Committee for Risk Assessment

RAC

Annex 1

Background document

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

Methyloxirane (Propylene Oxide)

EC number: 200-879-2
CAS number: 75-56-9

CLH-O-0000004152-85-03/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

06 June 2014

CLH report

Proposal for Harmonised Classification and Labelling

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

Substance Name: Methyloxirane (Propylene Oxide)

EC Number: **200-879-2**

CAS Number: **75-56-9**

Index Number: **603-055-00-4**

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Version number: **2** **Date:** **August 2013**

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Part A.

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Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 SUBSTANCE

Table 1: Substance identity

Substance name:	Methyloxirane (Propylene Oxide)
EC number:	200-879-2
CAS number:	75-56-9
Annex VI Index number:	603-055-00-4
Degree of purity:	> 99%
Impurities:	Impurities are not present at concentrations that affect the Classification and Labelling of this substance.

1.2 HARMONISED CLASSIFICATION AND LABELLING PROPOSAL

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation	**Directive 67/548/EEC (Dangerous Substances Directive; DSD)**
Current entry in Annex VI, CLP Regulation	Flam. Liq. 1 (H224) Carc. 1B (H350) Muta. 1B (H340) Acute Tox. 4* (H332) Acute Tox. 4* (H312) Acute Tox. 4* (H302) Eye Irrit. 2 (H319) STOT SE 3 (H335) Skin Irrit. 2 (H315)	F+; R12 Carc. Cat. 2; R45 Muta. Cat. 2; R46 Xn; R20/21/22 Xi; R36/37/38
Current proposal for consideration by RAC	Change classification for acute toxicity: replace Acute Tox 4* (H302) with Acute Tox 4 (H302), replace Acute Tox 4*	Change classification for skin irritation: delete Xi; R38.

	(H332) with Acute Tox 3 (H331), and replace Acute Tox 4* (H312) with Acute Tox 3 (H311). Change classification for skin irritation: delete Skin Irrit. 2 (H315).	
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Flam. Liq. 1 (H224) Carc. 1B (H350) Muta. 1B (H340) Acute Tox. 3 (H331) Acute Tox. 3 (H311) Acute Tox. 4 (H302) Eye Irrit. 2 (H319) STOT SE 3 (H335)	F+; R12 Carc. Cat. 2; R45 Muta. Cat. 2; R46 Xn; R20/R21/22 Xi; R36/37

1.3 PROPOSED HARMONISED CLASSIFICATION AND LABELLING BASED ON CLP REGULATION AND/OR DSD CRITERIA

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	No change		Not classified	Conclusive but not sufficient for classification
2.2.	Flammable gases	No change		Not classified	Conclusive but not sufficient for classification
2.3.	Flammable aerosols	No change		Not classified	Conclusive but not sufficient for classification
.4.	Oxidising gases	No change		Not classified	Conclusive but not sufficient for classification
2.5.	Gases under pressure	No change		Not classified	Conclusive but not sufficient for classification
2.6.	Flammable liquids	No change (Flam. Liq. 1 H224)		Flam. Liq. 1 H224	
2.7.	Flammable solids	No change		Not classified	Conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures	No change		Not classified	Conclusive but not sufficient for classification
2.9.	Pyrophoric liquids	No change		Not classified	Conclusive but not sufficient for classification
2.10.	Pyrophoric solids	No change		Not classified	Conclusive but not sufficient for classification
2.11.	Self-heating substances and mixtures	No change		Not classified	Conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases	No change		Not classified	Conclusive but not sufficient for classification
2.13.	Oxidising liquids	No change		Not classified	Conclusive but not sufficient for classification
2.14.	Oxidising solids	No change		Not classified	Conclusive but not sufficient for

					classification
2.15.	Organic peroxides	No change		Not classified	Conclusive but not sufficient for classification
2.16.	Substance and mixtures corrosive to metals	No change		Not classified	Conclusive but not sufficient for classification
3.1.	Acute toxicity - oral	Acute Tox. 4 H302 (* removed)		Acute Tox. 4* H302	
	Acute toxicity - dermal	Acute Tox. 3 H311		Acute Tox. 4* (H312)	
	Acute toxicity - inhalation	Acute Tox. 3 H331		Acute Tox. 4* (H332)	
3.2.	Skin corrosion / irritation	Not classified		Skin Irrit. 2 (H315)	conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation	No change (Eye Irrit. 2 H319)		Eye Irrit. 2 H319	
3.4.	Respiratory sensitisation	No change		Not classified	Conclusive but not sufficient for classification
3.4.	Skin sensitisation	No change		Not classified	Conclusive but not sufficient for classification
3.5.	Germ cell mutagenicity	No change (Muta. 1B H340)		Muta. 1B H340	
3.6.	Carcinogenicity	No change (Carc. 1B H350)		Carc. 1B H350	
3.7.	Reproductive toxicity	No change		Not classified	Conclusive but not sufficient for classification
3.8.	Specific target organ toxicity –single exposure	No change (STOT SE 3 H335)		STOT SE 3 H335	
3.9.	Specific target organ toxicity – repeated exposure	No change		Not classified	Conclusive but not sufficient for classification
3.10.	Aspiration hazard	No change		Not classified	Conclusive but not sufficient for classification
4.1.	Hazardous to the aquatic environment	No change		Not classified	Conclusive but not sufficient for classification

5.1.	Hazardous to the ozone layer	No change		Not classified	Conclusive but not sufficient for classification

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling:

Labelling based on the classification now proposed is shown below.

Signal word: Danger
Hazard pictograms: GHS02, GHS06, GHS08
Hazard statements: H224, H302, H311, H319, H331, H335, H340, H350

Proposed notes assigned to an entry:

None

Table 4: Proposed classification according to DSD

Hazardous property	Proposed classification	Proposed SCLs	Current classification [1)]	Reason for no classification [2)]
Explosiveness	No change		Not classified	Conclusive but not sufficient for classification
Oxidising properties				Conclusive but not sufficient for classification
Flammability	No change (F+; R12)		F+; R12	
Other physico-chemical properties *[Add rows when relevant]*	No change		Not classified	Conclusive but not sufficient for classification
Thermal stability	No change		Not classified	Conclusive but not sufficient for classification
Acute toxicity	No change (Xn; R20/21/22)		Xn; R20/21/22	
Acute toxicity – irreversible damage after single exposure	No change		Not classified	Conclusive but not sufficient for classification
Repeated dose toxicity	No change		Not classified	Conclusive but not sufficient for classification
Irritation / Corrosion	Xi; R36/37		Xi; R36/37/38	
Sensitisation	No change		Not classified	Conclusive but not sufficient for classification
Carcinogenicity	No change (Carc. Cat. 2; R45)		Carc. Cat. 2; R45	
Mutagenicity – Genetic toxicity	No change (Muta. Cat. 2; R46)		Muta. Cat. 2; R46	
Toxicity to reproduction – fertility	No change		Not classified	Conclusive but not sufficient for classification
Toxicity to reproduction – development	No change		Not classified	Conclusive but not sufficient for classification
Toxicity to reproduction – breastfed babies. Effects on or via lactation	No change		Not classified	Conclusive but not sufficient for classification
Environment	No change		Not classified	Conclusive but not sufficient for classification

[1)] Including SCLs
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling:

Labelling based on the classification now proposed is shown below (T used on label due to mutagenicity/carcinogenicity classifications, as in 1272/2008 Annex VI Table 3.2).

Indication of danger: F+, T
R-phrases: R: 45-46-12-20/21/22-36/37
S-phrases: S45-53

2 BACKGROUND TO THE CLH PROPOSAL

This dossier was prepared by the lead registrant of propylene oxide. The Netherlands agree with the proposed changes.

2.1 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

Propylene oxide was a priority substance in the Existing Chemicals program (EEC) 793/93 and the final European Union Risk Assessment Report for this substance was published in 2002 (2nd Priority List, Volume 23) EU RAR. (2002). Propylene oxide was classified and labelled according to the 28th ATP of Directive 67/548/EEC.

This currently harmonised classification of propylene oxide (methyloxirane) resulted from a number of regulatory reviews and discussions. Records of a March 1999 CMR WG meeting include the following relevant information:

First discussion of new proposals for substances already in Annex I:
Methyloxirane; propylene oxide (C064), (603-055-00-4).
Proposal: [F+; R12] : [Carc. Cat. 2; R45] : [Muta. Cat. 3; R40] : [Xn; R20/21/22] : [Xi; R36/37/38]. Rapporteur: UK.
ECBI/20/97 – Add.10 UK, Classification proposals for the 603 substances
ECBI/09/99 S, propylene oxide (C064), Segerbaeck et al., 1998 (study on DNA adducts/^{32}P-postlabelling
ECBI/09/99 – Add.1 UK, classification proposal for propylene oxide (C064), health effects

The substance is on the 2nd ESR Priority List with UK as rapporteur. The present Annex I classi-fication is F+; R12 : Carc. Cat.2; R45 : Xn; R20/21/22 : Xi; R36/37/38. Nota E. No specific concentration limits. Last revision with the 12.ATP. - In December 1997 it has been agreed not to classify for dangers to the environment.
UK had provided a summary on the health effects of the substance with a classification proposal, which found support by the Group, with the exception of the category 3 proposal for mutagenic effects.
The subsequent discussion focused on the observations of adducts to testicular DNA in the study by Segerbaeck et al., 1998. UK pointed out that the mutagenicity category 2 criteria are specific for germ cells. Adducts to germ cell DNA, however, had not been studied by Segerbaeck et al., and that the findings had, thus, been too unspecific to meet the criteria. DK drew the Group's attention to the classification of the structural analogue ethylene oxide with Muta. Cat. 2; R46, which they stated should be allocated to propylene oxide as well; this view was supported by S and FIN. FIN added that the lipophilic and hydrophilic chemical nature of propylene oxide should guarantee an even distribution in the organism, including the germ cells. UK, before giving a final view, wanted to examine the full range of

the structure activity relationship. Industry drew attention to well-documented differences between ethylene and propylene oxide, which they felt should be taken into consideration when drawing conclusions on the in vivo mutagenicity of propylene oxide. Both ethylene and propylene oxide had been tested twice in dominant lethal assays and while the former was positive, the latter had been negative in both studies.
The Group took note of the unresolved issue in the Risk Assessment under the ESR programme whether the substance was a skin sensitiser, based on four not well documented cases of sensitisation in laboratory technicians. These limited human data, together with a negative result in a non-standardised and non-guideline split adjuvant study in animals, did not seem sufficient to the Rapporteur to propose classification with R43. While the majority of the Group concurred with the UK interpretation, DK was strongly in favour of R43. S and FIN supported DK, also on account of propylene oxide's reactive nature being an epoxide, but stated they could accept no classification due to the limitations of the positive human evidence.

Conclusion:
The Group confirmed the current classification of propylene oxide with F; R12 : Carc. Cat. 2; R45 : Xn; R20/21/22 : Xi; R36/37/38. Nota E. Further discussion of the categorisation for mutagenicity was carried forward to the next meeting.
In an e-mail to the ECB, dated 16 April 1999, UK has suggested that propylene oxide (methyloxirane) is referred to the Specialised Experts for mutagenicity. UK offered to act as the lead country for preparation of the documentation on propylene oxide for discussion by the Specialised Experts at their Meeting, 1-2 September 1999.

Minutes of a subsequent Commission WG on C&L of Dangerous Substances (October 1999) show that this conclusion was confirmed:
Propylene oxide; methyloxirane (C064), (603-055-00-4).
Proposal: F+; R12 : Carc. Cat. 2; R45 : [Muta. Cat. 2; R46] : Xn; R20/21/22 : Xi; R36/37/38.
Rapporteur: UK.
ECBI/20/97 – Add.10 UK, Classification proposals for the 603 substances
ECBI/09/99 S, propylene oxide (C064), Segerbaeck et al., 1998 (study on DNA adducts/32P-postlabelling
ECBI/09/99 – Add.1 UK, classification proposal for propylene oxide (C064), health effects
ECBI/49/99 – Rev. 2 Second revision/Final version of Draft Conclusions of the Meeting of Specialised Experts, Arona, 1-2 September 1999

The substance is on the 2nd ESR Priority List with UK as rapporteur. The present Annex I classification is F+; R12 : Carc. Cat.2; R45 : Xn; R20/21/22 : Xi; R36/37/38. Nota E. No specific concentration limits. Last revision with the 12.ATP. - In December 1997 it has been agreed not to classify for dangers to the environment. – In March 99 the Group supported the UK proposal to classify with F+; R12 : Carc. Cat. 2; R45 : Xn; R20/21/22 : Xi; R36/37/38. Limited evidence from four human cases, together with a negative result in a non-guideline split adjuvant study in animals seemed insufficient to the Group to classify for skin sensitisation. On mutagenicity, the Group noted that the observation of adducts to testicular DNA in a recently published study by Segerbaeck et al., 1998, might justify classification with Muta. Cat. 2; R46. After the meeting, UK suggested that propylene oxide is referred to the Specialised Experts for mutagenicity. UK acted as the lead country for preparation of the documentation. – In September 99 the Specialised Experts felt that the new data matched the criteria for classification with Muta. Cat. 2; R46. However, the

predominating view was that the biological significance of the very low levels of adducts observed was questionable and there was doubt about the potential mutagenicity of propylene oxide to germ cells.
The Group adopted the view of the Specialised Experts that propylene oxide should be classified in Category 2 for mutagenicity.

Conclusion:
The Group agreed to classify propylene oxide with F; R12 : Carc. Cat. 2; R45 : Muta. Cat. 2; R46 : Xn; R20/21/22 : Xi; R36/37/38. Nota E. Symbol F+; T. R-phrases 45-46-12-20/21/22-36/37/38. S-phrases 53-45. Nota E. No specific concentration limits. The proposal would be sent to DG ENV for possible inclusion in a future TPC.

2.2 SHORT SUMMARY OF THE SCIENTIFIC JUSTIFICATION FOR THE CLH PROPOSAL

Acute Toxicity: study data collated for REACH registration purposes have provided the following information on propylene oxide. More complete details of each cited study are given in Part B, section 4.2 of this report and in the IUCLID file which accompanies the report.

Acute oral toxicity: in the key rat study, LD50 was determined to be between 382 and 587 mg/kg bw. A supporting experimental study found 0% mortality at 300 mg/kg and 100% mortality at 1000 mg/kg. Three other studies (secondary source information from the EU RAR) cited oral LD50 values for rats, mice and Guinea pigs ranging from >500 to 950 mg/kg.

Acute inhalation toxicity (vapour exposure): rat 4h LC50 in the key study was 9.95 mg/l. From mortality data of the (US NTP) experimental supporting study, 4h LC50 values of 7.1 - 9.0 mg/l (rats, both sexes), 3.0 - 7.1 mg/l (male mice) and 2.0 - 2.6 mg/l (female mice) can be deduced. In another supporting study, mortality data indicated that the 4h LC50 value for both rats and Guinea pigs was above, but close to, 9.5 mg/l. Values of 4h LC50 listed in two other studies (secondary source information from the EU RAR) ranged from 4.1 to 9.5 mg/l.

Acute dermal toxicity: a rabbit LD50 value of 950 mg/kg was determined in the key study. The supporting study (secondary source information from the EU RAR) lists another rabbit LD50 value of 1250 mg/kg, but as full experimental detail is not available for either study and the key study used 4h open application of test material (probably not maximising exposure) the lower value of 950 mg/kg is taken forward for assessment.

Based on these results, the correct classifications for propylene oxide under EU CLP (Regulation (EC) No. 1272/2008) are Acute toxicity Category 3 for inhalation and dermal exposure (H331 and H311), Acute toxicity Category 4 for oral administration (H302). Under DSD (Directive 67/548/EEC), the correct classification is Xn; R20/21/22.

A change to the current acute toxicity classification of propylene oxide is accordingly now proposed.

Irritation / Corrosion: study data collated for REACH registration purposes (including results of new tests *in vitro* and *in vivo*) have provided the following information on skin

irritation. More complete details of each cited study are given in Part B, section 4.4 of this report and in the IUCLID file which accompanies the report.
No adequately documented reports of human skin irritation associated with propylene oxide exposure are available.
New studies:
- an initial assessment of propylene oxide skin irritancy/corrosion potential was performed using the *in vitro* EPISKIN test. In this test the substance is applied topically to the *stratum corneum* surface, at the air interface, so that undiluted and/or end use dilutions can be tested directly. The test identifies corrosive chemicals based on observations of cytotoxicity following short term exposure using the EPISKIN model. Corrosive chemicals are able to penetrate the *stratum corneum* and are sufficiently cytotoxic to cause cell death in the underlying cell layers. Toxicity is determined by the metabolic conversion of the vital dye MTT to formazan by viable cells in the test material treated cultures relative to the negative controls. Validation studies have shown that tests employing human skin models are able to reliably distinguish between known skin corrosives and non-corrosives. No significant cytotoxicity was seen following propylene oxide treatment. The test material was considered to be Non-Corrosive to the skin.
- propylene oxide was also tested *in vivo* using rabbits (according to OECD 404 and GLP). Scoring for erythema and oedema showed only minor and transient reactions to treatment which were fully resolved within 48 - 72h, demonstrating the low skin irritancy of this substance.

A single published report (>50 years old and lacking details of methods and results) described severe local reactions in rabbits to occluded skin application of both undiluted and diluted (aqueous 20 and 10% solutions) propylene oxide. These included erythema and oedema after exposures longer than 6 minutes and scar formation after “severer” exposure. The authors of this report stated that (unspecified) evidence indicated that diluted solutions were more irritating that undiluted propylene oxide. However numbers of rabbits tested, timings of skin observations, individual reactions, the nature of the patch coverings and quantities of test substance applied are unreported. This makes definitive interpretation of the reported findings impossible. This investigation is described as “poorly reported” in the EU RAR for propylene oxide. In addition, the claim of skin damage due to short-term application of a 10% solution of propylene oxide is contradicted by observations of no significant irritation after repeated application of a 10% solution to Guinea pig skin during a skin sensitisation assay.

It is concluded that, notwithstanding earlier suggestions of possible skin damaging activity, the key studies provided reliable investigation of possible irritant activity and, on the basis of those results, propylene oxide should not be classified irritating to skin.

According to Directive 67/548/EEC, this substance is presently classified as Xi; R36/37/38 and according to EU CLP (Regulation EC No. 1272/2008), the classification is Category 2 for skin; H315 (Causes skin irritation). However, as described above the available test data indicate that skin irritation classification for propylene oxide is not warranted.
Therefore it is proposed that the skin irritation classification of propylene oxide be removed.

2.3 CURRENT HARMONISED CLASSIFICATION AND LABELLING

2.3.1 CURRENT CLASSIFICATION AND LABELLING IN ANNEX VI, TABLE 3.1 IN THE CLP REGULATION

Flam. Liq. 1	H224: Extremely flammable liquid and vapour.
Carc. 1B	H350: May cause cancer.
Muta. 1B	H340: May cause genetic defects.
Acute Tox. 4 *	H302: Harmful if swallowed.
Acute Tox. 4 *	H312: Harmful in contact with skin.
Acute Tox. 4 *	H332: Harmful if inhaled.
Eye Irrit. 2	H319: Causes serious eye irritation.
STOT SE 3	H335: May cause respiratory irritation.
Skin Irrit. 2	H315: Causes skin irritation

2.3.2 CURRENT CLASSIFICATION AND LABELLING IN ANNEX VI, TABLE 3.2 IN THE CLP REGULATION

Classification:
F+; R12
Carc. Cat. 2; R45
Muta. Cat. 2; R46
Xn; R20/R21/22
Xi; R36/37/38

Labelling:
F+; T
R: 45-46-12-20/21/22-36/37/38
S: 45-53

2.4 CURRENT SELF-CLASSIFICATION AND LABELLING

Currently the applicant, Lead Registrant for joint registration of propylene oxide, applies the classification and labelling specified in the CLP Regulation, Annex VI).

Consideration of the notified classification and labelling data for methyloxirane shown on the ECHA website (C&L Inventory entries submitted by notifiers) shows that with few exceptions the current, harmonised classification and labelling is used by manufacturers/suppliers of the substance. There are two separate entries relating to the joint (full) registration of the substance:

- one is the Annex VI CLP Regulation
- the second includes UN GHS; under UN GHS rules, Aquatic Acute 3, H402 applies in addition to those endpoints classified in accordance with the CLP Regulation, and both UN GHS and CLP classifications were included in the submitted Lead Registrant dossier.

Divergent minority opinions on classification of the substance (such as that of the single notifier claiming methyloxirane is not classified as a hazardous substance) appear to be frank errors.

2.4.1 CURRENT SELF-CLASSIFICATION AND LABELLING BASED ON THE CLP REGULATION CRITERIA

2.4.2 CURRENT SELF-CLASSIFICATION AND LABELLING BASED ON DSD CRITERIA

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Changes to classification for two categories of endpoint are now proposed:

- skin irritation. Data review for the purpose of REACH registration identified that existing skin irritation data were inconclusive. New and definitive testing was therefore conducted: this generated reliable evidence (both *in vitro* and *in vivo*) that showed that the criteria for classification as a skin irritant are not met by propylene oxide. To correct what is now clearly an incorrect classification for this endpoint and ensure that the rules set out in Regulation 1272/2008 are applied, it is necessary that a revised, harmonised classification should be disseminated.

- acute toxicity. Data review for the purpose of REACH registration identified reliable oral, inhalation, and dermal toxicity studies, the latter two of which demonstrate a higher level of acute hazard than that indicated by the corresponding minimum classifications listed in table 3.2 of Regulation 1272/2008 Annex VI. Although the current harmonised classifications for these endpoints (Acute 4*) permit those companies party to the joint registration in which the studies are described to assign higher (Acute Category 3) classifications now, it is appropriate to ensure that other companies supplying propylene oxide also recognise and alert their customers to the higher classifications in respect to inhalation and dermal exposure, and confirm clearly the status of the acute oral toxicity classification. This is best done by amendment of the harmonised classification.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

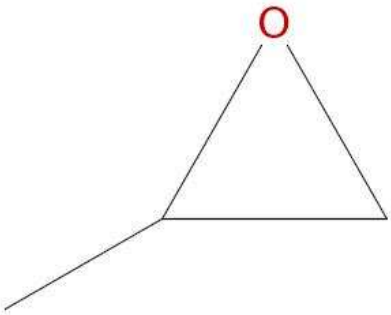
1 IDENTITY OF THE SUBSTANCE

1.1 NAME AND OTHER IDENTIFIERS OF THE SUBSTANCE

Table 5: Substance identity

EC number:	**200-879-2**
EC name:	**Methyloxirane**
CAS number (EC inventory):	**75-56-9**
CAS number:	**75-56-9**
CAS name:	**Oxirane, 2-methyl-**
IUPAC name:	**Methyloxirane**
CLP Annex VI Index number:	**603-055-00-4**
Molecular formula:	**C3H6O**
Molecular weight range:	**58.0791**

Structural formula:



1.2 COMPOSITION OF THE SUBSTANCE

Table 6: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Methyloxirane	> 99%		

Current Annex VI entry:

Table 7: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
			Impurities are not present at concentrations that affect the Classification and Labelling of this substance

Current Annex VI entry:

Table 8: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks

Current Annex VI entry:

1.2.1 COMPOSITION OF TEST MATERIAL

1.3 PHYSICO-CHEMICAL PROPERTIES

Table 9: Summary of physico - chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance at 20°C and 101,3 kPa	liquid Colour: Colourless Odour: sweetish, ether-like	Harlan Laboratories Ltd. (2010a)	
Melting/freezing point	-112˚C	Oetting FL. (1964)	
Boiling point	35˚C at 103.30-104.13 kPa	Harlan Laboratories Ltd. (2010a)	
Relative density	0.830 at 20˚C	Harlan Laboratories Ltd. (2010a)	
Vapour pressure	74000 Pa at 25˚C.	Harlan Laboratories Ltd. (2010b)	
Surface tension	71.5 mN/m at 21 ˚C in 1.06 g/L aqueous solution	Harlan Laboratories Ltd. (2010a)	
Water solubility	42.5-45.0% w/w (ca. 425-450 g/L) at 20˚C and pH = 8	Harlan Laboratories Ltd. (2010a)	
Partition coefficient n-octanol/water	<1	Shell Research Ltd. (1986)	A value of 0.055 as the mean of the two measured log values is estimated (from Hansch and Leo (1989), and Deneer et al. (1988))
Flash point	-38 ˚C at 100.75 kPa	Harlan Laboratories Ltd. (2010b)	
Flammability	The substance is extremely flammable		Based on the values for flash point and boiling point
Explosive properties	The substance is non explosive		Estimated: Although this substance contains an epoxide functionality which can indicate potential explosive properties, its oxygen balance is -220, indicating that the substance is non-explosive.
Self-ignition temperature	> 400 ˚C at 100.49-101.83 kPa		
Oxidising properties	The substance is non		Estimated: based on chemical structure (does not contain

	oxidising.		oxygen or halogen atoms chemically bonded to nitrogen or oxygen)
Granulometry			Not relevant as this substance (a liquid) is manufactured and marketed in a non-solid form
Stability in organic solvents and identity of relevant degradation products			Not a critical property for this substance
Dissociation constant			Not relevant as the substance does not contain chemical groups that can undergo dissociation.
Viscosity	0.374 mm2/s at 20 ˚C 0.447 mm2/s at 0 ˚C	Harlan Laboratories Ltd. (2010a)	

2 MANUFACTURE AND USES

Not relevant for this dossier.

2.1 MANUFACTURE

2.2 IDENTIFIED USES

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Not relevant for this dossier: no change to the existing harmonized classification in respect of physico-chemical properties is proposed.

Table 10: Summary table for relevant physico-chemical studies

Method	Results	Remarks	Reference

3.1

3.1.1 SUMMARY AND DISCUSSION OF

3.1.2 COMPARISON WITH CRITERIA

3.1.3 CONCLUSIONS ON CLASSIFICATION AND LABELLING

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Toxicokinetics are not relevant for this report and are not considered in this dossier.

4.1.1 NON-HUMAN INFORMATION

4.1.2 HUMAN INFORMATION

4.1.3 SUMMARY AND DISCUSSION ON TOXICOKINETICS

4.2 ACUTE TOXICITY

Table 11: Summary table of relevant acute toxicity studies

Method	Results	Remarks	Reference
Oral rat (Wistar) male/female 5/sex/dose gavage equivalent or similar to OECD Guideline 401 (Acute Oral Toxicity)	LD50: 382 — 587 mg/kg bw (male/female) Further details of reactions to treatment not given	2 (reliable with restrictions) key study experimental result Test material (EC name): methyloxirane (purity not specified)	Shell Research Ltd. (1968)
Oral rat (laboratory stock) male/female gavage groups of 5 rats dosed at 300 or 1000 mg/kg (Reference also cited in EU RAR (2002))	300 mg/kg bw: 0% mortality 1000 mg/kg bw: 100% mortality Post-treatment weight gains normal at 300 mg/kg	2 (reliable with restrictions) supporting study experimental result Test material (EC name): methyloxirane	Rowe et al. (1956)
Oral EU RAR (2002): methyloxirane European Commission Guinea pig Secondary source: review of experimental reports	Guinea pig LD50 690 mg/kg bw Detailed information on reactions to treatment not available.	2 (reliable with restrictions) supporting study review of reported studies Test material (EC name): methyloxirane	EU RAR (2002) (Primary source cited as Smyth et al 1941)
Oral	Rat LD50 950 mg/kg bw	2 (reliable with	EU RAR (2002)

EU RAR (2002): methyloxirane European Commission rat Secondary source: review of experimental reports	Detailed information on reactions to treatment not available.	restrictions) supporting study review of reported studies Test material (EC name): methyloxirane	(Primary source cited as Smyth et al. 1969)
Oral EU RAR (2002): methyloxirane European Commission rat, mouse review of experimental reports	Rat LD50 520 mg/kg bw Mouse LD50 630 mg/kg bw Guinea pig LD50 660 mg/kg bw Detailed information on reactions to treatment not available.	2 (reliable with restrictions) supporting study review of reported studies Test material (EC name): methyloxirane	EU RAR (2002) (Primary source cited as Antonova et al. 1981)
Inhalation: rat (Wistar) male/female 4/sex/dose vapour (whole body) 3000, 3450, 4050, 4280, 4500, 5260, 5970 ppm equivalent or similar to OECD Guideline 403 (Acute Inhalation Toxicity)	LC50 (4 h): 4197 ppm (male/female) (9.95 mg/L) Excessive lachrymation and eye irritation followed by sedation, with respiratory difficulty, piloerection and blood-stained mucous discharge from the nose and mouth was seen in all test animals. Times to onset were dose related. Respiratory difficulty continued for several hours in the rats surviving exposure: survivors. at the end of the 14 day observation period appeared normal.	2 (reliable with restrictions) key study experimental result Test material (EC name): methyloxirane (purity not specified)	Shell Research Ltd. (1977)
Inhalation: rat (F344/N) mouse (B6C3F1) 5/sex/dose vapour (whole body) Rats: 1277, 2970, 3794, 3900 ppm Mice: 387, 859, 1102, 1277, 2970 ppm equivalent or similar to OECD Guideline 403 (Acute Inhalation Toxicity) (Reference also cited in EU RAR (2002))	LC50 values inferred from mortality data Rat LC50 (4h): >2970- >3794 ppm (male/female) (>7.1- >9.0 mg/l) Mouse LC50 (4h): >1277- >2970 ppm (male) (>3.0- >7.1 mg/l) Mouse LC50 (4h): >859- >1102 ppm (female) (>2.0- >2.6 mg/l) Dyspnoea and red nasal discharge seen at 1102 ppm (mice) or 2907 ppm (rats) and higher concentrations	2 (reliable with restrictions) supporting study experimental result Test material (EC name): methyloxirane. Purity>99%	US National Toxicology Program NTP TR 267 (1985)
Inhalation: Rat Guinea pig	LC50 (4h): ca. 9.5 mg/l (between 9.5 and 19.0 mg/l) (rat and Guinea pig) Rat mortality at 9.5 mg/l 4/10 after	2 (reliable with restrictions) supporting study	Rowe et al. (1956)

vapour (whole body) standard acute test method (Reference also cited in EU RAR (2002))	4h, 10/10 after 7h exposure. Guinea pig mortality after 4h 1/5 at 9.5 mg/l, 10/10 at 19 mg/l	experimental result Test material (EC name): methyloxirane	
Inhalation: EU RAR (2002): methyloxirane European Commission rat, mouse vapour Secondary source: review of experimental reports	Rat LC50 (30 min)): ca. 17 mg/l (inferred from mortalities in RAR) Mouse LC50 (4h): 4.12 mg/l Rat mortality after 30 minutes exposure 50% at 17.1 mg/l, 100% at 34.1 mg/l	2 (reliable with restrictions) supporting study review of reported studies Test material (EC name): methyloxirane	EU RAR (2002) (Primary source cited as Jacobson et al. 1956)
Inhalation: EU RAR (2002): methyloxirane European Commission rat vapour Secondary source: review of experimental reports	Rat LC50 (4h): 9.48 mg/l	2 (reliable with restrictions) supporting study review of reported studies Test material (EC name): methyloxirane	EU RAR (2002) (Primary source cited as Weil et al. 1963)
Dermal: rabbit Coverage: open Single skin penetration LD50 for rabbits	LD50: 1.15 mL/kg bw (950 mg/kg bw) Detailed information on reactions to treatment not available.	2 (reliable with restrictions) key study experimental result Test material (EC name): methyloxirane	Smyth et al. (1969)
Dermal: EU RAR (2002): methyloxirane European Commission rabbit Secondary source: review of experimental reports	LD50 1250 mg/kg bw Detailed information on reactions to treatment not available.	2 (reliable with restrictions) supporting study review of reported studies Test material (EC name): methyloxirane	EU RAR (2002) (Primary source cited as Weil et al. 1963)

4.2.1 NON-HUMAN INFORMATION

4.2.1.1 ACUTE TOXICITY: ORAL

An acute oral toxicity study is available that is comparable to OECD guideline 401 in which 5 rats per sex per dose were used. No details on findings were reported, except the LD50 values. From this study an LD50 range of 382-587 mg/kg was obtained (Shell Research Ltd., 1968). This is

considered the key study (as the identified primary data source which included a calculated LD50 range).

A supporting experimental study using 5 rats (mixed sexes)/group found 0% mortality at 300 mg/kg and 100% mortality at 1000 mg/kg. Post-treatment weight gains of the 300 mg/kg group was described as normal. Three other studies (EU RAR expert review secondary source listings of available data on acute toxicity) cited oral LD50 values for rats, mice and Guinea pigs ranging from >500 to 950 mg/kg. All of these studies are summarised in Table 11 above.

4.2.1.2 ACUTE TOXICITY: INHALATION

An acute inhalation toxicity study is available that is comparable to OECD guideline 403 (Shell Research Ltd., 1977); groups of 4 rats/sex/group were whole-body exposed to methyloxirane vapour at 7 different concentrations in the range 3000-5970 ppm. The test atmospheres were generated dynamically by nearly saturating part of the total air flow to the test chambers with propylene oxide vapour. This was accomplished by passing a controlled airflow through a wick-type saturator maintained at 0 °C in an ice/water bath with air stirring. The air/vapour mixture from the saturator was then blended with a controlled flow of clean air in a 2 L mixing vessel. The generated atmosphere then passed from the mixing vessel into the test chambers.

4 Male and 4 female rats were housed in two glass exposure chambers supplied from a single atmospheric generator. Following the 4h exposure period, the surviving animals were transferred to cages for a 14 d post-exposure observation period. At the end of this period the animals were killed. Half hourly observations of the general health and behaviour of each animal were made. Pathological examination was not performed.

At 3000 and 3450 ppm, no animals died. At 4050 ppm, 3 females died. At 4280 ppm, 2 males and 2 females died. At 4500 ppm 3 males and a4 females died and at 5260 and 5970 ppm all animals died. The results gave rise to a 4h LC50 of 4197 ppm (9.95 mg/L). This is considered the key study (as the identified primary data source with analytical confirmation of test atmospheres which reported a precisely calculated LC50 value).

A (US NTP) supporting study using 5 animals/sex/group exposed rats to 4 different vapour concentrations (1277–3900 ppm) and mice to 5 different concentrations (387-2970 ppm); Mortality data in rats: at 1277 ppm 0 m and 0 f; at 2970 ppm 1 m and 2f; at 3794 ppm 4m and 4 f; at 3900 ppm 3m and 3 f. Mortality data in mice: at 387 ppm 0m and 1f; at 859 ppm 0m and 0 f; at 1102 ppm 2m and 4 f; at 1277 ppm 2 m and 5 f and at 2970 ppm 5 m and 5 f. No LC50 values were calculated in the study, however, from the reported results, 4h LC50 values of >7.1 - >9.0 mg/l (rats, both sexes), >3.0 - >7.1 mg/l (male mice) and >2.0 - >2.6 mg/l (female mice) can be deduced. In another supporting study, rats (5-15 females/group) and Guinea pigs (5-10 females/group) were exposed at 4 concentrations in the range 2000-16000 ppm: mortality data indicated that the 4h LC50 value for both rats and Guinea pigs was above, but close to, 9.5 mg/l. 4h LC50 values listed in two other studies (secondary source information: EU RAR expert reviews) ranged from 4.1 to 9.5 mg/l. All studies are summarised in Table 11 above.

4.2.1.3 ACUTE TOXICITY: DERMAL

An acute dermal toxicity study is available that predates GLP and OECD guidelines; however, reporting of this study provides sufficient details to contribute to assessments (Smyth et al., 1969). This study elicited a dermal LD50 of 950 mg/kg. This is considered the key study (as the sole identified primary data source).

The supporting study (secondary source: EU RAR expert review) lists another rabbit LD50 value of 1250 mg/kg, but as full experimental detail is not available for either study and the key study used 4h open application of test material (probably not maximising exposure) the lower value of 950 mg/kg is taken forward for assessment. Both studies are summarised in Table 11 above.

4.2.1.4 ACUTE TOXICITY: OTHER ROUTES

Acute toxicity by other routes is not considered as part of this dossier.

4.2.2 HUMAN INFORMATION

Very limited acute toxicity information is reported for humans. A summary of a single case of poisoning reported that an individual exposed to 1500 ppm after 10 min exhibited respiratory tract and eye irritation and, after 2 hrs, became cyanotic and collapsed but with medical assistance recovered after 14 hrs (Gosselin, 1984). The EU RAR (2002) concluded this information to be of questionable reliability due to lack of details on exposure.

4.2.3 SUMMARY AND DISCUSSION OF ACUTE TOXICITY

Acute toxicity data from animal studies for oral, dermal, and inhalation exposure routes are available.

Acute oral toxicity: rat LD50 from the key study (test performed using methods comparable to OECD guideline 401) is 382-587 mg/kg bw. This is supported by several other reported acute oral toxicity results for rats, mice and Guinea pigs: all LD50 values are within the range >300 to 950 mg/kg bw.

Acute inhalation toxicity: rat 4h LC50 from the key study is 9.95 mg/l. This is supported by the results of several other reported acute inhalation toxicity investigations, performed using rats, mice and Guinea pigs. These reported mortality patterns are compatible with the key study LC50 value and/or indicated comparable 4h EC50 values (range 3.0 to circa 9.5 mg/l).

Acute dermal toxicity: rabbit LD50 from the key study is 950 mg/kg bw. One other rabbit LD50 value (1250 mg/kg bw) is available, but neither study is reported with full experimental detail and since no cover was applied to the test site in the key study (perhaps reducing the applied dose through volatilization losses) the appropriate and cautious approach is to accept the lower (950 mg/kg bw) LD50 value.

There is only limited information on acute toxicity in humans and this does not substantively contribute to the characterization of propylene oxide acute toxicity.

4.2.4 COMPARISON WITH CRITERIA

Acute toxicity data by oral, inhalation, and dermal routes indicate propylene oxide is toxic or harmful. The studies for the oral and inhalation route performed in rats concluded an oral LD50 of 382-587 mg/kg bw and a 4h LC50 of 9.95 mg/l, respectively. The LC50 values are clearly below the saturated vapour concentration of 1735 mg/L. For the dermal route, an LD50 of 950 mg/kg bw was concluded in rabbits. Therefore the substance meets the criteria for classification on grounds of acute toxicity.

Relevant CLP (Regulation 1272/2008) criteria are as follows.
Acute Category 4:

- oral LD50 between 300 and 2000 mg/kg bw
- inhalation 4h LC50 (vapours) between 10 and 20 mg/l
- dermal LD50 between 1000 and 2000 mg/kg bw.

Acute Category 3:
- oral LD50 between 50 and 300 mg/kg bw
- inhalation 4h LC50 (vapours) between 2 and 10 mg/l
- dermal LD50 between 200 and 1000 mg/kg bw.

Hence the available data now indicate that the appropriate classification for propylene oxide is Acute Tox 4, H302 (Harmful if swallowed), Acute Tox 3 H331 (Toxic if inhaled) and Acute Tox 3, H311 (Toxic in contact with skin).

Relevant DSD (Directive 67/548/EEC) criteria are as follows.
Harmful (Xn):
- oral LD50 between 200 and 2000 mg/kg bw
- inhalation 4h LC50 (vapours) between 2 and 20 mg/l
- dermal LD50 between 400 and 2000 mg/kg bw.

Toxic (T):
- oral LD50 between 25 and 200 mg/kg bw
- inhalation 4h LC50 (vapours) between 0.5 and 2 mg/l
- dermal LD50 between 50 and 400 mg/kg bw.

Hence the available data now indicate that the appropriate classification for propylene oxide is harmful (Xn) for all three routes of administration (with R20/21/22).

4.2.5 CONCLUSIONS ON CLASSIFICATION AND LABELLING

It is therefore proposed that the harmonised classification of propylene oxide should be changed to that shown here.

Conclusions on classification and labelling
The appropriate classifications for propylene oxide in respect of acute toxicity are as follows.
Under CLP criteria:
Acute Tox. 3 (H331)
Acute Tox. 3 (H311)
Acute Tox. 4 (H302)

Under DSD criteria:
Xn; R20/R21/22.

Labelling (in accordance with these classifications) should be as shown earlier in section 1.3 of this report.

RAC evaluation of acute toxicity - oral, dermal, inhalation
Summary of the Dossier submitter's proposal The substance presently has an entry in Annex VI of the CLP Regulation for acute toxicity as Acute Tox. 4* (the asterisk denoting a minimum classification) for all routes.

Based on five oral studies in rats, mice and guinea pigs, it was concluded by the DS that the LD_{50} was in the range of 382-587 mg/kg, thus fulfilling the criteria for oral Acute Tox. 4; H302.

Based on results of five studies using the inhalation route in rats, mice and guinea pigs, it was concluded that the LD_{50} was 9.95 mg/L, warranting classification as Acute Tox. 3; H311.

For the dermal route, two studies in rabbits were presented, resulting in an LD_{50} of 950 mg/kg bw, thereby warranting classification as Acute Tox. 3; H331.

Comments received during public consultation

Three MSCAs commented and all were in favour of the proposal.

Assessment and comparison with the classification criteria

Acute toxicity: oral
In the key acute oral toxicity study on male rats (Shell Research Ltd., 1968), the LD_{50} was determined to be between 382 and 587 mg/kg bw. This was supported by several other reported acute oral toxicity results for rats, mice and guinea pigs: all LD_{50} values were within the range >300 to 950 mg/kg bw (Rowe et al., 1956; Smyth et al., 1941; Smyth et al., 1969; Antonova et al., 1981). Methyloxirane therefore fulfils the criteria in the CLP Regulation for acute toxicity hazard category 4 (300 mg/kg bw < ATE ≤ 2 000 mg/kg bw). Therefore the asterisk indicating minimum classification (*) for acute toxicity category 4; H302 is no longer necessary.

Acute toxicity: inhalation
In the key acute inhalation toxicity study (Shell Research Ltd., 1977) the LC_{50} (male/female, vapour, whole body exposure) was 9.95 mg/L. This was supported by the results from several other reported acute inhalation toxicity investigations performed using rats, mice and guinea pigs (Rowe et al., 1956; Jacobson et al., 1956; Weil et al., 1963). The reported doses causing mortality were consistent with the key study LC_{50} value and/or indicated comparable 4h EC_{50} values (range from 2.0 to circa 19 mg/L (vapour, whole body exposure). According to the CLP Regulation, methyloxirane vapour fulfils the criteria for category 3 for acute inhalation toxicity hazard categories (2.0 mg/L < ATE ≤ 10.0 mg/L). Changing the classification for acute inhalation toxicity from category 4, H332* to category 3; H331 is warranted.

Acute toxicity: dermal
In the key acute dermal toxicity study (Smyth et al., 1969) in rabbits, the LC_{50} was 950 mg/kg bw. This value was used as the basis for the proposal to classify as Acute Tox. 3, H311. In the supporting study in rabbits, the LD_{50} value was 1 250 mg/kg bw (Weil et al., 1963). The appropriate and cautious approach is to accept the lower LD_{50} value (950 mg/kg bw). Methyloxirane fulfils the criteria in the CLP Regulation for acute toxicity hazard category 3 (200 mg/kg bw < ATE ≤ 1 000 mg/kg bw) and therefore the proposal of the DS to change the classification for acute dermal toxicity from Acute Tox. 4*; H312 to Acute Tox. 3; H311 is supported.

4.3 SPECIFIC TARGET ORGAN TOXICITY – SINGLE EXPOSURE (STOT SE)

Specific target organ toxicity – single exposure has not been considered as part of this dossier.

4.3.1 SUMMARY AND DISCUSSION OF SPECIFIC TARGET ORGAN TOXICITY – SINGLE EXPOSURE

4.3.2 COMPARISON WITH CRITERIA

4.3.3 CONCLUSIONS ON CLASSIFICATION AND LABELLING

4.4 IRRITATION

4.4.1 SKIN IRRITATION

Table 12: Summary table of relevant skin irritation studies

Method	Results	Remarks	Reference
in vitro study The EPISKIN model is a three-dimensional reconstituted human epidermis model consisting of adult human-derived epidermal keratinocytes seeded on a dermal substitute consisting of a collagen type I matrix coated with type lV collagen. Coverage: open (use of the Episkin model kit) OECD guideline 431 (In vitro skin corrosion: human skin model test)	relative mean tissue viability: 96.4 (mean) (Time point: 240 minutes) relative mean tissue viability: 119.4 (mean) (Time point: 60 minutes) relative mean tissue viability: 141.3 (mean) (Time point: 3 minutes) relative mean tissue viability: 5.6 (mean) (Time point: 240 minutes) (positive control)	1 (reliable without restriction) key study experimental result Test material (EC name): methyloxirane	Harlan Laboratories Ltd. (2010c)
rabbit (New Zealand White) 0.5 mL applied for 4 hrs Coverage: semiocclusive (shaved) Observation at 1, 24, 48 and 72 hrs after removal patch OECD Guideline 404 (Acute Dermal Irritation / Corrosion) EU Method B.4 (Acute Toxicity: Dermal Irritation / Corrosion) 2 test animals	not irritating Erythema score: 1 of max. 4 (mean) (Time point: 24 hours) (fully reversible within: 72 hours) (the individual score was 2 for one rabbit only) 0.5 of max. 4 (mean) (Time point: 48 hours) (fully reversible within: 72 hours) (one rabbit scored 1) 0 of max. 4 (mean) (Time point: 72 hours) Edema score: 0.5 of max. 4 (mean) (Time point: 24 hours) (fully	1 (reliable without restriction) key study experimental result Test material (EC name): methyloxirane	Harlan Laboratories Ltd. (2010d)

	reversible within: 48 hours) 0 (mean) (Time point: 48 and 72 hours)		

rabbit Coverage: occlusive (shaved abdomen) Undiluted and diluted (10%, 20% solutions in water) applied. No information on volumes applied Exposure 1-60 minutes Observation period 6-7 days Little detail on study design or methods No information on number of test animals	Treatments 6 min or longer resulted in hyperemia and oedema. "Severer" treatments resulted in scar formation. Severity said to be proportional to exposure time. The authors state that (unspecified) evidence indicated the 10% and 20% solutions were more irritating than undiluted test substance.	4 (not assignable) Experimental result Test material (EC name): methyloxirane (purity essentially 100%)	Rowe et al. (1956)
Guinea pig (males) 4 topical applications (3 for 2 days, last for 24h) under semiocclusive dressing. 2 wks later, one open, topical application. 0.1 ml of 10% solution applied in each case. Observation at 24 and 48 h post treatment Skin sensitisation assay, modified Maguire method (10 test animals)	Very slight oedema seen after first treatment (4/10 animals). Also seen after 2nd treatment (1/10 animals). No other reactions.	2 (reliable with restrictions) Experimental result Test material (EC name): methyloxirane	Dow Chemical Company (1982)
rabbit (Vienna White) Coverage: semiocclusive (clipped) Company in-house method: single 4h exposure, similar to EU method B.4 with observations at 15 and 30 minutes, 24, 48 and 120 hours and 8 days after removal of the patch test 2 female rabbits	No skin reactions observed after treatment	2 (reliable with restrictions) Experimental result Test material (EC name): methyloxirane (purity not stated)	BASF (1981a)
rabbit (Vienna White) Coverage: semiocclusive (clipped) Company in-house method: similar to EU method B.4 0.5 ml was applied. Observations at 15 and 30 minutes, 24, 48 and 120 hours and 8 days after removal of the patch test, repeated application of a patch dipped in test substance: - 4 times consecutively (5 minutes application each time) - then once more, with the patch	No skin reactions observed after treatment	2 (reliable with restrictions) Experimental result Test material (EC name): methyloxirane (purity not stated)	BASF (1981b)

held in position for 4h under semiocclusive conditions 2 female rabbits			
rabbit (Vienna White) Coverage: occlusive (shaved) Company in-house method: 1 ml test substance applied onto dorsal skin, then covered by an occlusive dressing for 20h (shorter treatments and application to ears also included, but results not supplied). 2 rabbits	Grade 3 erythema at 0, 24 and 72h post treatment. 24 + 72h mean oedema scores 2, 1.33. Skin lesions still evident 8 days post treatment	2 (reliable with restrictions) but not giving results relevant for classification Experimental result Test material (EC name): methyloxirane (purity not stated)	BASF (1962)

4.4.1.1 NON-HUMAN INFORMATION

Two key studies, performed to resolve uncertainty arising from reported observations in old studies, are available. In the *in vitro* EPISKIN test, test substance was applied topically to the *stratum corneum* surface, to determine cytotoxicity. Corrosive chemicals are able to penetrate *the stratum corneum*, causing cell death in the underlying cell layers. Toxicity is determined by comparing conversion of the vital dye MTT to formazan (via metabolism in viable cells) in treated and control cultures. No significant cytotoxicity was seen following propylene oxide treatment, so the test material was considered non-corrosive to the skin. Propylene oxide was then also tested *in vivo* using rabbits (in accordance with OECD 404 and GLP). Scoring for erythema and oedema showed only minor and transient reactions to treatment which were fully resolved within 48 - 72h, demonstrating the low skin irritancy of this substance.

Older company in-house studies of propylene oxide irritancy had investigated skin irritation after single (4h) or multiple (repeated application of a patch dipped in test substance: 4 x 5 min plus 1 x 4h on the same test site) application of 0.5 ml to the skin of rabbits, with semiocclusive coverage. No reactions at application sites were observed. In a separate rabbit study, 1 ml propylene oxide was applied to the skin for 20h under occlusive dressings: this higher level of exposure resulted in local reactions (erythema and oedema) which were not fully resolved after 8 days (skin encrustation persisting). The relative contributions to the observed effects in this latter study of non-specific reaction to prolonged occlusion and increased local propylene oxide dose (through 1 ml application and reduced possibilities for volatilisation loss) are unknown.

A published report (>50 years old and lacking details of methods and results) described severe local reactions in rabbits to occluded skin application of both undiluted and diluted (aqueous 20 and 10% solutions) propylene oxide. These included erythema and oedema after exposures longer than 6 minutes and scar formation after “severer” exposure. The report authors stated that (unspecified) evidence indicated that diluted solutions were more irritating that undiluted propylene oxide. However numbers of rabbits tested, timings of skin observations, individual reactions, the nature of the patch coverings, and quantities of test substance applied are unreported. This makes definitive interpretation of the reported findings impossible. This investigation is described as “poorly reported” in the EU RAR for propylene oxide. In addition, the claim of skin damage due to short-term application of a 10% solution of propylene oxide is contradicted by observations of no significant irritation after repeated application of a 10% solution to Guinea pig skin during a skin

sensitisation assay (which included 4 semiocclusive plus 1 open skin applications to each of 10 animals).

It is concluded that the key studies provided reliable investigation of possible irritant activity, resolving uncertainty arising from previously available test data and, on the basis of these, propylene oxide should not be classified irritating to skin.

4.4.1.2 HUMAN INFORMATION

No reliable human information is available.

4.4.1.3 SUMMARY AND DISCUSSION OF SKIN IRRITATION

There are no adequately documented reports of human skin irritation associated with propylene oxide exposure. Results obtained in recent and reliable studies (both *in vitro* and *in vivo*) clearly show that propylene oxide does not cause significant local reaction following dermal contact. These results are sufficient to overcome uncertainty raised by earlier work, some of which suggested skin irritating activity.

4.4.1.4 COMPARISON WITH CRITERIA

In the key studies, propylene oxide caused only minor and transient local reaction following skin contact in rabbits.

Relevant CLP (Regulation 1272/2008) criteria for classification in respect of skin irritation are as follows.

[1] Mean value 2.3 – 4.0 for erythema/eschar or oedema in at least 2 of 3 tested animals from 24, 48 and 72h scores or, if reactions are delayed, from scores on 3 consecutive days after onset of skin reactions; or
[2] Inflammation that persists to the end of the observation period normally 14 days in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling; or
[3] In some cases where there is pronounced variability of response among animals, with very definite positive effects related to chemical exposure in a single animal which are less than the above criteria.

Hence the available data now indicate that no classification of propylene oxide in respect of skin irritation is appropriate.

Relevant DSD (Directive 67/548/EEC) criteria for classification as Xi, R38 in respect of skin irritation are as follows.
[1] Substances and preparations which cause significant inflammation of the skin which persists for at least 24 hours after an exposure period of up to four hours determined on the rabbit according to the Annex V test method. Inflammation of the skin is significant if:
- the mean value of the scores for either erythema and eschar formation or oedema formation, calculated over all the animals tested, is 2 or more; or
- in the case where the Annex V test has been completed using three animals, either erythema and

eschar formation or oedema formation equivalent to a mean value of 2 or more calculated for each animal separately has been observed in at least two animals. (In both cases 24, 48 and 72h scores are used to calculate mean values).
Inflammation is also significant if it persists in at least two animals at the end of the observation time. Particular effects e.g., hyperplasia, scaling, discoloration, fissures, scabs and alopecia, should be taken into account.
Relevant data may also be available from non-acute animal studies.
[2] Substances and preparations which cause significant inflammation of the skin, based on practical observations in humans on immediate, prolonged or repeated contact.
[3] Organic peroxides, except where evidence to the contrary is available.

Hence the available data now indicate that no classification of propylene oxide in respect of skin irritation is appropriate.

4.4.1.5 CONCLUSIONS ON CLASSIFICATION AND LABELLING

No classification of propylene oxide in respect of skin irritation is warranted.

4.4.2 EYE IRRITATION

Not relevant for this dossier: no change to the existing harmonised classification in respect of eye irritation is proposed.

Table 13: Summary table of relevant eye irritation studies

Method	Results	Remarks	Reference

4.4.2.1 NON-HUMAN INFORMATION

4.4.2.2 HUMAN INFORMATION

4.4.2.3 SUMMARY AND DISCUSSION OF EYE IRRITATION

4.4.2.4 COMPARISON WITH CRITERIA

4.4.2.5 CONCLUSIONS ON CLASSIFICATION AND LABELLING

4.4.3 RESPIRATORY TRACT IRRITATION

Not relevant for this dossier: no change to the existing harmonised classification in respect of respiratory irritation is proposed.

4.4.3.1 NON-HUMAN INFORMATION

4.4.3.2 HUMAN INFORMATION

4.4.3.3 SUMMARY AND DISCUSSION OF RESPIRATORY TRACT IRRITATION

4.4.3.4 COMPARISON WITH CRITERIA

4.4.3.5 CONCLUSIONS ON CLASSIFICATION AND LABELLING

4.5 CORROSIVITY

Corrosive or irritant action on the skin has been considered in section 4.4.1 of this report: no further consideration of corrosivity is required.

Table 14: Summary table of relevant corrosivity studies

Method	Results	Remarks	Reference

4.5.1 NON-HUMAN INFORMATION

4.5.2 HUMAN INFORMATION

4.5.3 SUMMARY AND DISCUSSION OF CORROSIVITY

4.5.4 COMPARISON WITH CRITERIA

4.5.5 CONCLUSIONS ON CLASSIFICATION AND LABELLING

RAC evaluation of skin corrosion/irritation
Summary of the Dossier submitter's proposal The substance currently has an entry in Annex VI of the CLP Regulation entry as Skin Irrit. 2; H315. The dossier submitter has proposed removal of this hazard class based on the results obtained in recent and reliable studies (both *in vitro* and *in vivo*) that clearly show that propylene oxide does not cause any significant local reaction following dermal contact. The results from older, less reliable studies, some of which indicated skin irritation, were considered not to be sufficient for classification. **Comments received during public consultation** Three MSCA commented and all were in favour of the proposal. **Assessment and comparison with the classification criteria** The proposal to remove the classification of methyloxirane as "Skin Irrit. 2; H315" is

based on the following two studies on skin irritation/corrosion.

The first study was the *in vitro* EPISKIN test based on the OECD technical guideline (TG) 431 performed in accordance with GLP (Harlan Laboratories Ltd. 2010c) in which good tissue viability was demonstrated. In this test no significant cytotoxicity was seen following methyloxirane treatment, and therefore the test material was considered to be non-corrosive to the skin.

In the second key study methyloxirane was tested *in vivo* using two rabbits, in line with OECD TG 404 and GLP (Harlan Laboratories Ltd., 2010d). The mean scores for skin erythema in both rabbits were 1, 0.5 and 0, respectively, after patch removal at 24, 48 and 72 hours.

The mean score for skin oedema in both rabbits 24h after patch removal was 0.5; however 48 hours and 72 hours after patch removal the scores for oedema were 0.

In none of the tested rabbits did the mean values for erythema or oedema from gradings at 24, 48 and 72 hours after patch removal reach 2.3 and the signs of inflammation disappeared completely 72 hours after removal of the patches containing the tested substance (Harlan Laboratories Ltd., 2010d). Therefore the CLP criteria for skin irritation were not met.

In the third (supportive) study on rabbits, no skin reaction was observed after a 4-hour occlusive dermal exposure (BASF 1981a).

In a fourth supportive study on rabbits (BASF 1981a) with a multiple application of substance on the skin (4 x5 mins, then 1 application for 4 hours) and observation up to 8 days, no skin reaction was observed after treatment.

In the fifth supportive study on guinea pigs (Dow Chemical Company, 1982), very slight oedema was seen in 4 of 10 guinea pigs after the first topical application of methyloxirane for 24 hours under a semi-occlusive dressing and in 1 of 10 animals after a second such application during the induction phase in the modified Maguire method for skin sensitisation. These observations did not indicate significant skin irritation properties for methyloxirane in guinea pigs.

There were two studies (BASF, 1962 and Rowe et al. 1965) which may suggest classification for skin irritation. However, the duration of dermal exposure was not described in the Rowe et al. (1965) study and in the BASF (1962) study, dermal exposure with occlusive dressing was 20 hours following application of 1 mL test substance instead of application of 0.5 ml and 4 hours exposure as recommended in OECD (TG) 404. In the BASF (1962) study it was reported that at the end of the 20 hour exposure period the residual test substance was not removed from skin.

In the second study (Rowe et al., 1965), the volume of substance applied onto the skin was also not described and the number of rabbits tested, timings of skin observations and individual skin reactions were not reported. Both studies (BASF, 1962 and Rowe et al., 1965) used occlusive patch covering instead of semi-occlusive dressing for the duration of the exposure as required in OECD TG 404.

Giving greater weight to the evidence from studies conducted in line with the OECD 404 and 431 test guidelines and taking into account the negative results in three supportive studies, RAC is of the opinion that methyloxirane does not warrant classification as a skin irritant and the classification "Skin Irrit. 2; H315" for methyloxirane should be removed.

4.6 SENSITISATION

No classification in respect of sensitisation is included in the existing harmonised classification and none is considered appropriate. Further consideration in this report is not required.

4.6.1 SKIN SENSITISATION

Table 15: Summary table of relevant skin sensitisation studies

Method	Results	Remarks	Reference

4.6.1.1 NON-HUMAN INFORMATION

4.6.1.2 HUMAN INFORMATION

4.6.1.3 SUMMARY AND DISCUSSION OF SKIN SENSITISATION

4.6.1.4 COMPARISON WITH CRITERIA

4.6.1.5 CONCLUSIONS ON CLASSIFICATION AND LABELLING

4.6.2 RESPIRATORY SENSITISATION

No classification in respect of respiratory sensitisation is included in the existing harmonised classification and none is considered appropriate. Further consideration in this report is not required.

Table 16: Summary table of relevant respiratory sensitisation studies

Method	Results	Remarks	Reference

4.6.2.1 NON-HUMAN INFORMATION

4.6.2.2 HUMAN INFORMATION

4.6.2.3 SUMMARY AND DISCUSSION OF RESPIRATORY SENSITISATION

4.6.2.4 COMPARISON WITH CRITERIA

4.6.2.5 CONCLUSIONS ON CLASSIFICATION AND LABELLING

4.7 REPEATED DOSE TOXICITY

No classification in respect of repeated dose toxicity is included in the existing harmonised classification and none is considered appropriate. Further consideration in this report is not required.

Table 17: Summary table of relevant repeated dose toxicity studies

Method	Results	Remarks	Reference

4.7.1 NON-HUMAN INFORMATION

4.7.1.1 REPEATED DOSE TOXICITY: ORAL

4.7.1.2 REPEATED DOSE TOXICITY: INHALATION

4.7.1.3 REPEATED DOSE TOXICITY: DERMAL

4.7.1.4 REPEATED DOSE TOXICITY: OTHER ROUTES

4.7.1.5 HUMAN INFORMATION

4.7.1.6 OTHER RELEVANT INFORMATION

4.7.1.7 SUMMARY AND DISCUSSION OF REPEATED DOSE TOXICITY

4.7.1.8 SUMMARY AND DISCUSSION OF REPEATED DOSE TOXICITY FINDINGS RELEVANT FOR CLASSIFICATION ACCORDING TO DSD

4.7.1.9 COMPARISON WITH CRITERIA OF REPEATED DOSE TOXICITY FINDINGS RELEVANT FOR CLASSIFICATION ACCORDING TO DSD

4.7.1.10 CONCLUSIONS ON CLASSIFICATION AND LABELLING OF REPEATED DOSE TOXICITY FINDINGS RELEVANT FOR CLASSIFICATION ACCORDING TO DSD

4.8 SPECIFIC TARGET ORGAN TOXICITY (CLP REGULATION) – REPEATED EXPOSURE (STOT RE)

4.8.1 SUMMARY AND DISCUSSION OF REPEATED DOSE TOXICITY FINDINGS RELEVANT FOR CLASSIFICATION AS STOT RE ACCORDING TO CLP REGULATION

4.8.2 COMPARISON WITH CRITERIA OF REPEATED DOSE TOXICITY FINDINGS RELEVANT FOR CLASSIFICATION AS STOT RE

4.8.3 CONCLUSIONS ON CLASSIFICATION AND LABELLING OF REPEATED DOSE TOXICITY FINDINGS RELEVANT FOR CLASSIFICATION AS STOT RE

4.9 GERM CELL MUTAGENICITY (MUTAGENICITY)

Not relevant for this dossier: no change to the existing harmonised classification in respect of germ cell mutagenicity is proposed.

Table 18: Summary table of relevant in vitro and in vivo mutagenicity studies

Method	Results	Remarks	Reference

4.9.1 NON-HUMAN INFORMATION

4.9.1.1 IN VITRO DATA

4.9.1.2 IN VIVO DATA

4.9.2 HUMAN INFORMATION

4.9.3 OTHER RELEVANT INFORMATION

4.9.4 SUMMARY AND DISCUSSION OF MUTAGENICITY

4.9.5 COMPARISON WITH CRITERIA

4.9.6 CONCLUSIONS ON CLASSIFICATION AND LABELLING

4.10 CARCINOGENICITY

Not relevant for this dossier: no change to the existing harmonised classification in respect of carcinogenicity is proposed.

Table 19: Summary table of relevant carcinogenicity studies

Method	Results	Remarks	Reference

4.10.1 NON-HUMAN INFORMATION

4.10.1.1 CARCINOGENICITY: ORAL

4.10.1.2 CARCINOGENICITY: INHALATION

4.10.1.3 CARCINOGENICITY: DERMAL

4.10.2 HUMAN INFORMATION

4.10.3 OTHER RELEVANT INFORMATION

4.10.4 SUMMARY AND DISCUSSION OF CARCINOGENICITY

4.10.5 COMPARISON WITH CRITERIA

4.10.6 CONCLUSIONS ON CLASSIFICATION AND LABELLING

4.11 TOXICITY FOR REPRODUCTION

No classification in respect of toxicity to reproduction is included in the existing harmonised classification and none is considered appropriate. Further consideration in this report is not required.

Table 20: Summary table of relevant reproductive toxicity studies

Method	Results	Remarks	Reference

4.11.1 EFFECTS ON FERTILITY

4.11.1.1 NON-HUMAN INFORMATION

4.11.1.2 HUMAN INFORMATION

4.11.2 DEVELOPMENTAL TOXICITY

4.11.2.1 NON-HUMAN INFORMATION

4.11.2.2 HUMAN INFORMATION

4.11.3 OTHER RELEVANT INFORMATION

4.11.4 SUMMARY AND DISCUSSION OF REPRODUCTIVE TOXICITY

4.11.5 COMPARISON WITH CRITERIA

4.11.6 CONCLUSIONS ON CLASSIFICATION AND LABELLING

4.12 OTHER EFFECTS

No classification in respect of other effects is included in the existing harmonised classification and none is considered appropriate. Further consideration in this report is not required.

4.12.1 NON-HUMAN INFORMATION

4.12.1.1 NEUROTOXICITY

4.12.1.2 IMMUNOTOXICITY

4.12.1.3 SPECIFIC INVESTIGATIONS: OTHER STUDIES

4.12.1.4 HUMAN INFORMATION

4.12.2 SUMMARY AND DISCUSSION

4.12.3 COMPARISON WITH CRITERIA

4.12.4 CONCLUSIONS ON CLASSIFICATION AND LABELLING

5 ENVIRONMENTAL HAZARD ASSESSMENT

No classification in respect of environmental hazard is included in the existing harmonised classification and none is considered appropriate. Further consideration in this report is not required.

5.1 DEGRADATION

Table 21: Summary of relevant information on degradation

Method	Results	Remarks	Reference

5.1.1 STABILITY

5.1.2 BIODEGRADATION

5.1.2.1 BIODEGRADATION ESTIMATION

5.1.2.2 SCREENING TESTS

5.1.2.3 SIMULATION TESTS

5.1.3 SUMMARY AND DISCUSSION OF DEGRADATION

5.2 ENVIRONMENTAL DISTRIBUTION

5.2.1 ADSORPTION/DESORPTION

5.2.2 VOLATILISATION

5.2.3 DISTRIBUTION MODELLING

5.3 AQUATIC BIOACCUMULATION

Table 22: Summary of relevant information on aquatic bioaccumulation

Method	Results	Remarks	Reference

5.3.1 AQUATIC BIOACCUMULATION

5.3.1.1 BIOACCUMULATION ESTIMATION

5.3.1.2 MEASURED BIOACCUMULATION DATA

5.3.2 SUMMARY AND DISCUSSION OF AQUATIC BIOACCUMULATION

5.4 AQUATIC TOXICITY

Table 23: Summary of relevant information on aquatic toxicity

Method	Results	Remarks	Reference

5.4.1 FISH

5.4.1.1 SHORT-TERM TOXICITY TO FISH

5.4.1.2 LONG-TERM TOXICITY TO FISH

5.4.2 AQUATIC INVERTEBRATES

5.4.2.1 SHORT-TERM TOXICITY TO AQUATIC INVERTEBRATES

5.4.2.2 LONG-TERM TOXICITY TO AQUATIC INVERTEBRATES

5.4.3 ALGAE AND AQUATIC PLANTS

5.4.4 OTHER AQUATIC ORGANISMS (INCLUDING SEDIMENT)

5.5 COMPARISON WITH CRITERIA FOR ENVIRONMENTAL HAZARDS (SECTIONS 5.1 – 5.4)

5.6 CONCLUSIONS ON CLASSIFICATION AND LABELLING FOR ENVIRONMENTAL HAZARDS (SECTIONS 5.1 – 5.4)

6 OTHER INFORMATION

Not relevant for this dossier.

7 REFERENCES

(All data sources relevant to the proposed classification changes are detailed in the associated IUCLID file, submitted with this report).

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8 NO ANNEXES