Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

1,2-epoxybutane

EC number: 203-438-2
CAS number: 106-88-7

CLH-O-0000002824-72-02/F

Adopted

11 September 2013

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

In accordance with Article 37 (4) of (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: 1,2-epoxybutane

EC number: 203-438-2

CAS number: 106-88-7

The proposal was submitted by **Germany** and received by the RAC on **6 February 2013.**

In this opinion, all classifications are given firstly in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS) and secondly, according to the notation of 67/548/EEC, the Dangerous Substances Directive (DSD).

PROCESS FOR ADOPTION OF THE OPINION

Germany 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 February 2013**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **25 March 2013**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by RAC: **Riitta Leinonen**

Co-rapporteur, appointed by RAC: **João Carvalho**

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 **11 September 2013** 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 1,2-epoxybutane 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		
					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	603-102-00-9	1,2-epoxybutane	203-438-2	106-88-7	Flam. Liq. 2 Carc. 2; Acute Tox. 4* Acute Tox. 4* Acute Tox. 4* Eye Irrit. 2 STOT SE 3 Skin Irrit. 2 Aquatic Chronic 3	H225 H351 H332 H312 H302 H319 H335 H315 H412	GHS02 GHS08 GHS07 Dgr	H225 H351 H332 H312 H302 H319 H335 H315 H412	
Dossier submitters proposal	603-102-00-9	1,2-epoxybutane	203-438-2	106-88-7	Removal of Aquatic Chronic 3	Removal of H412		Removal of H412	
RAC opinion	603-102-00-9	1,2-epoxybutane	203-438-2	106-88-7	Removal of Aquatic Chronic 3	Removal of H412		Removal of H412	
Resulting Annex VI entry if agreed by COM	603-102-00-9	1,2-epoxybutane	203-438-2	106-88-7	Flam. Liq. 2 Carc. 2 Acute Tox. 4* Acute Tox. 4* Acute Tox. 4* Eye Irrit. 2 STOT SE 3 Skin Irrit. 2	H225 H351 H332 H312 H302 H319 H335 H315	GHS02 GHS08 GHS07 Dgr	H225 H351 H332 H312 H302 H319 H335 H315	

Classification and labelling in accordance with the DSD

	Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits
Current Annex VI entry	603-102-00-9	1,2-epoxybutane	203-438-2	106-88-7	F; R11 Carc. Cat. 3; R40 Xn; R20/21/22 Xi; R36/37/38 R52-53	F; Xn R: 11-20/21/22-36/37/38-40-52/53 S: (2-)9-16-29-36/37-61	
Dossier submitters proposal	603-102-00-9	1,2-epoxybutane	203-438-2	106-88-7	Removal of R52-53	Removal of R52/53 S61	
RAC opinion	603-102-00-9	1,2-epoxybutane	203-438-2	106-88-7	Removal of R52-53	Removal of: R52/53 S61	
Resulting Annex VI entry if agreed by COM	603-102-00-9	1,2-epoxybutane	203-438-2	106-88-7	F; R11 Carc. Cat. 3; R40 Xn; R20/21/22 Xi; R36/37/38	F; Xn R: 11-20/21/22-36/37/38-40 S: (2-)9-16-29-36/37	

SCIENTIFIC GROUNDS FOR THE OPINION

RAC general comment

The only hazard classes considered by RAC were those for the environment.

Please note that references cited here can be found in the CLH report and/or the background document to the opinion; references not quoted in the above documents are however included at the end of this opinion for the sake of convenience.

ENVIRONMENTAL HAZARD ASSESSMENT

RAC evaluation of environmental hazards

Summary of the Dossier submitter's proposal

1,2-epoxybutane currently has a harmonised classification as Aquatic Chronic 3 according to CLP and R52-53 according to DSD.
This substance was originally added to Annex I of the DSD in the 25th ATP (Commission Directive 1998/98/EC). The main argument for the classification at that time was the lack of data on biodegradation. The dossier submitter (DS) proposed to remove the environmental classification of 1,2-epoxybutane due to new experimental results showing that the substance is readily biodegradable.

Degradation

The photodegradation of 1,2-epoxybutane in air was estimated by calculation according to EPIWin, AOP v1.92. The substance is expected to degrade by photochemical processes indirectly by reaction with hydroxyl radicals in the atmosphere with a half-life (DT_{50}) of about 8.8 days.

Hydrolysis was studied by experimental determination of the half-life of 1,2-epoxybutane (non GLP compliant study, half-life=156 hours at pH=7). Although the half-life is shorter than 16 days at pH=7, there is no information regarding the half-life at pH 4 and 9, nor is there information on the degradation products that may be formed.

Biodegradation of 1,2-epoxybutane was studied in three ready biodegradation tests. The tests were performed according to GLP and various relevant guidelines: ISO TG 14593 (Draft, 1996, CO_2-Headspace Test), OECD TG 301A (Doc Die-Away Test) and OECD TG 301 C (Modified MITI Test (I)). In all the tests, the inoculum was not adapted and since 1,2-epoxybutane is moderately volatile (Henry´s law =21.48 Pa.m3/mol) closed systems (ISO 14593, OECD 301C) were indicated for testing. For that reason the DOC-Die-Away test (OECD 301A) was prepared in a closed test system. Therefore specially designed 1 litre shake flasks were used, which were filled with 500 mL mineral medium and a sufficient amount of test substance. After closing the test flasks, the remaining space was considered as the headspace volume of air. In both studies with closed flasks (ISO 14593, OECD 301A) abiotic controls were performed to assess volatilisation. There was no indication of volatilisation during the 28 days incubation period.

In the case of the headspace test conducted according to ISO TG 14593, the 10-day-time window requirement was not fulfilled since CO2 production was measured at intervals of 7 days (on days 7 ,14, 21 and 28). The results showed that the lag phase lasted for about 8 to 10 days and the pass level was reached after approximately 19 to 20 days. The DS argues that also in the Closed Bottle test (OECD TG 301D), where a 7-day measuring interval was used, a 14-day window may be applied instead of a 10-day time-window. As a result of this interpretation the DS concludes that the 14-day window can be used and that the substance is readily biodegradable. Also in the DOC-Die-away test (OECD 301A) the degradation exceeded 90% DOC removal after 28 days, but missed the 10-day window for 70% degradation. The MITI I (OECD 301C) is excluded from the 10 day-time window requirement, and therefore the DS concluded that the substance is ready biodegradable because after 28 days the O_2 consumption was >=100%.

For all three reported guideline studies the pass level for ready biodegradability of 1,2-epoxybutane was reached within a 28 day time period. Based on all available data on biodegradation of 1,2-epoxybutane, the DS concluded that the substance can be assessed as ready biodegradable, and consequently also rapidly degradable.

Bioaccumulation

1,2-epoxybutane has a measured log K_{ow} of 0.68 (non-GLP compliant study, 25 °C, purity 99,1%) but this study was performed without considering the pH.

No bioaccumulation studies are available.

The DS concluded that based on the log K_{ow}, accumulation of the substance in organisms is not anticipated.

Aquatic toxicity

No chronic aquatic toxicity data are available.

The available short-term tests for 1,2-epoxybutane were conducted with fish, invertebrates and algae, but all were non-GLP compliant.

Table 1. Acute aquatic toxicity values for each trophic level

Species	**Test Guideline**	**Test type**	**Result**
Golden *orfe (Leuciscus idus L.,* golden variety*)*	DIN 38 412, L15 (1982),non-GLP	static	96h LC_{50}>100 mg/L (nominal)
Daphnia magna	EU Method C.2 (Acute Toxicity for Daphnia), non-GLP	static	EC_{50} 48h:70 mg/L (nominal)
Scenedesmus subspicatus	DIN 38412, Part 9, cell multiplication inhibitory test , non-GLP	static	ECr_{50} 72h>500 mg/L (nominal)

The most sensitive species tested is the aquatic invertebrate *Daphnia magna*. The moving average was used to calculate the EC_{50} (48h), resulting in a value of 70 mg/L.
The nominal test concentrations were 7.81, 15.6, 31.2, 62.5, 125, 250 and 500 mg/L.

The results of the acute aquatic toxicity tests are based on nominal values, since the test concentration was not analytically verified during the tests. According to the DS, based on high water solubility of 86.8 g/L at 25 °C in combination with moderate volatility (Henry's law = 21.48 Pa.M3/mol), it can be expected that the test substance concentration was constant during the short test duration of between 48 and 96 hours. This expectation is confirmed by the sterile controls of the biodegradation studies (headspace and DOC-Die-Away test). Evaporation could be determined by decreasing the DOC concentration in the sterile controls. No DOC removal was observed during the 28 days test duration and therefore volatilisation is negligible.

Comments received during public consultation

One Member State (MS) agreed with the DS's proposal not to classify 1,2-epoxybutane for environmental hazards.

Three MSs wanted more detailed information on the biodegradation studies.

Two MSs did not agree with the conclusion drawn concerning rapid degradability based on the information available in the CLH Report and requested better justification for this conclusion.

Information requested about the OECD 301C (MITI I) study included e.g. the amount of the test substance, test conditions, results for each day of the oxygen consumption measurement, results

from the positive control, and results from toxicity controls. The DS explained that the OECD 301C (MITI I) test is commonly prepared in closed test vessels. In this particular test a control measurement was carried out (test substance without inoculum), to show the loss of test substance during the 28 days test duration. At the end of the test, 94 % recovery of the test substance was determined in the control flasks. Furthermore, in all three parallel flasks (test substance with inoculum) of the MITI I test, biodegradation rates of 88 - 91 % were determined. Since the biodegradation rates were estimated from the oxygen consumption, a parameter which directly correlates with the metabolic rate, significant abiotic losses of test item can be excluded. Additional information provided by the DS in the Response to Comments document (RCOM) is presented in the section "Additional key elements".

Three MSs requested clarification concerning the ISO 14593 test. One MS suggested that the test was an inherent test from which no conclusion on ready biodegradability could be drawn. The DS explained that ISO 14593 describes the headspace method, which was the origin of the ready biodegradability test according to OECD 310 as well as of the inherent biodegradability test OECD 302D which mainly differ in the concentration and the adaptation of the used inoculum. In this case it can be concluded that the test described did not significantly deviate from one conducted according to OECD 310. The following information was given: 34 mg/L test substance was added to the test vessel which corresponds to 19 mg C/L. A concentration of 4 mg/L (dry substance) non-adapted activated sludge was used as the inoculum. The other MS wondered what was meant by an "8-day adaption phase" mentioned in the registration dossier while in the CLH Report it is mentioned that "As it is required for ready tests the used inoculum was not adapted in all three cases". The DS responded that the wording "8-day adaptation phase" described the lag phase at which 10 % degradation was reached. To exclude any further misunderstanding the term lag phase might be more appropriate. The third MS wanted more information on the degradation curve in order to more precisely examine the compliance the 10-day window. The degradation curve can be seen in RCOM.

Concerning the OECD 301A test, one MS pointed out that the conclusion of this test should have been "not readily degradable" because the requirement of the 10-day window was not fulfilled. Moreover, the test should have been better described because the guideline is not designed to be used with volatile substances. The DS responded by explaining that specially designed 1 litre shake flasks were used, which were filled with 500 mL mineral medium and a sufficient amount of the test substance. After closing the test flasks the remaining space results in a headspace volume of air. At the end of the test degradation exceeded 90 % but missed the 10-day window.

The DS's conclusion on the three biodegradation tests was that they did not show conflicting results because there were only small differences in terms of their kinetics, whereas the pass levels were reached in all three cases. Following later receipt of the test report for the OECD 301C (MITI I) test the DS informed RAC that this should be considered as the key study for classification purposes.

Two MS commented on the fact that there are only acute aquatic toxicity studies available and that the results were based on nominal concentrations and no analytical monitoring of test concentrations was done despite the fact that the substance is volatile (Henry's law constant 21.48 $Pa.m^3/mol$). The CLH Report does not mention whether 1,2-epoxybutane was tested in open or closed vessels, or whether the studies were carried out under static or flow-through conditions. They considered it to be impossible to evaluate the validity of the tests with the information given. One MS pointed out that there are uncertainties in the statement that the concentrations of 1,2-epoxybutane were constant in sterile controls in the biodegradation studies and thus, the concentrations are also expected to be constant in the aquatic toxicity studies. The biodegradability studies were reported to be conducted in closed systems whereas open systems seem to have been used for the acute aquatic toxicity studies. Based on the available information, it cannot be assumed that the test substance concentrations were between 80-120% of nominal throughout the study. Without further information the MS did not consider the studies to be reliable. The MS noted that 1,2-epoxubutane had been evaluated in the OECD HPV chemical assessment program where it was stated that the aquatic toxicity studies were performed in open systems. They also added a copy of ECOSAR (v1.00) predictions to the comments and in their view the substance falls within the applicability domain of the models. The predictions show higher toxicity than is reported in the CLH Report. It is of interest that the ChV value for fish is

predicted to be < 1 mg/L suggesting that 1,2-epoxybutane may have chronic aquatic toxicity effects in fish. The ChV is defined as the geometric mean of the no observed effect concentration (NOEC) and the lowest observed effect concentration (LOEC). This can be mathematically represented as CHV = 10^([log(LOEC x NOEC)]/2). Due to the limited information provided on the conditions of the aquatic toxicity studies, the MS expressed serious doubts about the reliability of the studies. One MS considered that they do not support the DS's proposal to remove the classification Aquatic Chronic 3, H412 based on the information available in the CLH report.

The DS responded that the aquatic toxicity studies are from 1988 and performed according to standards of that time and that negligible losses of the test item would be expected as indicated by the sterile control of the aforementioned biodegradation study (headspace of the OECD 301A) in which no DOC removal was observed during the 28 days test. Nevertheless, the DS agreed to support the test results with QSAR calculations (ECOSAR v1.11) for acute toxicity. The DS justified the reasons for not providing long term toxicity studies by the substance being readily biodegradable, long-term exposure not being expected and release to the environment being negligible.

Assessment and comparison with the classification criteria

Degradation

The RAC agreed with the DS proposal to consider 1,2-epoxybutane as readily/rapidly degradable based on 88 - 91 % degradation in the OECD 301C (MITI I) test.

Bioaccumulation

The RAC agreed that 1,2-epoxybutane has a low potential to bioaccumulate based on the log K_{ow} of 0.68.

Aquatic Toxicity

There is no valid experimental acute toxicity data on 1,2-epoxybutane. Despite the fact that the substance is volatile (Henry's law constant 21.48 Pa.m3/mol), the acute test results are based on nominal concentrations and no analytical monitoring of test concentrations was performed. Therefore, it cannot be assumed that the test substance concentrations were between 80-120% of nominal throughout the study, and due to the volatility of the substance the real effect values are most likely lower.

it was noted that here is no experimental chronic data available.

The RAC is of the opinion that 1,2-epoxybutane falls within the applicability domain of the EPIWIN v.4.11 models used to estimate acute toxicity and that the results are reliable and adequate to be used in a weight of evidence approach as required by CLP.

Acute QSAR values

The lowest QSAR value was an LC_{50} (96 h) of 30.1 mg/L for fish. Both the LC_{50} (48 h) value for Daphnid and the EC_{50} (96 h) value for green algae were calculated as greater than 100 mg/L.

Acute nominal tested values used in a weight of evidence evaluation
LC_{50}(96h), fish, > 100 mg/L; EC_{50}(48h), *Daphnia magna*, 70 mg/L; ECr_{50}(72h), algae, > 500 mg/L. Due to the volatility of the substance the actual effect values are most likely lower.

Conclusion on classification

1,2-Epoxybutane is considered to be readily/rapidly degradable and unlikely to bioaccumulate. Because there are no valid toxicity data, a weight of evidence approach was used when assessing aquatic toxicity. According to the acute QSAR estimates and the results from the tests without actual measured concentrations, RAC concluded that the acute toxicity is in the range of 10 to 100 mg/L ($10 < L(E)C_{50} \leq 100$ mg/L). For chronic toxicity there are no experimental data available nor are there any reliable QSAR data available.

The RAC therefore concluded that 1,2-epoxybutane does not fulfil the classification criteria according to CLP. The substance does not fulfil the criteria for Aquatic Acute Cat. 1. There are no chronic toxicity data available so the surrogate approach was used to assess the need for chronic classification. The toxicity range in Aquatic Chronic 3 is $10 < L(E)C_{50} \leq 100$ mg/L but since 1,2-epoxybutane is rapidly degradable and not bioaccumulative, no classification is warranted.

According to the DSD criteria, where classification is based on a combination of acute toxicity ($10 < L(E)C_{50} \leq 100$ mg/L) and lack of ready biodegradability 1,2-epoxybutane would not be classified either.

RAC concluded that the DS's proposal to remove the Aquatic Chronic 3 classification according to CLP and R52-53 classification according to DSD is justified.

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).