4/5 males and 4/5 females at the high-dose group and one female at the mid-dose group it was also found that the base of the epiglottis was covered by metaplastic squamous epithelium (graded as minimal in 7/10 animals and slight in 1/10 animals at 1.07 mg/L; graded minimal in all animals at 0.246 mg/L). Aside from nasal cavity and epiglottis, also a minimal to mild increase in the thickness of the respiratory epithelium of small and terminal bronchi and minimal to mild increase of mucous cells within the larger bronchi were observed. The proportion of animals affected was somewhat lower at mid-concentration in comparison with those exposed at top concentration, although severity of effects was comparable.

At the lowest concentration of 0.0482 mg/L, no effects were observed in the respiratory tract, thus NOAEC of 0.0482 mg/L, equal approximately to calculated vapour pressure of 2-phenoxyethanol (0.057 mg/L) at a room temperature, was proposed by DS.

No similar adverse effects in respiratory tract were observed in the acute inhalation study in rats (single 8 hour exposure at saturated vapour concentration of 0.057 mg/L), but the concentration used in this acute inhalation toxicity study was well below those causing effects in repeated inhalation exposure and comparable to NOAEC for repeated exposure. Therefore, the assessment of acute inhalation toxicity was considered as insufficient due to lack of data.

Taking into account that the minimal to mild metaplasia in the nasal cavity and larynx of rats exposed to aerosol of 2-phenoxyethanol for short repeated exposure may indicate its potential of irritation on respiratory epithelium at high concentration during single exposure, the DS is of the opinion that the substance warrants classification as STOT SE 3 with hazard statement H335: May cause respiratory irritation.

### Comments received during public consultation

One MSCA pointed out that minimal to mild metaplasia in the nasal cavity and in the larynx, observed in rats exposed for 14 days by inhalation to 2-phenoxyethanol could be taken into consideration while discussing a need for classification as STOT RE.

Two industrial stakeholders indicated that no evidence of respiratory tract irritation can be concluded based on results of the acute inhalation toxicity study, and due to the reversibility of the metaplasia resulting from short repeated exposure, this effect does not provide evidence sufficient for classification of 2-phenoxtethanol as STOT SE 3 or STOT RE. It was also noted that there are no occupational case reports indicating irritation of the respiratory tract by 2-phenoxyethanol.

### Assessment and comparison with the classification criteria

In the acute inhalation toxicity study, only the effects caused by exposure to saturated vapour of 2-phenoxyethanol were taken into account, without considering potential effects of the exposure to aerosol of the substance, which might be much higher than concentration of saturated vapour. Therefore, the acute inhalation study does not provide sufficient data for assessment of specific target organ toxicity - single exposure.

However, the results of 14-day repeated inhalation toxicity study in rats provide sufficient evidence of respiratory tract irritation (RTI), of minimal to mild severity, cause by 2-phenoxyethanol at concentrations approximately 5-20 times higher than the concentration used in the acute inhalation toxicity study. These data can be used for assessment of respiratory tract irritation.

As indicated in Annex I, section 3.8.2.2.1. of the Regulation (EC) 1272/2008 (CLP Regulation) about the criteria for STOT SE 3: "(d) 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" and "(e) this special classification would occur only when more severe organ effects including in the respiratory system are not observed."

It has been noted that the effects found in the histopathological examinations of rats exposed by inhalation for 14 days, were limited to respiratory epithelium in nasal cavity, epiglottis, small, terminal and larger bronchi, no indication of damage of olfactory epithelium in nasal cavity was provided. Taking into account the severity of these effects (mostly graded as minimal to mild), they might possibly not meet the criteria for STOT RE. Yet, they provide sufficient evidence of an irritation potential of 2-phenoxyethanol on the respiratory tract that needs to be addressed. RAC therefore supports the DS' proposal for **STOT SE 3; H335 – May cause respiratory irritation**.

## RAC evaluation of serious eye damage/irritation

### Summary of the Dossier Submitter's proposal

A 1983 study is available in the REACH registration dossier for 2-phenoxyethanol. This study was carried out according to OECD TG 401, but predating GLP requirements, in Russian White rabbits (3/sex). One eye of each rabbit was treated with 2-phenoxyethanol (0.1 mL undiluted) and the animals were observed for 21 days. An irritative response was observed, mainly to the cornea with a score of 1 in all animals (mean scores over 24, 48 and 72 h). The corneal opacity observed was reversible within 15 days for all animals except one who continued to have corneal opacity at the end of the 21 day study period. The results indicate that 2-phenoxyethanol caused irreversible irritation to the eyes of rabbits.

Another eye irritation study (Anonymous, 1983) was carried out using Vienna White rabbits, following OECD TG 405, but predating requirements of GLP. 2-Phenoxyethanol (0.1 mL of undiluted technical grade, purity unknown) was instilled into one eye of three rabbits (1 male and 2 females) and left in place for an observation period of 15 days. During this time, irritation was observed which was exhibited as corneal opacity, iris lesions and redness and swelling of the conjunctiva in all animals. The score for corneal opacity in all 3 animals was ≥ 1. Additionally, a response occurring in at least one animal and in at least one time point was pupil narrowness, scarred retraction of the eyelid, marginal corneal vascularisation and suppuration. The symptoms had resolved in 2/3 animals by the end of the 15 day observation period. However, the third animal displayed a slight corneal opacity on day 15, restricted to less than one quarter of the corneal area.

In conclusion, 2-phenoxyethanol caused adverse effects in the eyes of rabbits that were not completely reversible within observation periods (21 and 15 days) in the above studies.

The REACH registration dossier contains 9 more studies, none of which were performed according to test guidelines and all with limitations in their reporting (diluted material used, no scoring at all time points or very limited data in reporting), therefore, these studies are not suitable for classification purposes. Eight of the nine studies indicated that 2-phenoxyethanol caused irritation to the eye. One of these indicated that the irritation was more serious (15% dilution in propylene glycol) with signs of corneal necrosis (study carried out in 1949) and one showed no irritation at all – however, in this study, the test substance was diluted in water (2.2% aqueous solution). Only three out of these eight studies provided information on reversibility of effects. All eye irritation was resolved within 14 days or less.

The classification of 2-phenoxyethanol for Eye Dam. 1 was proposed by DS.

## Comments received during public consultation

Two MSCA supported the proposed classification as Eye Dam. 1.

Two companies did not agree with proposed classification as Eye Dam. 1. According to their comments, 2-phenoxyethanol produces a reversible irritation and the classification as eye irritant category 2 is more appropriate.

## Assessment and comparison with the classification criteria

In two acceptable guideline eye irritation studies the responses (mean 24-72h scores) found for corneal opacity in all rabbits (six in first study, 3 in second study) were within a range of ≥ 1 and ≤ 3) thus fulfilling the score criteria for Eye Irrit. 2; H319. In the second study in 3 out of 3 rabbits mean 24-72h scores for iritis was 1 also fulfilling criteria for Eye Irrit. 2; H319. Thus, at a minimum, 2-phenoxyethanol should be classified in category 2 for eye irritation.

In one study (1983), the undiluted 2-phenoxyethanol (0.1 mL) was administered to conjunctival sac of three rabbits, and was washed out after 24h of administration. One rabbit of the 3 tested continued to have corneal opacity until the end of the study observational period of 15 days. This study period was shorter than the usual observation period of 21 days and the corneal opacity observed was reported as mild and affecting less than one quarter of the corneal area. It is noted however that the finding in this one animal may be less reliable, as also the untreated eye was affected.

Since some doubts may remain due to the shorter observation period of this study, the first study taken from the REACH registration dossier allays this time as 1 of the 6 tested animals also had corneal opacity by the end of the 21 day study period that had not fully resolved. In this study,

2-phenoxyethanol was applied as undiluted test substance (0.1 mL) and was not washed out 24h after administration.

Two other studies are included in the REACH registration dossier, but not suitable for classification purposes (not performed to test guidelines and severe limitation in reporting) In one study the instillation of a 15% dilution of 2-phenoxyethanol in propylene glycol caused severe corneal necrosis of the rabbit eye (study carried out in 1949) and in the second study carried out in 1962, 2-phenoxyethanol was reported to severely damage the eyes of rabbits.

Therefore, taking into account all available evidence, the classification criterion of CLP regulation (Table 3.3.1 of Annex I) for irreversible effects to the eye (Eye Dam. 1) is met on the basis that the opacity of cornea was not fully reversed within an observation period of 21 days in one out of six rabbits in a reliable study and no clear evidence on full reversibility of eye effects from other available studies.

Noting that criteria are met, RAC supports the DS' proposal for classification of 2-phenoxyethanol for **serious eye damage, category 1 (Eye Dam. 1; H318 – Causes serious eye damage)**.

## RAC evaluation of specific target organ toxicity – repeated exposure (STOT RE)

### Summary of the Dossier Submitter's proposal

DS provided results of several repeated dose toxicity studies in two animal species: three 90-day studies in rats carried out by the oral route (dietary, gavage and drinking water administration) and one 2-year carcinogenicity study in rats (dietary), in mice: one 90-day study (drinking water administration) and one 2-year carcinogenicity study (dietary). There was also a 90-day dermal study in rabbits.

One 14-day inhalation repeated toxicity study showing local adverse effects in nasal and larynx respiratory epithelium was considered by DS in justification for STOT SE 3; H335.

Since no adverse effects were found in these repeated dose toxicity studies at doses below classification guidance values for specific target organ toxicity, DS considered that 2-phenoxyethanol does not warrant classification for specific target organ toxicity following repeated exposure.

### Comments received during public consultation

One MSCA pointed out that minimal to mild metaplasia in the nasal cavity and in the larynx, observed in rats exposed for 14 days by inhalation to 2-phenoxyethanol should be taken into consideration while discussing a need for classification as STOT RE.

One industrial stakeholder supported no classification of 2-phenoxyethanol as STOT RE.

### Assessment and comparison with the classification criteria

None of the several oral repeated dose toxicity studies in rats and mice provided evidence of adverse effects occurring in any internal organ or tissue meeting classification criteria for STOT RE 1 or 2 at doses below the relevant guidance values for these categories. Only at oral doses of 400 mg/kg bw/day or higher in 90-day studies or at doses of 510/795 mg/kg bw/day in two year carcinogenicity study, well above the guidance values for STOT RE 2, 2-phenoxyethanol caused adverse effects in rats in kidney of moderate severity.

The histopathological changes observed in the respiratory tract of rats following exposure for 14 days by inhalation to 2-phenoxyethanol at 0.246 mg/L and 1.070 mg/L, but not at 0.0482 mg/L, point to an irritation potential of 2-phenoxyethanol. The severity of these effects (mostly graded as minimal to mild) did not depend upon concentration, but more animals were affected at higher concentration. These effects occurred, when applying Haber's rule, below the guidance values for STOT RE 2, which would be $0.12 < C \leqslant 1.2$ mg/L for 14 day exposure, however they might not be sufficiently severe for classification with STOT RE 2. In fact, these effects were already used for classification of 2-phenoxyethanol to subcategory STOT SE 3. Taking into account that no adverse effects meeting classification criteria for STOT RE 1 and 2 were observed in the repeated-dose oral, dermal and inhalation toxicity studies in rats and mice, RAC is of the opinion that 2-phenoxyethanol **does not warrant classification for specific target organ toxicity**.

## 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).