Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Methyloxirane (Propylene Oxide)

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

CLH-O-0000004152-85-03/F

Adopted

06 June 2014

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CLH-O-0000004152-85-03/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemicals name: Methyloxirane (Propylene Oxide)

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

The proposal was submitted by **The Netherlands** and received by the RAC on **26 August 2013.**

All classifications are given in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS); the notation of 67/548/EEC, the Dangerous Substances Directive (DSD) is no longer given.

PROCESS FOR ADOPTION OF THE OPINION

The Netherlands has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation*** on **6 September 2013**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **21 October 2013**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by the RAC: **Boguslaw Baranski**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation.

The RAC opinion on the proposed harmonised classification and labelling was reached on **06 June 2014** and the comments received are compiled in Annex 2.

The RAC Opinion was adopted by **consensus**.

OPINION OF THE RAC

The RAC adopted the opinion that **Propylene Oxide** should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)	
Current Annex VI entry	603-055-00-4	Propylene oxide;1,2-epoxypropane; Methyloxirane	200-879-2	75-56-9	Flam. Liq. 1 Carc. 1B Muta. 1B Acute Tox. 4* Acute Tox. 4* Acute Tox. 4* Eye Irrit. 2 STOT SE 3 Skin Irrit. 2	H224 H350 H340 H332 H312 H302 H319 H335 H315	GHS02 GHS08 GHS07 Dgr	H224 H350 H340 H332 H312 H302 H319 H335 H315		
Dossier submitters proposal	603-055-00-4	Propylene oxide;1,2-epoxypropane; Methyloxirane	200-879-2	75-56-9	Acute Tox. 4 Acute Tox. 3 Acute Tox. 3 ~~Skin Irrit. 2~~	H302 H331 H311 ~~H315~~		H302 H331 H311 ~~H315~~		
RAC opinion	603-055-00-4	Propylene oxide;1,2-epoxypropane; Methyloxirane	200-879-2	75-56-9	Acute Tox. 4 Acute Tox. 3 Acute Tox. 3	H302 H331 H311		H302 H331 H311		
Resulting Annex VI entry if agreed by COM	603-055-00-4	Propylene oxide;1,2-epoxypropane; Methyloxirane	200-879-2	75-56-9	Flam. Liq. 1 Carc. 1B Muta. 1B Acute Tox. 4 Acute Tox. 3 Acute Tox. 3 Eye Irrit. 2 STOT SE 3	H224 H350 H340 H302 H331 H311 H319 H335	GHS02 GHS08 GHS07 Dgr	H224 H350 H340 H302 H331 H311 H319 H335		

SCIENTIFIC GROUNDS FOR THE OPINION

HUMAN HEALTH HAZARD ASSESSMENT

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 $\leqslant$ 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 $\leqslant$ 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 $\leqslant$ 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.

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.

ANNEXES:

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and rapporteurs' comments (excl. confidential information).