

Comments on the CLH report for 2-phenoxyethanol (CAS 122-99-6)

Summary:

The below mentioned comments are in response to the submitted harmonized classification and labelling dossier for 2-phenoxyethanol¹ (version 1; June 2018). We agree with the proposed classification and labelling for acute toxicity (oral) and with the non-classification of the endpoints acute toxicity (inhalation), STOT SE (category 1 and 2) and STOT RE.

However, we disagree with the proposed harmonized classification and labelling of the endpoints eye irritation and respiratory tract irritation (RTI) after single exposure. The available data which are discussed below support a classification of 2-phenoxyethanol as an eye irritant category 2 (H319) and do not support a classification of 2-phenoxyethanol for RTI after single exposure (STOT SE3; H335).

Eye irritation:

The dossier submitter proposed in the harmonized classification and labelling dossier for 2-phenoxyethanol¹ (version 1; June 2018) to classify 2-phenoxyethanol as eye irritant category 1 (H318). This proposal was particularly based on the evaluation of two *in vivo* eye irritation studies that showed effects on the cornea until the end of the respective observation period.

We agree that available data show that 2-phenoxyethanol is a substance that is irritant for the eye. However, based on the available data and a weight-of-evidence approach we do not agree that a harmonized classification as an eye irritant category 1 is warranted. We analyzed the available data with focus on the above-mentioned cornea effects and elaborated in a weight-of-evidence approach that those effects can be considered reversible.

The rapporteur used two guideline-conform non-GLP animal studies (ref. 1, 2) to conclude about the eye irritation potential of 2-phenoxyethanol. Both studies are from the 1980s and used technical 2-phenoxyethanol as test substances. In the first study (ref. 1) 2-phenoxyethanol (Marlophen P1; purity >99%) was applied as undiluted test substance (0.1 mL). The test substance was applied to six rabbits (3 of each gender) and was not washed out 24h after administration. Effects on the eyes were rated according to the Draize scheme and study authors used a scoring system to classify the grading of the irritancy. Phenoxyethanol induced a score of 23.9 of 110, which was described as a mild irritancy.

2-Phenoxyethanol induced effects on the cornea, the iris and conjunctivae. The maximal grades and the average (24, 48, 72h) scores of the positive responses were well below the thresholds for classification as category 1 eye irritant but supported a category 2 (H319) classification.

Critical for above-mentioned classification proposal were the cornea effects, of which some slight but residual effects were observed after 21 days of administration. From a formalistic point of view this could be an argument according to the CLP criteria to warrant a category 1 (CLP Annex I 3.3.2.1.1.: “[...] effects on the cornea [...] that are not expected to reverse or have not fully reversed within an observation period of normally 21 days [...]”). However, evaluating the time course of the cornea effects with respect to the grading and affected surface of the cornea, those effects are expected to be reversible (table 1).

¹ <https://echa.europa.eu/harmonised-classification-and-labelling-consultation/-/substance-rev/20501/term>

Table 1: Evaluation of cornea effects (ref. 1)

Animal	1h		24h		48h		72h		8d		15d		21d	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B
#1	0	0	1	4	1	4	1	3	1	1	0	0	0	0
#2	0	0	1	4	1	3	1	2	0	0	0	0	0	0
#3	1	4	1	4	1	4	1	3	1	1	0	0	0	0
#4	0	0	1	4	1	4	1	4	1	2	0	0	0	0
#5	1	4	1	4	1	4	1	4	1	1	0	0	0	0
#6	1	3	1	4	1	4	1	3	1	3	1	2	1	1

A: opacity degree of density according to Draize; B: area of cornea involved.

As shown in table 1, the opacity of the cornea was only minimally affected (max score = 1; “scattered or diffuse area, details of iris clearly visible”) in all animals at all points in time (well below CLP threshold for category 1: ≥ 3), only the affected area increased between 1h and 72h after administration, but then obviously decreased in all animals. Animal #6 showed a slower recovery compared to animals #1-5 and was the only affected animal after 21d. However, in line with the other animals the affected cornea recovered already and showed a score of 1 in only $< \frac{1}{4}$ of the cornea at termination of the study. As all other animals showed a completely reversible effect on the cornea over time, it is not expected that the cornea effects in animal #6 would be irreversible. In conclusion, classification as eye irritant category 2 would be appropriate considering the strengths and the expected reversibility of the overall effects in light of the CLP criteria.

The reversibility of the cornea effects is confirmed by the second study (ref. 2), which is the key study in the REACh registration dossier. However, after close inspection of the study raw data we can contribute additional information and could confirm that the documentation of the study summary (and consequently the registration dossier) did not reflect the raw data appropriately (see asterisk below in table 2).

Undiluted 2-phenoxyethanol (0.1 mL; monophenylglycol techn., purity unspecified) was administered in three rabbits, but was washed out after 24h of administration. Effects on the eyes were rated according to the Draize scheme. The maximal grades and the average (24, 48, 72h) scores of the positive responses were well below the CLP thresholds for classification as category 1 eye irritant.

Table 2: Evaluation of cornea effects (ref. 2)

Animal	1h		24h		48h		72h		8d		15d		21d	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B
#1	0	0	1	4	1	4	1	4	1	2	1*	1*	n.d.	n.d.
#2	0	0	1	4	1	4	1	4	1	2	0	0	n.d.	n.d.
#3	0	0	1	4	2	4	2	4	1	2	0	0	n.d.	n.d.

A: opacity degree of density according to OECD; B: area of cornea involved; n.d.: not determined; *: handwritten note of the study author: both eyes (treated and control) showed symptoms. Recommendation to set the scores to 0/0 (grade/area).

As shown in table 2, the opacity of the cornea was minimally to moderately affected (max score = 2; “easily discernible translucent areas, details of iris slightly obscured”) in all animals (CLP threshold for category 1: ≥ 3). The affected area of the cornea increased between 1h and 72h after administration, but then obviously decreased very fast in all animals and independent of the strength of the cornea effect. Animal #1 was the only affected animal after 15d and showed a corneal opacity score of 1 but only in $< \frac{1}{4}$ of the cornea. A longer observation period (21d) was unfortunately not included in that study. However, detailed inspection of the study raw data unraveled that the study author included a handwritten note for the observation after 15d. He observed that both eyes (treated and control eye) of animal #1 showed symptoms after 15 days and he recommended therefore to set the scoring of animal #1 after 15d to 0/0 (grade/area), as

this might not be a treatment-related effect. This result, however, was not transferred appropriately to the study summary, but the raw data can be provided to the rapporteur if required.

Including this note of the study author in the evaluation of the study, complete reversibility (or at least an equivocal result in animal #1) was observed after 15d. In line with the first study again all animals showed a decrease in strength of the cornea effects over time and, thus, it is not expected that the (potential) cornea effects in animal #1 after 15d are irreversible, even without taking the note of the study author into account. The marginal corneal vascularization which was seen in animals in absence of corneal opacity confirmed the onset of a regeneration process. In conclusion, classification as eye irritant category 2 would be appropriate comparing the overall study results with the CLP criteria.

Further eye irritation studies were included in the REACh dossier², but either they are not suitable to conclude about the classification, i.e. no mean scores at 24/48/72h were available, or reversibility was not investigated. However, as stated in the CLH proposal, further studies (e.g. Dow, 1994; Anonymous, 1990; BASF, 1963 (ref. 3)) confirmed that all eye irritation was resolved within 14 days or less. One of those studies is discussed in detail below. In this study (ref. 3) reversibility of cornea effects induced by 2-phenoxyethanol within 8 days was observed. The study documentation is limited, but the study supports the weight of evidence approach to conclude about the reversibility of the cornea effects.

2-phenoxyethanol (arophor; purity unspecified) was administered in two rabbits as undiluted test substance (0.05 mL). The substance was not washed out 24h after administration. 2-phenoxyethanol induced effects on the cornea, the iris and conjunctivae. However, the maximal grades observed were well below the thresholds for classification as category 1 eye irritant.

Table 3: Evaluation of cornea effects (ref. 3)

Animal	1h		24h		48h		72h		8d		15d		21d	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B
#1	1	n.d.	1	n.d.	n.d.	n.d.	n.d.	n.d.	0	n.d.	n.d.	n.d.	n.d.	n.d.
#2	1	n.d.	1	n.d.	n.d.	n.d.	n.d.	n.d.	0	n.d.	n.d.	n.d.	n.d.	n.d.

A: opacity degree of density according to OECD; B: area of cornea involved; n.d., not determined.

As shown in table 3, the opacity of the cornea was minimally affected (max score = 1; “scattered or diffuse area, details of iris clearly visible”) in both animals. The affected area of the cornea was not documented. However, all effects were completely reversible after 8d.

More information on the reversibility of eye irritation effects is available from literature. However, sufficient documentation is not available. For example, in Patty’s toxicology (5th edition, volume 7) it was cited that instillation of 2-phenoxyethanol into the rabbit eye resulted in slight irritation, iritis, and slight to moderate corneal injury that healed in about 1 week (Keeler and Rampy, unpublished, 1974).

Guideline conform animal studies showed that 2-phenoxyethanol has an eye irritant property. Irritation scores for corneal opacity, iritis, conjunctival redness or oedema support a classification of 2-phenoxyethanol as eye irritant category 2 (H319) according to CLP criteria. Regarding the reversibility of cornea effects three available studies were analyzed in detail. Two studies showed a reversible effect on the cornea within 15 days or less. This is supported by additional 3 studies which are not discussed in detail. One study shows a limited effect in 1 animal on <¼ of the cornea. However, considering all available data, including the overall data of the latter study (reversibility of effects in all other animals within 15d) it is not expected that the effects in 1 animal are of irreversible nature. Current evaluations of historical serious eye irritation *in vivo* data indicated that a category 1 classification based only on persistence of low-level conjunctival effects (score 1) in 1 animal in the absence of any other category 1-triggering effects is highly questionable (ref. 4).

In conclusion, without performing an additional *in vivo* eye irritation study in conformity to the current OECD 405 guideline, there is no clear evidence from the available weight-of-evidence approach that a classification of 2-phenoxyethanol as eye irritant category 1 is warranted. Neither the available mean or the maximal irritation scores nor the reversibility of the cornea effects clearly support classification as category 1 eye irritant according to CLP-criteria. However, the available data strongly support a classification of 2-phenoxyethanol as eye irritant category 2 (H319) according to CLP criteria.

Respiratory tract irritation:

The dossier submitter proposed in the harmonized classification and labelling dossier for 2-phenoxyethanol (version 1; June 2018) to classify 2-phenoxyethanol as STOT SE3 (H335). This proposal was particularly based on the evaluation of an *in vivo* repeated dose inhalation study that showed effects on the respiratory epithelium after repeated inhalation (14 days) of 2-phenoxyethanol aerosol.

The CLP criteria for classification in STOT SE category 3 only cover the transient effects of 'respiratory tract irritation (RTI)' and 'narcotic effects'. These are "*effects which adversely alter human function for a short duration after exposure and from which humans may recover in a reasonable period without leaving significant alteration of structure or function*".

To conclude about RTI after single exposure appropriate data should be evaluated according to CLP regulation. Article 5 (2) of the CLP regulation states that available information should be identified (paragraph 1) and "*manufacturers, importers and downstream users shall examine the information referred to in paragraph 1 to ascertain whether it is adequate, reliable and scientifically valid for the purpose of the evaluation pursuant to Chapter 2 of this Title.*". The CLP guidance furthermore states that evaluation of a STOT SE category 3 "respiratory tract irritation" is particularly based on human data and comprise "*localized redness, oedema, pruritis and/or pain that impair function with symptoms such as cough, pain, choking, and breathing difficulties*". It further states that "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)". CLP Annex I: 3.8.2.1.5 adds that for RTI **after single exposure** "the standard animal studies in rats or mice that provide information are acute toxicity studies which can include clinical observations and detailed macroscopic and microscopic examination to enable the toxic effects on target tissues/ organs to be identified.".

There are no occupational case reports available to deduce a causal relationship between 2-phenoxyethanol exposure and RTI, i.e. human data on RTI induced by 2-phenoxyethanol is not available. However, two acute animal inhalation studies are available. The first study (ref. 3) is an inhalation risk test which was performed with 2-phenoxyethanol (arophor; purity unspecified) vapour atmosphere that was saturated either at 20°C or at 100°C. 12 rats per group were exposed for 8h each. Animals were observed for 7 days post exposure. No mortality and no exposure-related symptoms were observed which would give an indication for local irritancy (e.g. dyspnoea, rhinitis, etc.). Therefore, no histopathological examination was included directly after single inhalation. In another acute inhalation study (ref. 5) 3 rats were exposed with saturated phenoxyethanol vapor at room temperature for 7h. No mortalities were observed as well as no signs of intoxication. In both acute studies no obvious signs of RTI (e.g. dyspnoea, rhinitis, etc.) were observed after a single administration and after 7 days, respectively. The saturated vapor concentration of 2-phenoxyethanol is about 50 mg/m³. Hence, it is shown by the acute studies that single exposure with saturated 2-phenoxyethanol vapor does not warrant a classification with STOT SE3.

This is furthermore confirmed in a guideline-conform and GLP-compliant 14d inhalation study with 2-phenoxyethanol (ref. 6). Three test substance concentrations were used to identify potential effects of 2-phenoxyethanol after repeated inhalation. The lowest concentration of 48.2 mg/m³ of 2-phenoxyethanol represents a saturated vapor concentration and was identified as the NOAEC. No treatment-related symptoms were observed. At the LOAEC of 246 mg/m³ signs of local irritation were observed after 14d of inhalation (6h daily, 5d per week) (symptoms described in the CLH proposal).

In total three studies showed that no obvious RTI was induced by single or repeated administration of saturated vapor of 2-phenoxyethanol. In conclusion, saturated vapor of 2-phenoxyethanol does not pose a hazard of respiratory tract irritation.

The critical effect in the 14d inhalation study in rats was the local irritation of the respiratory tract, particularly the nose, induced by highly concentrated 2-phenoxyethanol aerosols. However, this was dependent on the aerosol concentration. The amount of aerosol in the animal study increased from 20% at the NOAEC (48.2 mg/m³) to 90% at the LOAEC (246 mg/m³). The local effects observed at the LOAEC are most likely induced by aerosol impactation. Those aerosol-based effects are not observed at the NOAEC of 48.2 mg/m³ and are therefore also unlikely to occur in the concentration range of the recently established OEL of 5.7 mg/m³ (AGS, Germany, 2018). Furthermore, it cannot be derived from the 14d repeated inhalation study, that a single exposure with comparable aerosol concentrations (90%) of 2-phenoxyethanol would induce comparable irritant effects.

In addition to those formal and scientific/technical arguments, it is highly unlikely that exposure with highly concentrated 2-phenoxyethanol occurs in reasonably expected uses. At standard workplaces, which fall under the scope of REACh or BPR, regulatory limit values must be met. For 2-phenoxyethanol those limit values were recently set under different European regulations. For short-term exposure this OEL is 5.7 mg/m³ under REACh regulation (AGS, Germany, 2018) and 1.93 mg/m³ under the biocidal product regulation BPR (BPC-EChA, 2018). Those limit concentrations are far below the saturated vapor concentration of 2-phenoxyethanol (see above: which did not pose a hazard of RTI). In addition, in biocidal applications were 2-phenoxyethanol aerosols potentially could reach the respiratory tract (e.g. trigger spray applications for surface disinfection), 2-phenoxyethanol is only present in very low concentrations of <5%. Thus, no potential scenario can be foreseen in which a potential RTI hazard induced by single exposure to highly concentrated 2-phenoxyethanol aerosols is likely or relevant.

To sum up the above-mentioned arguments:

- Available data show that saturated vapor of 2-phenoxyethanol including low amounts of aerosol (20%) does not pose a hazard of RTI after single and repeated inhalation.
- Current occupational exposure limits are well below the saturated vapor concentration of 2-phenoxyethanol
- Exposure with highly concentrated 2-phenoxyethanol aerosol in reasonably expected uses is highly unlikely
- Highly concentrated (90%) 2-phenoxyethanol aerosols show RTI after repeated inhalation, however, available studies are not suitable and not in accordance with CLP criteria to derive a hazard induced by 2-phenoxyethanol aerosols after single inhalation

As the CLP guidance states in accordance with annex I, 3.8.2.1.5 that acute animal studies are the standard studies that provide information about RTI after single exposure, the available acute studies using saturated vapor of 2-phenoxyethanol should be used accordingly to describe a potential hazard of RTI for reasonably expected uses, however, no marked RTI hazard was identified after single exposure.

Thus, in line with available scientific data and the principles of proportionality we propose not to include a classification with STOT SE3 in the harmonized classification and labelling proposal of 2-phenoxyethanol, because 1) RTI was not observed after single exposure, 2) phenoxyethanol vapor does not pose a RTI hazard, 3) the available repeated-dose study is not suitable to derive a RTI hazard after single inhalation of highly concentrated phenoxyethanol aerosols and 4) reasonably expected scenarios in which exposure to highly concentrated 2-phenoxyethanol aerosols could occur cannot be foreseen.

However, if the rapporteur concludes that STOT SE3 is warranted e.g. on a precautionary basis, we propose to establish a specific concentration limit for classification as STOT SE3 (RTI) which might be, in a simplistic approach, deduced from the irritation thresholds for eye irritation category 2 (SCL: 10%).

Acute oral toxicity:

The dossier submitter proposed in the harmonized classification and labelling dossier for 2-phenoxyethanol (version 1; June 2018) to classify 2-phenoxyethanol as acute toxic (oral) category 4 (H302). Available data clearly demonstrate that the LD₅₀ for 2-phenoxyethanol is 1,840 mg/kg. Thus, it is in the range of 300 < ATE ≤ 2,000 mg/kg bw and should be classified according to the CLP criteria with acute toxic (oral) category 4 (H302). We fully agree with this part of the harmonized classification proposal.

Other toxicological endpoints:

The dossier submitter proposed in the harmonized classification and labelling dossier for 2-phenoxyethanol (version 1; June 2018) no classification 2-phenoxyethanol for the endpoints acute toxicity (inhalation), STOT SE (category 1 and 2) and STOT RE. The dossier submitter concluded that available data was conclusive but not sufficient for classification and labelling. We fully agree with this part of the harmonized classification proposal.

References:

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