Committee for Risk Assessment

RAC

Annex 1

Background document

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

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

13 June 2019

CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

International Chemical Identification: 2-Phenoxyethanol

EC Number: 204-589-7

CAS Number: 122-99-6

Index Number: 603-098-00-9

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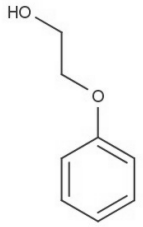
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	*2-(phenoxy)ethanol, 1-Hydroxy-2-phenoxyethane, 2-phenoxy-1-ethanol*
Other names (usual name, trade name, abbreviation)	2-phenoxyethanol, (2-hydroxy-ethyl)-phenyl ether
ISO common name (if available and appropriate)	-
EC number (if available and appropriate)	204-589-7
EC name (if available and appropriate)	2-phenoxyethanol
CAS number (if available)	122-99-6
Other identity code (if available)	-
Molecular formula	$C_8H_{10}O_2$
Structural formula	
SMILES notation (if available)	OCCOC1=CC=CC=C1
Molecular weight or molecular weight range	138.16 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	*Not relevant*
Description of the manufacturing process and identity of the source (for UVCB substances only)	*Not relevant*
Degree of purity (%) (if relevant for the entry in Annex VI)	Minimum 98.5 % purity

1.2 Composition of the substance

2-Phenoxyethanol includes no isomers or additives. A number of confidential impurities are present, however none of these are relevant for the classification of the substance.

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**
2-Phenoxyethanol	**> 98.5 %**	**Acute Tox. 4* (H302) Eye Irrit. 2 (H319)**	**See Figure 1 below**

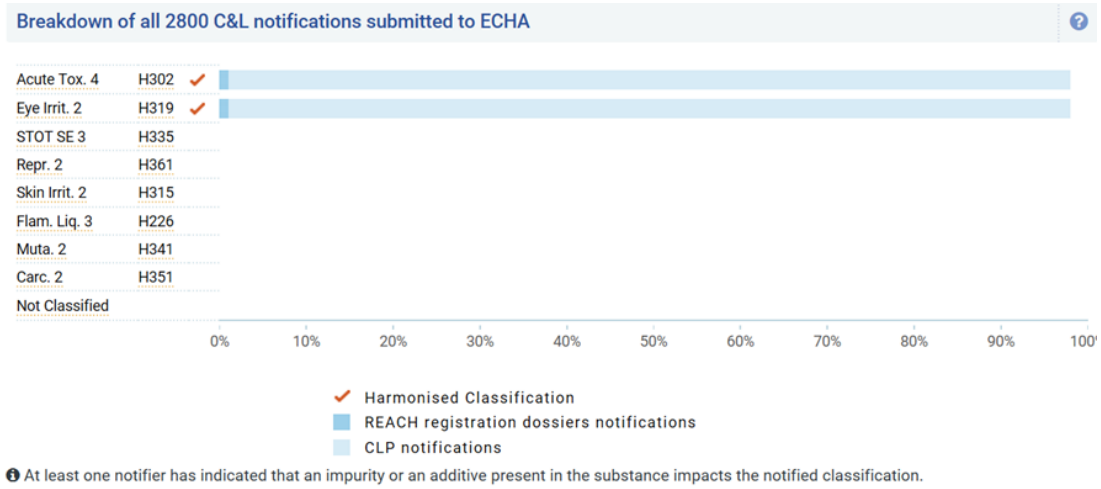


Figure 1: Breakdown of all C&L notifications submitted to ECHA (Taken from the "brief profile" of 2-phenoxyethanol available on the ECHA website at the time of submission).

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 3:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	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* Eye Irrit. 2	H302 H319	GSH07 Wng	H302 H319			
Dossier submitters proposal	603-098-00-9	2-phenoxyethanol	204-589-7	122-99-6	**Modify:** Acute Tox. 4 Eye Dam. 1 **Add:** STOT-SE 3 (respiratory tract irritation)	**Retain:** H302 **Modify:** H318 **Add:** H335	**Retain:** GSH07 **Add:** GSH05 Dgr	**Retain:** H302 **Modify:** H318 **Add:** H335		**Add:** **Oral:** ATE = 1394 mg/kg bw	
Resulting Annex VI entry if agreed by RAC and COM	603-098-00-9	2-phenoxyethanol	204-589-7	122-99-6	Acute Tox. 4 Eye Dam. 1 STOT-SE 3 (respiratory tract irritation)	H302 H318 H335	GSH07 GSH05 Dgr	H302 H318 H335		**Oral:** ATE = 1394 mg/kg bw	

Table 4: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	*Hazard class not assessed in this dossier*	No
Flammable gases (including chemically unstable gases)	*Hazard class not assessed in this dossier*	No
Oxidising gases	*Hazard class not assessed in this dossier*	No
Gases under pressure	*Hazard class not assessed in this dossier*	No
Flammable liquids	*Hazard class not assessed in this dossier*	No
Flammable solids	*Hazard class not assessed in this dossier*	No
Self-reactive substances	*Hazard class not assessed in this dossier*	No
Pyrophoric liquids	*Hazard class not assessed in this dossier*	No
Pyrophoric solids	*Hazard class not assessed in this dossier*	No
Self-heating substances	*Hazard class not assessed in this dossier*	No
Substances which in contact with water emit flammable gases	*Hazard class not assessed in this dossier*	No
Oxidising liquids	*Hazard class not assessed in this dossier*	No
Oxidising solids	*Hazard class not assessed in this dossier*	No
Organic peroxides	*Hazard class not assessed in this dossier*	No
Corrosive to metals	*Hazard class not assessed in this dossier*	No
Acute toxicity via oral route	***Harmonised classification proposed***	**Yes**
Acute toxicity via dermal route	*Hazard class not assessed in this dossier*	No
Acute toxicity via inhalation route	***Data conclusive but not sufficient for classification***	**Yes**
Skin corrosion/irritation	*Hazard class not assessed in this dossier*	No
Serious eye damage/eye irritation	***Harmonised classification proposed***	**Yes**
Respiratory sensitisation	*Hazard class not assessed in this dossier*	No
Skin sensitisation	*Hazard class not assessed in this dossier*	No
Germ cell mutagenicity	*Hazard class not assessed in this dossier*	No
Carcinogenicity	*Hazard class not assessed in this dossier*	No
Reproductive toxicity	*Hazard class not assessed in this dossier*	No
Specific target organ toxicity-single exposure	***Harmonised classification proposed***	**Yes**
Specific target organ toxicity-repeated exposure	***Data conclusive but not sufficient for classification***	**Yes**
Aspiration hazard	*Hazard class not assessed in this dossier*	No
Hazardous to the aquatic environment	*Hazard class not assessed in this dossier*	No
Hazardous to the ozone layer	*Hazard class not assessed in this dossier*	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

2-Phenoxyethanol is an existing biocidal active substance, registered under REACH. It was originally included in Annex I to Directive 67/548/EEC and the harmonised classification has been translated in Annex VI of CLP (See table 3). 2-Phenoxyethanol is currently classified for acute oral toxicity (Acute Tox 4*, H302: Harmful if swallowed) and eye irritation (Eye Irrit 2, H319: Causes serious eye irritation). In alignment with the biocides review process and by using data from the publically available REACH registration dossier, this proposal seeks to update and amend the existing Annex VI entry for 2-Phenoxyethanol utilising all available information.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

2-Phenoxyethanol is an active substance in the meaning of Regulation (EU) No 528/2012, therefore there is no requirement for justification that action is needed at Community level.

5 IDENTIFIED USES

2-Phenoxyethanol is used as a biocide in a range of products and articles including fillers, plasters, modelling clays and lubricants. It is also used in machine wash liquids and detergents, paints and in cooling liquids. It is used in products used both professionally and by consumers.

6 DATA SOURCES

Biocides Products Regulation:

Draft Competent Authority Report: UK, December 2016: Document IIA (dCAR)

REACH Regulation:

Registration dossier: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/15160

* Minimum classification

7 PHYSICOCHEMICAL PROPERTIES

Table 5: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Clear, colourless liquid	dCAR: A3.3.3.1 (Murray, S. 2007)	Visual inspection
Melting/freezing point	9.1 °C (Purity 99.9 %) 11.8 ± 0.2 °C (Purity 98 ± 0.6 %)	dCAR: A3.3.1.1 (Erstling, K. 2001a) (Russel, M.W. 2002)	Method A1, GLP OECD 102, GLP
Boiling point	244.3 °C (Purity 99.9 %) 245.5 °C (Purity 99.4 %)	dCAR: A3.3.1.2 (Erstling, K. 2001a) (Griffin, K.A. 2002)	Method A2, GLP OECD 103, GLP
Relative density	1.1071 g/ml at 20°C	dCAR: A3.3.1.3 (Erstling, K. 2001a)	Method A3, GLP (Purity 99.9 %)
Vapour pressure	0.01 hPa at 20 °C	dCAR: A3.3.2.0 (Olf, G. 2002)	Method A4, GLP (Purity 99.9 %)
Surface tension	Result: 70.7 mN/m Temp: 19.9 °C Not surface active	dCAR: A3.3.13 (Brekelmans, M.J.C. 2007)	Method A5, GLP not stated (Purity 99.9 %)
Water solubility	pH temp. result dH_2O 10°C 27 g/l dH_2O 20°C 27 g/l dH_2O 30°C 28 g/l 5 10°C 24 g/l 5 20°C 24 g/l 5 30°C 25 g/l 7 10°C 25 g/l 7 20°C 25 g/l 7 30°C 26 g/l 9 10°C 26 g/l 9 20°C 27 g/l 9 30°C 27 g/l	dCAR: A3.3.5 (Erstling, K. 2001b)	Method A6, GLP (Purity 99.9 %)
Partition coefficient n-octanol/water	pH temp. log Pow 5 23 °C 1.2 7 23 °C 1.2 9 23 °C 1.2	dCAR: A3.3.9 (Erstling, K. 2002)	Method A8, GLP (Purity 99.9 %)
Flash point	126 °C (Pensky-Martens closed cup method)	dCAR: A3.3.12 (Brekelmans, M.J.C. 2007)	Method A9, GLP (Purity 99.9 %)
Flammability including auto-flammability	2-Phenoxyethanol is a non-flammable liquid, it is not pyrophoric and does not emit flammable	dCAR: A3.3.11 (Löffler, U. 1999)	Due to the chemical properties of the substance, testing according to EEC guidelines A10 (for solids), A11 (for gases), A12

Property	Value	Reference	Comment (e.g. measured or estimated)
	gases in contact with water. AIT = 475 °C at 997 – 1001 hPa		(contact with water), A13 (pyrophoric properties, contact with air), A15 (AIT >400 °C) and A16 (for solids) is not appropriate.
Explosive properties	Not explosive	dCAR: A3.3.15 (Löffler, U. 2000)	The substance has no chemical groups indicating explosive properties. This statement agrees with the recommendations of appendix 6 in the Manual of Tests and Criteria of the United Nations
Oxidising properties	No oxidizing properties	dCAR: A3.3.16 (Löffler, U. 2000)	The substance has no chemical groups indicating oxidizing properties. This statement agrees with the recommendations of appendix 6 in the Manual of Tests and Criteria of the United Nations.
Dissociation constant	Calculated pKa = 14.78 (No dissociation is expected. Solubility in water and partition co-efficient are not affect by pH)	dCAR: A3.3.6	The chemical structure indicates that no dissociation is to be expected.
Viscosity	41 mPa.s at 19.8 ± 0.4°C 19 mPa.s at 40.5 ± 0.5°C	dCAR: A3.3.14 (Brekelmans, M.J.C. 2007)	OECD 114, GLP

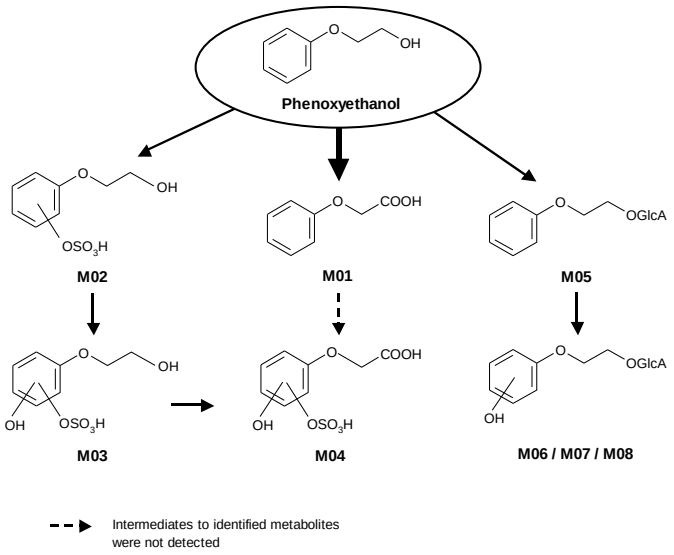
8 EVALUATION OF PHYSICAL HAZARDS

Physical hazards are not addressed in this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

The toxicokinetics of 2-phenoxyethanol have been investigated *in vivo* in rats by the oral route and *in vitro* in rats and humans.

Table 6: Summary table of toxicokinetic studies

Method	Results	Reference
Oral toxicokinetics study in rats following a single and repeated dosing (gavage) OECD 417 GLP ^{14}C-2Phenoxyethanol (min. 99 % 2-phenoxyethanol) in 0.5 % carboxymethyl cellulose Radiochemical purity 97.9 % Chemical purity 96.5 % Single doses: 31 – 1031 mg/kg bw Repeated doses: 423 mg/kg bw/day unlabelled material for 14 days followed by a single dose of 423 mg/kg bw ^{14}C-2-Phenoxyethanol on the 15th day Wistar rats: generally 4/sex/group (but 3-4 females/group for some experiments)	**Absorption** Rapid and extensive from the GI tract – approx. 100 % oral bioavailability. **Distribution** Following a single dose of either 40 or 400 mg/kg bw, radioactivity was distributed to all organs examined. The highest tissue concentrations were found in the GI tract, peaking at 4.5 h post-dosing and by 14 h no radioactivity was detected in the brain, muscle, heart, bone, uterus, testes/ovaries, pancreas or thyroid at either dose tested. **Excretion** Rapid excretion, mainly urinary. Following both single and repeated dosing approximately 95 % and 90 % of radioactivity was excreted in the urine by 72 hours post-dosing (males and females respectively)	dCAR: Doc IIA Section 3.1 (Anon. 2007a)
Oral metabolism study in rats following a single and repeated dosing (gavage) OECD 417 GLP ^{14}C-2Phenoxyethanol (min. 99 % 2-phenoxyethanol) in 0.5 % carboxymethyl cellulose Radiochemical purity 97.9 % Chemical purity 96.5 % Single doses: 40 and 400 mg/kg bw Repeated doses: 423 mg/kg bw/day unlabelled material for 14 days followed by a single dose of 423 mg/kg bw ^{14}C-2-Phenoxyethanol on the 15th day Wistar rats: 4 females/group	**Metabolism** 2-Phenoxyethanol was extensively metabolised in vivo in rats. The major urinary metabolite was found to be 2-phenoxyacetic acid (M01) (56.6 – 63.7 % of the dose 24 h after dosing). **Proposed metabolic pathway in rats:**  	dCAR: Doc IIA; Section 3.1 (Anon. 2007b)

Method	Results	Reference
	Unchanged 2-phenoxyethanol was detected only in low amounts (< 0.7 %)	
In vitro metabolism study using mouse, rat, rabbit and human microsomes Non-guideline GLP Purity: 99.7 % Liver S9 homogenate from: CD-1 mice (pool from 100) Spague Dawley rats (pool from 100) New Zealand White rabbits (pool from 2) Human (7 donors) All females. Incubation time: 0, 1, 5, 10, 20, 60 and 120 min Concentration of 2-phenoxyethanol: 10 – 1000 µg/mg protein	Similar metabolic profile was obtained in all species. Major metabolite was 2-phenoxyacetic acid – 27 % in both rats and humans Rate of metabolism at 1 mM was highest in: Human > rat > mouse > rabbit	dCAR: Doc IIA; Section 3.1 (Anon. 2006)

9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

The absorption, distribution, metabolism and excretion of 2-phenoxyethanol have been investigated in several well-conducted studies.

Following single and repeated oral doses, 2-phenoxyethanol was rapidly and extensively absorbed from the gastrointestinal tract of rats. Based on the urinary and biliary excretion data and distribution measurements, the oral absorption was close to 100 %. No accumulation of 2 phenoxyethanol occurred but a saturation of excretion occurred with increasing doses. Radioactive material was distributed to all organs and tissues examined, with the highest concentrations being found in the GI tract. By 14 h after dosing, most of the radioactivity was cleared. The substance was rapidly and almost completely metabolised, with the major metabolite 2-phenoxyacetic acid found in all species tested (*in vitro* and *in vivo*). The proposed metabolic profile can be found in Table 6. Elimination after oral administration occurred mainly via the urine and was almost complete by 72 hours after dosing. There were no differences in the end-points between the sexes or with single or repeat oral doses.

10 EVALUATION OF HEALTH HAZARDS

The human health hazards of 2-phenoxyethanol are summarised below. Reference should be made to the draft Competent Authority Report – CAR – UK (December 2016), Document IIA, Section 3 (hereby referred to as the dCAR) and the publically available REACH registration report for 2-phenoxyethanol.

10.1 Acute toxicity - oral route

Table 7: Summary table of animal studies on acute oral toxicity

There are a number of acute oral toxicity studies available, all carried out in rats. Many of these studies are somewhat outdated, and most have deficiencies in their reporting. Three of these studies, carried out in the 1970s and 80s were documented in the dCAR and have been included in the table below (Anon., 1982, Anon 1980 and Anon. 1970). A further 11 studies were provided in the REACH registration for 2-phenoxyethanol, all adding to the weight of evidence for classification, but most were not in sufficient detail to report below. Of these 11 studies, one 1983 study was carried out according to OCED guidelines and reported to a suitable level of detail, therefore only this study has been considered below.

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance,**	**Dose levels, duration of exposure**	**Value LD_{50}**	**Reference**
Acute oral toxicity study OECD 401 Non-GLP (study predates requirements) Gavage	Rat, Wistar Males and females (5/sex/dose)	2-Phenoxyethanol (technical grade) Purity 80 % In carboxymethyl cellulose	681, 1470, 3160 and 5000 mg/kg bw	Males: 3256 mg/kg bw Females: 1472 mg/kg bw Combined: 2192 mg/kg bw	dCAR: Doc IIA; Section 3.2 (Anon.1982)
Acute oral toxicity study OECD 401 Non-GLP (study pre-dates requirements) Gavage	Rat, Wistar Males and females (5/sex/dose)	2-Phenoxyethanol (Marlophen P1) Purity > 99 % No vehicle	794, 1000, 1250, 1580, 1990, 2510 mg/kg bw	1850 mg/kg bw	Study report (taken from REACH registration) 1983
Acute oral toxicity study Non-OECD guideline Non-GLP (study pre-dates requirements) Gavage	Rat, Sprague Dawley Males and females (5/sex/dose)	2-Phenoxyethanol Purity ≥ 92 % No vehicle	0.464, 1.0, 2.15, 4.64, 10.0 ml/kg[#] (equivalent to: 514, 1107, 2380, 5136, 11070 mg/kg bw)	Males: 1394 mg/kg bw Females: 2579 mg/kg bw Combined: 1987 mg/kg bw	dCAR: Doc IIA; Section 3.2 (Anon. 1980)
Acute toxicity range-finding study Non-guideline Non-GLP	Rat, strain not specified Males and females (5/sex/dose)	2-Phenoxyethanol Purity > 99 No vehicle	1.0, 1.2, 3.2, 5, 10 ml/kg[#] (equivalent to: 1107, 1328, 3542, 5535, 11070 mg/kg bw) 14 d post-	Males and females combined: 1439 mg/kg bw	dCAR: Doc IIA; Section 3.2 (Anon. 1970)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels, duration of exposure	Value LD_{50}	Reference
			exposure period		

[#] conversion to mg/kg was made based on 2-phenoxyethanol having a specific gravity of 1.107 g/ml

10.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

In a 1982 study, carried out according to OECD guidelines (study predated GLP requirements), Wistar rats (5/sex/dose) were administered an oral dose of 0, 681, 1470, 3160 or 5000 mg/kg phenoxyethanol in carboxymethyl cellulose. Mortality occurred from a dose of 1470 mg/kg bw and all deaths occurred within 24 h of dosing. In general, females appeared to be more susceptible to 2-phenoxyethanol than males. Clinical signs included dyspnoea, apathy, staggering, atony, deficiency in pain and cornea reflexes, exsiccosis and exophthalmos. At necropsy, animals that died 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 an oral dose of 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 mortum examination of the deceased revealed reddened mucosa of the stomach and small intestine and red spots on the lung surface. Surviving animals recovered completely after 7 days, but were 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 an oral dose of 2-phenoxyethanol equivalent to 0, 514, 1107, 2380, 5136 or 11070 mg/kg. 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 an 1970s acute range-finding study carried out in rats (strain not specified) (not guideline or GLP). Males and females (5/sex/dose) received an oral dose of 2-phenoxyethanol at a dose 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 given was for males and females combined.

The results of the four well-reported studies available give a range of LD_{50} values in rats between 1394 – 3256 mg/kg bw.

A further 10 oral acute toxicity studies in rats were provided in the REACH registration for 2-phenoxyethanol. These studies were carried out between the years 1938 and 1988, none were performed according to guidelines and all had at least some deficiencies in their reporting, making them less reliable for classification purposes. The LD_{50} values were broadly in line with those of the described studies above and ranged between 1260 mg/kg bw and 3400 mg/kg bw.

10.1.2 Comparison with the CLP criteria

Four studies have been described in detail, two of which carried out according to test guidelines and two others providing supportive data. In addition to this, 10 more studies are available adding to the weight of evidence for classification.

For the four studies described above, the LD_{50} values ranged between 1394 mg/kg bw and 3256 mg/kg bw. These values were supported by a number of lower quality studies carried out in rats, where LD_{50}s ranged between 1260 mg/kg bw and 3400 mg/kg bw.

Therefore, the results of the available acute oral toxicity studies, all performed in rats, provide a consistent toxicological view for this endpoint.

According to CLP, classification is based on the lowest acute toxicity estimate (ATE) value available i.e. the lowest ATE in the most sensitive appropriate species tested. However, expert judgement may allow another ATE value to be used in preference, provided this can be supported by a robust justification.

2-Phenoxyethanol meets the criteria for classification in acute oral toxicity category 4 (300 < ATE ≤ 2000). The lowest LD_{50} value of 1394 mg/kg bw shall be used as the Acute Toxicity Estimate (ATE).

10.1.3 Conclusion on classification and labelling for acute oral toxicity

Acute Tox. 4; H302: harmful if swallowed ATE = 1394 mg/kg bw

10.2 Acute toxicity – dermal route

This endpoint is not addressed in this dossier.

10.3 Acute toxicity - inhalation route

One acute inhalation study in rats and 14-day inhalation study in rats are available.

Table 8: Summary table of animal studies on acute inhalation toxicity

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance, , form and particle size (MMAD)**	**Dose levels, duration of exposure**	**Value** LC_{50}	**Reference**
Acute inhalation study Non-guideline Non-GLP	Rats, strain not specified Sex not specified 12/dose	2-Phenoxyethanol Purity unknown Saturated vapour	57 mg/m^3 8 h exposure	> 57 mg/m^3 (≡ 0.057 mg/l)	dCAR: Doc IIA; Section 3.2 (Anon. 1963)

Table 9: Summary table of other studies relevant for acute inhalation toxicity

Type of study/data	**Test substance,**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
14-Day inhalation study OECD 412 GLP Nose-only	Rats, Wistar Males and females (5/sex/dose)	2-Phenoxyethanol Purity > 99.9 % Aerosol (dusts and mists) MMAD: 1 – 1.2 µm Doses: 0, 48.2, 246, 1070 mg/m^3 Exposure: 6 h/day 5 days/week for 14 d	LC_{50} > 1070 mg/m^3(≡ 1 mg/l)	dCAR: Doc IIA; Section 3.5 (Anon. 2007c)

10.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

There is one acute inhalation study available in rats. The study was not carried out according to guidelines nor was it performed to GLP standards. Very little detail was 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 intake was 57 mg/m^3 (0.057 mg/l) (calculation made following Section 3.1.2.3.2, Guidance of the Application of the CLP Criteria conversions). Exposure did not result in any deaths or any clinical signs, therefore the LC_{50} was > 0.057 mg/l.

Further information is 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 esposed to 2-phenoxyethanol (nose-only) at doses of 0, 48.2, 246 or 1070 mg/m^3 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 > 1070 mg/m^3 (1.07 mg/l).

10.3.2 Comparison with the CLP criteria

The results of an acute toxicity study in rats report an LC_{50} value of > 57 mg/m^3 (≡ 0.057 mg/l) (vapour). This is supported by an LC_{50} of > 1070 mg/m^3 (≡ > 1.07 mg/l) (dusts/mists) derived from a sub-acute inhalation toxicity study, also carried out in rats. As 2-phenoxyethanol has not been tested above 1 mg/l and there were no deaths below this concentration, no classification is proposed for acute toxicity by the inhalation route.

10.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Not classified.

Data conclusive but not sufficient for classification.

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}s 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**.

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**.

10.4 Skin corrosion/irritation

This end point will not be considered in this dossier.

10.5 Serious eye damage/eye irritation

A number of eye irritation studies were available in the REACH Registration, but only two of these were provided with sufficient study details to be useful for classification purposes. Of these two studies, detailed below, only one was reported in the dCAR (Anon. 1983).

Table 10: Summary table of animal studies on serious eye damage/eye irritation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results - Observations and time point of onset - Mean scores/animal - Reversibility	Reference
Eye irritation study	Rabbits, Russian	2-Phenoxyethanol	0.1 ml undiluted	Average scores (24, 48 and 72 h): Cornea: 1, 1, 1, 1, 1, 1	Unamed study report 1983 (taken

OECD 405 Non-GLP (study pre-dated requirements)	White n=6 (3/sex)	(Marlophen P1) Purity > 99 %	1, 24, 48, 72 hours and 8, 15 and 21 days after application	Iris: 0.3, 0, 1, 1.7, 1.3, 0.7 Conjunctival redness: 1, 1.3, 0.67, 0.67, 0.3, 1.3 Conjunctival chemosis: 0.3, 0.3, 0.3, 0, 0.3, 0 Reversible in 5/6 animals Corneal opacity in 1/6 animals on day 21	from REACH registration)
Eye irritation study OECD 405 Non-GLP (study pre-dated requirements)	Rabbits, Vienna White n=3 (1 male, 2 females)	2-Phenoxyethanol (technical grade) Purity unknown	0.1 ml undiluted 1, 24, 48, 72 hours and 15 days after application	Average scores (24, 48 and 72 h): Cornea: 1, 1.3, 1.3 Iris: 1, 1, 1 Conjunctival redness: 2, 1.7, 1.3 Conjunctival chemosis: 1.3, 0.3, 0.3 Reversible in 2/3 animals Slight corneal opacity in 1/3 animals on day 15	dCAR: Doc IIA; Section 3.3.2 (Anon. 1983)

10.5.1 Short summary and overall relevance of the provided information on serious eye damage/eye irritation

A 1983 study is available in the REACH registration dossier for 2-phenoxyethanol. This study was carried out according to OECD guidelines, 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. Irritation 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 to the end of the 21 day study period.

To conclude, 2-phenoxyethanol caused irreversible irritation to the eyes of rabbits.

An eye irritation study was carried out using Vienna White rabbits, following OECD guidelines, but predating requirments to perform according to GLP (Anon. 1983). 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, occuring in at least one animal, at least one timepoint was pupil narrowness, scarred retraction of the eyelid, marginal corneal vascularisation and suppuration. 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 irritation to the eyes of rabbits that was found not to be completely reversible within a 15 day observation period.

The REACH registration contains a further 9 studies, none of which were performed to test guidelines and all limited in their reporting (diluted material used, no scoring at all or very limited data and reporting). 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. Of these eight studies only three provided information on reversibility of effects, in each of these studies, all eye irritation was resolved within 14 days or less.

Therefore, whilst these studies are not suitable for classification purposes, they offer further support that 2-phenoxyethanol causes eye irritation in animal studies.

10.5.2 Comparison with the CLP criteria

According to the CLP criteria, a substance shall be classified for reversible effects to the eyes (category 2) if, when applied to the eye of an animals, a substance produces:

At least in 2 of 3 tested animals, a positive response of:

Corneal opacity ≥ 1 and/or

Iritis ≥ 1, and/or

Conjunctival redness ≥ 2 and/or

Conjunctival chemosis ≥ 2

Calculated as the mean scores following grading at 24, 48 and 72 hours after instillation of the test material which fully reverses within an observation period of 21 days.

The results of two guideline eye irritation studies in rabbits both showed a score (average 24, 48, 72 h) of ≥ 1 for corneal opacity (in 6/6 rabbits and 3/3 rabbits respectively). Both studies clearly meet the criteria. At a minimum, 2-phenoxyethanol should be classified in category 2 for eye irritation. However, in one study (Anon. 1983), 1 of the 3 tested animals continued to have corneal opacity to the end of the study 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.

Where any doubt remains due to the shorter observation period of this study, the study taken from the REACH registration allays this as 1 of the 6 tested animals also had corneal opacity that had not fully resolved by the end of the 21 day study period. Therefore, in accordance with the classification criteria for category 1, it is proposed to classify for irreversible effects to the eye, category 1, 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.

10.5.3 Conclusion on classification and labelling for serious eye damage/eye irritation

Eye Dam. 1; H318: Causes serious eye damage.

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)**.

10.6 Respiratory sensitisation

This endpoint is not considered in this dossier.

10.7 Skin sensitisation

This end point is not considered in this dossier.

10.8 Germ cell mutagenicity

This end point is not considered in this dossier.

10.9 Reproductive toxicity

This endpoint is not considered in this dossier.

10.10 Specific target organ toxicity-single exposure

The most relevant study for consideration of STOT-SE is a 14-day repeated dose study, carried out by the inhalation route in rats.

Table 11: Summary table of animal studies on STOT SE

↑↓ denote an increase or decrease in a parameter with respect to the control value
abs. = absolute
rel. = relative

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
14-day inhalation study in rats Wistar (5/sex/group) OECD 412 GLP Rats were exposed to a mixture of vapour and aerosol. The Applicant confirms that at the LOAEL, there was very little vapour. Therefore, the guidance values used to assist in classification are those for aerosols (dusts and mists): Cat 1, C≤1.0 mg/L and Cat 2, 5.0 ≥ C > 1.0 mg/L	2-Phenoxyethanol (> 99.9 % pure) 0, 48.2, 246 or 1070 mg/m^3 (Equivalent to 0, 0.0482, 0.246 and 1.07 mg/l) Nose only exposure MMAD: 1 – 1.2 µm 6 h/day, 5 days/week for 14 days (10 exposures)	**<u>1070 mg/m^3 (1.07 mg/l):</u>** ***Organ weights:*** ↑ Lung weight in males (abs. 20.4 % and rel. 19.3 %)* ***Histopathology:*** Degeneration/squamous metaplasia of respiratory epithelium in the nasal cavity (5/5 males and 5/5 females) Hyperplasia of the respiratory epithelium in the nasal cavity (5/5 males and 5/5 females) Inflammatory cell infiltrates in the submucosa of the nasal cavity (5/5 males, 3/5 females) Metaplastic squamous epithelium of base of epiglottis (4/5 males, 4/5 females) Minimal to mild hypertrophy of respiratory epithelium (5/5 males, 4/5 females) Minimal to mild hyperplasia of mucous cells (5/5 males, 4/5 females) **<u>246 mg/m^3(0.246 mg/l):</u>** ***Organ weights:*** ↑ Lung weight (abs.) in males (11.8 %)* ***Histopathology:*** Degeneration/squamous metaplasia of respiratory epithelium in the nasal cavity (1/5 males and 3/5 females) Hyperplasia of the respiratory epithelium in the nasal cavity (5/5 males and 5/5 females) Inflammatory cell infiltrates in the submucosa of the nasal cavity (5/5 males, 4/5 females) Metaplastic squamous epithelium of base of epiglottis (1/5 females only) Minimal to mild hypertrophy of respiratory epithelium (5/5 males, 4/5 females) Minimal to mild hyperplasia of mucous cells (3/5 males and females)	dCAR: Doc IIA; Section 3.5 (Anon. 2007c)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
		48.2 mg/m^3 (0.048 mg/l): No treatment-related effects. NOAEC: 48.2 mg/m^3 (0.048 mg/l)	

10.10.1 Short summary and overall relevance of the provided information on specific target organ toxicity – single exposure

The acute oral and inhalation studies are summarised in section 10.1 (refer to tables 7 and 8).

Four acute oral studies in rats are presented. Clinical signs observed included dyspnoea, apathy, agitation, tremor, ataxia and lethargy. In animals that died, necropsy revealed congestion and/or slightly inflated lungs and in some cases reddened glandular stomachs. These signs were considered signs of general toxicity, generally occurring at doses leading to impending death and are not considered further under STOT-SE.

An acute inhalation study is also available. Little information was provided but no deaths or clinical signs were reported at the single tested vapour concentration of 0.057 mg/l. However, the results of a 14-day repeated dose study in rats provide information pertinent to this endpoint.

An inhalation study in Wistar rats was carried out according to OECD test guidelines and GLP. Animals (5/sex/dose) were exposed to 2-phenoxyethanol (nose-only exposure) at a vapour concentration of 0, 48.2, 246 or 1070 mg/m^3 for 6h/day, 5 days/week for 14 days (equivalent to 0, 0.0482, 0.246 and 1.07 mg/l). Due to the low vapour pressure of 2-phenoxyethanol a mixture of vapour and aerosol was tested. The Applicants state that at the LOAEL [246 mg/m^3 (taken from the dCAR)], there was very little vapour and exposure was mostly due to the aerosol form of the test substance.

No clinical signs of toxicity were observed and there were no treatment-related changes to haematological or clinical chemistry parameters. Following histopathological examination, the respiratory tract, with substance-related lesions to the nasal cavity and larynx, and the lungs were the target organs. Only animals in the top two dose groups were affected. In males, lung weight was increased (abs. 20.4 % and rel. 19.3 % at 1.07 mg/l and rel. 11.8 % at 0.246 mg/l). All other organ weights measured showed no statistical or biologically relevant changes compared to the control group. Minimal to mild degeneration of the respiratory epithelium was observed in the anterior part of the nasal septum and the lateral nasal wall of the nasal cavity; this was characterised by a decreased thickness of the epithelium with areas of squamous metaplasia. Minimal to mild inflammatory cell infiltrates (mainly comprising neutrophils, lymphocytes and plasma cells) occurred in the sub-mucosa of the septum. A hyperplasia/hypertrophy of the respiratory epithelium (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, was also diagnosed. In some animals, the epithelium showed cyst-like structures or an irregular organisation. Other findings included 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. In males and females of the top 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 the top dose and minimal in all animals affected in the mid dose).

These morphological changes occurring at the mid and top doses were considered indicative of respiratory irritation. No adverse effects were seen at the lowest exposure level.

10.10.2 Comparison with the CLP criteria

Specific target organ toxicity (single exposure) is defined as specific, non lethal target organ toxicity arising from a single exposure to a substance or mixture. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed and not specifically covered by the acute toxicity classifications should be included.

Classification in categories 1 and 2 is for substances causing non lethal "significant and/or severe toxic effects", with the dose level at which the effect occurs covering the basis for the categorisation. In the acute and repeated dose studies available there was no evidence of specific target organ toxicity relevant for classification in categories 1 or 2. Classification with STOT-SE 3 is reserved for substances/mixtures causing "transient effects" following a single exposure, specifically respiratory tract irritation (RTI) and narcotic effects.

A single inhalation study, designed with particular emphasis placed on potential effects to the respiratory tract was carried out for 14-days in rats. Signs of degeneration and metaplasia were noted in the nasal cavity and squamous metaplasia was observed in the larynx of mid and top dosed animals. The effects observed were generally described as minimal to mild, occurring from a dose of 246 mg/m^3 (0.246 mg/l). As the dose was increased to 1070 mg/m^3, more animals were affected but the severity remained the same.

The European Society of Toxicologic Pathology held an expert workshop on the toxicologic significance of squamous metaplasia of the larynx in rodents and its relevance to humans (Kaufmann et al., 2009), during which it was concluded that focal epithelial changes of the larynx epithelium occurring predominantly at the base of the epiglottis should be described as epithelial alterations rather than laryngeal squamous metaplasia. It is recognised that, in rodents, the epithelium lining at the base of the epiglottis is the area most susceptible to changes induced by respiratory irritants (Renne et al., 1993), and that most squamous metaplasia of the larynx is a reversible response to chronic irritation.

There were no such findings reported in the acute inhalation study (Section 10.3), however the dose used was similar to the lowest dose used in the 14-day study, at which no treatment-related effects were observed.

According to the guidance, there are currently no validated animal tests that deal specifically with RTI, however useful information may be obtained from single and repeated inhalation toxicity tests. Clinical observations such as hyperemia, edema, minimal inflammation, thickened mucous layer which are reversible and may be reflective of the characteristic clinical symptoms of RTI. This special classification would occur only when more severe organ effects including in the respiratory system are not observed.

The findings observed in the 14-day inhalation study are indicative of reversible signs of respiratory irritatation. Although there are no data following a single dose, the study period was short, only 14 days, and the exposure levels used were 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. Supporting this perspective is the ability of this substance to cause irritation to the eyes. Classification for STOT-SE 3, respiratory tract irritation, is warranted.

10.10.3 Conclusion on classification and labelling for STOT SE

STOT-SE Category 3; H335: May cause respiratory irritation.

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"**.

10.11 Specific target organ toxicity-repeated exposure

There are a number of repeated dose studies carried out by the oral, dermal and inhalation routes available in both the dCAR (UK) and the publically-available REACH registration dossier. Many of these studies were of limited quality and not suitable for classification purposes. Those containing robust study information are included below. Studies carried out by the oral route include three 90-day studies (dietary, gavage and drinking water administration) and a 2-year carcinogenicity study (dietary), all in rats and a 90-day study (drinking water administration) and 2-year carcinogenicity study in mice (dietary). Also available are a 90-day dermal study in rabbits and a 14-day inhalation study in rats (the latter is included in Section 10.10).

Table 11: Summary of animal studies on STOT RE

↑↓ denote an increase or decrease in a parameter with respect to the control value
abs. = absolute
rel. = relative
* P<0.05 ** P<0.01
NOAELs are specified as in the dCAR

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results**
ORAL STUDIES		
90-day oral study in rats Dietary Wistar (10/sex/group – main study, 5/sex/group satellite groups) OECD 408 GLP dCAR: Doc IIA; Section 3.5 (Anon. 2002) Guidance values to assist in classification: STOT-RE1: C ≤ 10, STOT-RE2: 10 < C ≤ 100 mg/kg bw/day	2-Phenoxyethanol (99.9 % pure) 0, 500, 2500, 10,000 ppm (equivalent to 0, 34, 169 and 697 mg/kg bw/day in males and 0, 50, 234 and 939 mg/kg bw/day in females) Satellite groups were treated with 0 or 10000 ppm for 13 weeks, followed by a 4 week recovery period.	**≤ 10,000 ppm (≤ 697/939 mg/kg bw/day):** No treatment-related effects at any dose. NOAEL: 10,000 ppm (697 mg/kg bw/day in males and 939 mg/kg bw/day in females)

90-day oral study in rats Gavage CD (15/sex/group) Non-guideline Non-GLP dCAR: Doc IIA; Section 3.5 (Anon. 1977) Guidance values to assist in classification: STOT-RE1: C ≤ 10, STOT-RE2: 10 < C ≤ 100 mg/kg bw/day	2-Phenoxyethanol (> 99 % pure) 0, 80, 400, 2000 mg/kg bw/day emulsified in tragacanth mucilage (0.5 %) (5 ml/kg)	**<u>2000 mg/kg bw/day:</u>** ***Observations:*** ↑ Mortality – 4/15 females ↓ Body weight gain – 17 %* lower than controls in males ***Organ weights:*** ↑ Liver – 48 %* greater than controls (abs. in females, rel. in males and females) ↑ Kidney – 25 %* greater than controls (abs. in females, rel. in males and females) ↑ Thyroid – 57 %* greater than controls (abs. in females, rel. in males and females) ***Haematology:*** ↓ Erythrocyte count – 19 %* in females (week 12) ↓ Packed cell volume – 10 %* in females ↓ Haemoglobin – 12 %* in females ***Clinical Chemistry:*** ↑ Alkaline phosphatase in males – percentage not given in the study report. ***Histopathology:*** **Kidneys:** Prominent groups of distended tubules with associated basophilic staining tubules and chronic inflammatory cell infiltration in 15/15 males and 11/15 females **<u>400 mg/kg bw/day:</u>** ***Histopathology:*** **Kidneys:** Prominent groups of distended tubules with associated basophilic staining tubules and chronic inflammatory cell infiltration in 3/15 males only **<u>80 mg/kg bw/day:</u>** No treatment-related effects. NOAEL: 80 mg/kg bw/day

90-day oral study in rats Drinking water Fischer344/DuCrj (10/sex/dose) OECD 408 GLP dCAR: Doc IIA; Section 3.5 (Anon. 2003a) Guidance values to assist in classification: STOT-RE1: C ≤ 10, STOT-RE2: 10 < C ≤ 100 mg/kg bw/day	2-Phenoxyethanol (99.9 % pure) 0, 1250, 2500, 5000, 10,000 and 20,000 mg/L (nominal in water) Equivalent to: 0, 96, 185, 369, 687 and 1514 mg/kg bw/day in males and 0, 163, 313, 652, 1000 and 1702 mg/kg bw/day in females	**<u>20,000 mg/l (1514/1702 mg/kg bw/day):</u>** ***Observations:*** Mortality: 1/10 males ↓ Bodyweight: 19 % lower than controls in males and females ↓ Food consumption: 20 % lower than controls in males and females ↓ Water consumption: 30-40 % lower than controls in females only ***Organ weights:*** ↑Kidney weight – rel. in males and females ↑ Liver weight – rel. in males and females ↑ Brain weight – rel. in males and females ***Haematology:*** ↓ Red blood cell count in males and females ↓ Platelet count in males and females ↓ Haemoglobin in males and females ↓ MCV in males and females ↓ MCH in males and females ***Histopathology:*** Slight to moderate urothelial hyperplasia of the renal pelvis in 6/10 males Slight to moderate urinary bladder transitional epithelial hyperplasia in 7/10 females and 1/10 males **<u>10,000 mg/l (687/1000 mg/kg bw/day):</u>** ***Observations:*** ↓ Food consumption: 10 % lower than controls in males and females ***Organ weights:*** ↑ Liver weight – rel. in males and females ↑ Brain weight – rel. in females only ↑Kidney weight – rel. in females only ***Haematology:*** ↓ Red blood cell count in males and females ↓ Platelet count in males and females ↓ Haemoglobin in females only ↓ MCV in males only ↓ MCH in males only ***Histopathology:*** Slight urothelial hyperplasia of the renal pelvis in 2/10 males Slight to moderate urinary bladder transitional epithelial hyperplasia in 2/10 females **<u>≤ 5000 mg/l (369/652 mg/kg bw/day):</u>** No treatment-related effects NOAEL: 5000 mg/l (369 mg/kg bw/day in males and 652 mg/kg bw/day in females).

Two-year carcinogenicity study in rats OECD 451 GLP Rat, Fischer F344, 50/sex/dose dCAR: Doc IIA; Section 3.7 (Anon. 2007d) Guidance values to assist in classification: STOT-RE1: C ≤ 1.25, STOT-RE2: 1.25 < C ≤ 12.5 mg/kg bw/day	0, 2500, 5000 and 10000 mg/l Purity 98.8 – 99.9 % (w/w) Administered orally in drinking water. Actual ingested dose: 124, 249 and 510 mg/kg bw/day in males and 191, 380 and 795 mg/kg bw/day in females Duration: 104 weeks	**<u>10000 mg/l (510/795 mg/kg bw/day):</u>** ***Observations:*** ↓ Body weight in females (11 %) ***Organ weights:*** ↑ Kidney weight – rel. in males and females ↑ Brain weight – rel. in males and females ***Histopathology:*** Slight to moderate renal pelvis urothelial hyperplasia in males Slight to moderate renal papillary mineralization and necrosis in males **<u>≤ 5000 mg/l (249/380 mg/kg bw/day):</u>** No treatment-related effects. NOAEL: 5000 mg/l (249 mg/kg bw/day in males and 380 mg/kg bw/day in females).

90-day oral study in the mouse Drinking water DBF1 mice (10/sex/dose) OECD 408 GLP dCAR: Doc IIA; Section 3.5 (Anon. 2003b) Guidance values to assist in classification: STOT-RE1: C ≤ 10, STOT-RE2: 10 < C ≤ 100 mg/kg bw/day	2-Phenoxyethanol (99.9 % pure) 0, 1250, 2500, 5000, 10,000 and 20,000 mg/l (nominal in water) (Equivalent to: 0, 182, 390, 765, 1178 and 2135 mg/kg bw/day in males and 0, 236, 478, 948, 1514 and 2483 mg/kg bw/day in females).	**<u>20,000 mg/l (2135/2483 mg/kg bw/day):</u>** ***Observations:*** ↓ Body weight in males (13 % lower than controls) ↓ Food consumption in males and females (10 % lower than controls) ↓ Water consumption in males and females (40 % lower than controls) ***Organ weights:*** ↑ Kidney – rel. in males and females and abs. in females only ↑ Liver – rel. in males ↑ Brain – rel. in males ↑ Heart – rel. in males ***Haematology:*** ↓ Haemoglobin in females only ↓ MCH in females only ↑ MCV in females only ↑ Reticulocytes in males only ***Clinical Chemistry:*** ↓ Phospholipids in males ↑ ALP in males **<u>10,000 mg/l (1178/1514 mg/kg bw/day):</u>** ***Observations:*** ↓ Water consumption in males and females (27 % lower than controls) ***Organ weights:*** ↑ Kidney – rel. in males and females and abs. in females only ***Clinical Chemistry:*** ↓ Phospholipids in males **<u>5000 mg/l (765/948 mg/kg bw/day):</u>** ***Observations:*** ↓ Water consumption in males and females (11 % lower than controls) ***Clinical Chemistry:*** ↓ Phospholipids in males **<u>≤ 2500 mg/l (≤ 390/478 mg/kg bw/day):</u>** No treatment-related findings. NOAEL: 5000 mg/l (765 mg/kg bw/day in males and 948 mg/kg bw/day in females).

Two-year carcinogenicity study in mice OECD 451 GLP B6D2F1 mice 50/sex/dose dCAR: Doc IIA; Section 3.7 (Anon. 2007e) Guidance values to assist in classification: STOT-RE1: C ≤ 1.25, STOT-RE2: 1.25 < C ≤ 12.5 mg/kg bw/day	0, 5000, 10000 and 20000 mg/l Purity 98.8 – 99.9 % (w/w) Administered orally in drinking water. Actual ingested dose: 468, 898 and 1701 mg/kg bw/day in males and 586, 1072 and 2058 mg/kg bw/day in females Duration: 104 weeks	**<u>20000 mg/l (1701/2058 mg/kg bw/day):</u>** ***Observations:*** ↓ Body weight in males (27 %) and in females (21 %) **<u>10000 mg/l (898/1072 mg/kg bw/day):</u>** ***Observations:*** ↓ Body weight in males (16 %) **<u>5000 mg/l (468/586 mg/kg bw/day):</u>** No treatment-related findings NOAEL: 5000 mg/l (468 mg/kg bw/day in males and 586 mg/kg bw/day in females).
DERMAL STUDIES		
90-day dermal study in rabbits New Zealand White (10/sex/dose) Similar to OECD 411 GLP dCAR: Doc IIA; Section 3.5 (Anon. 1986) Guidance values to assist in classification: STOT-RE1: C ≤ 20, STOT-RE2: 20 < C ≤ 200	2-Phenoxyethanol (99.9 % pure) 0, 50, 100, 150 or 500 mg/kg Occlusive 6 h/day, 5 days/week	**<u>≤ 500 mg/kg bw/day:</u>** There were no toxicologically significant findings at any dose. NOAEL: > 500 mg/kg

10.11.1 Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure

2-Phenoxyethanol has been tested for its effects following repeated exposure in a number of studies using rats, mice and rabbits by the oral and dermal routes. A 14-day study in rats following inhalation exposure is available but this has been discussed in Section 10.10 (Specific target organ toxicity following a single exposure).

Oral studies

Rats

In a 2002 guideline study carried out to GLP, Wistar rats (10/sex in the main group and 5/sex in the satellite group) were administered 0, 500, 2500 or 10,000 ppm of 2-phenoxyethanol/day (equivalent to 0, 34/50, 169/234 and 697/939 mg/kg bw/day males/females) for 13 weeks (main group) or 0 or 10,000 ppm for 13-weeks, followed by a 4-week recovery period (satellite group). There were no treatment-related findings at any dose in this study.

In a non-guideline, non-GLP study carried out in 1977, CD rats (15/sex/dose) were administered 0, 80, 400 or 2000 mg/kg bw 2-phenoxyethanol by gavage. There were no treatment-related findings at doses relevant for classification (STOT-RE 2: $10 < C \leq 100$ mg/kg bw/day).

Findings above doses relevent for classification ($\geq$ 400 mg/kg bw/day) were as follows. At the top dose of 2000 mg/kg bw/day there was an increase in mortality with 4/15 females dying (time of deaths not stated). Kidney weights were increased in the top dose group only (25 % increase in relative weight in males and females compared to controls) with some corresponding histopathological changes noted from a dose of 400 mg/kg bw/day. These changes included prominent groups of distended tubules and assoicated basophilic staining tubules and chronic inflammatory cell infilitration. Liver and thyroid weights were also increased at 2000 mg/kg bw/day in males and females but there was no associated histopathology.

In a guideline, GLP-compliant study conducted in 2003, Fischer rats (10/sex/dose) were administed 2-phenoxyethanol via their drinking water for 90-days. The doses given were 0, 1250, 2500, 5000, 10,000 or 20,000 mg/l (equivalent to 0, 96/163, 185/313, 369/652, 687/1000 and 1514/1702 mg/kg bw/day in males/females). There were no treatment-related findings at the one dose used that was relevant for classification (STOT-RE 2: $10 < C \leq 100$ mg/kg bw/day).

The main findings at doses $\geq$ 10,000 mg/l (687/1000 mg/kg bw/day) were limited to the kidney in males and the female urinary bladder. These were slight to moderate urothelial hyperplasia of the renal pelvis in males and slight to moderate urinary bladder transitional epithelial hyperplasia (mainly in females).

In a recently performed guideline carcinogenicity study, conducted according to GLP, 2-phenoxyethanol was administered in the drinking water of Fischer rats (50/sex/doses) at doses far higher than the guidance values for classification (STOT-RE 2: $1.25 < C \leq 12.5$ mg/kg bw/day). The doses administered were 0, 2500, 5000 and 10000 mg/l (equivalent to 0, 124/191, 249/380 and 510/795 mg/kg bw/day in males/females). Effects observed occurred at the top dose only and included a relative increase in brain and kidney weights and slight to moderate renal pelvis urothelial hyperplasia and slight to moderate renal papillary mineralization and necrosis in males only.

Overall, there were no toxicologically relevant findings in rats following oral dosing at doses relevant for classification.

Mice

In a 2003 guideline study in DBF1 mice, conducted according to GLP, animals received 2-phenoxyethanol in their drinking water for 90-days. Doses administered were 0, 1250, 2500, 5000, 10,000 or 20,000 mg/l (equivalent to 0, 182/236, 390/478, 765/948, 1178/1514 and 2135/2483 mg/kg bw/day in males/females). All doses used in this study were above the guideline values for classification (STOT-RE 2: $10 < C \leq 100$ mg/kg bw/day).

Treatment-related findings occurred from a dose of 5000 mg/l (765/948 mg/kg bw/day). These included an increase in kidney weight in males and females and an increase in liver, brain and heart weight in males only. There were no histopathological correlates to these findings.

In a recently performed, guideline study in B6D2F1 mice (50/sex/dose), animals were administered 2-phenoxethanol in their drinking water at doses of 0, 5000, 10,000 and 20,000 mg/l (equivalent to 0, 468/586, 898/1072 and 1701/2058 mg/kg bw/day in males/females) for 104 weeks. All doses used exceeded the guideline vales for classification (STOT-RE 2: $1.25 < C \leq 12.5$ mg/kg bw/day). Findings were limited to reductions in body weight from a dose of 10,000 mg/l (898/1072 mg/kg bw in males/females).

All studies in mice employed doses that exceeded the classification guidance values for specific target organ toxicity by the oral route. There was no evidence of any effects that might indicate a specific organ effect following dosing with 2-phenoxyethanol.

Dermal study

A 90-day dermal study in New Zealand White rabbits was carried out to a method similar to OECD guidelines and to GLP. Animals (10/sex/dose) received 2-phenoxethanol to the skin under occlusive conditions at a dose of 0, 50, 100, 150 or 500 mg/kg.for 6 h/day, 5 days/week. The results of this study revealed no toxicological relevant findings at any dose tested.

10.11.2 Comparison with the CLP criteria

2-Phenoxethanol has been tested following repeated dosing via oral and dermal routes (Section 10.11) and also in a 14 day inhalation study in rats (see Section 10.10).

In studies carried out by the oral route in rats and mice, there was no evidence of any toxicologically significant effects caused by 2-phenoxyethanol at doses relevant for classification. In a repeated dose study in rabbits via the dermal route, there were no toxicologically significant effects at any dose tested. In a 14-day inhalation study carried out in rats, effects to the respiratory tract were noted. These effects are considered to be indicative of short-term adaptive changes due to the irritant potential of 2-phenoxyethanol. Therefore, they have been considered under STOT-SE and are not deemed to be a repeated dosing effect. 2-Phenoxyethanol does not cause any specific target organ toxicity following repeated dosing and does not meet the criteria for classification for this endpoint.

10.11.3 Conclusion on classification and labelling for STOT RE

No classification

Data conclusive and but not sufficient for classification.

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**.

10.12 Aspiration hazard

Not assessed in this dossier.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not assessed in this dossier.

12 REFERENCES

Author	Date	Study title
Murray S	2007	Phenoxyethanol Appearance and Odour. BASF Biocides,

Author	Date	Study title
		Expert Judgement Non GLP, Unpublished
Russel MW	2002	Determination of the melting point of Phenoxyethanol. The Dow Chemical Company GLP, Unpublished
Erstling K	2001a	Determination of the Melting Point, Boiling Point, Thermal Stability, Relative Density of Phenoxyethanol. Bayer AG, Leverkusen, Germany GLP, Unpublished
Griffin KA	2002	Determination of the vapour pressure, boiling point, water solubility and octanol/water partition coefficient of Phenoxyethanol low phenol grade. The Dow Chemical Company GLP, Unpublished
Olf G	2002	New Edition. Determination of the vapour pressure for Phenoxyethanol. Bayer AG, Leverkusen, Germany GLP, Unpublished
Brekelmans MJC	2007	Determination of physico-chemical properties of Phenoxyethanol. 's-Hertogenbosch, The Netherlands GLP, Unpublished
Erstling K	2001b	Determination of the Water Solubility (Flask method) of Phenoxyethanol, and Amendment (2002). Bayer AG, Leverkusen, Germany, GLP, Unpublished
Erstling K	2002	Determination of the Partition Coefficient (n-octanol/water) Shake Flask Method Phenoxyethanol, and Amendment (2002). Bayer AG, Leverkusen, Germany, LEV, BB05047 GLP, Unpublished
Löffler U	1999	Test: Vapour pressure, Flashpoint, Explosion points, Autoignition temperature. BASF AG, Ludwigshafen/Rhein, Germany, Non GLP, Unpublished
Löffler U	2000	Expert judgement - Absence of explosive and oxidizing properties of 2-phenoxyethanol. BASF AG, Ludwigshafen/Rhein, Germany, Non GLP, Unpublished
REACH Registration dossier	1983	Acute oral tox study, REACH
REACH Registration dossier	1983	Eye irritation study, REACH
Kaufmann W, Bader R, Ernst H, Harada T, Hardisty J, Kittel B,	2009	1st international ESTP expert workshop: "Larynx squamous metaplasia." A re consideration of morphology and diagnostic approaches in rodent studies and its relevance for human risk assessment. Exp Toxicol Pathol. 2009;61:591–603. Published.
Renne., RA., Gideon, KM., Miller, RA., Mellick, PW., Grumbein, SL	1992	Histologic Methods and Interspecies Variations in the Laryngeal Histology of F344/N Rats and B6C3F1 Mice. Toxicol. Pathol. 1992; 20: 1: 44-51 Published.
Burger, GT., Renne, RA., Sagartz, JW., Ayres, PH., Coggins,	1989	Histologic changes in the respiratory tract induced by inhalation of xenobiotics: Physiologic adaptation or toxicity? Toxicology and Applied Pharmacology. 1989;

Author	Date	Study title
CRE., Mosberg, AT., Hayes, AW.		101; 3: 521-542 Published.

13 ANNEX – ANNEX I - CONFIDENTIAL REFERENCES FOR VERTERBRATE STUDIES (SEPARATE DOCUMENT)