**Committee for Risk Assessment**

**RAC**

Annex 1

# Background document

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

# 1,2-epoxybutane

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

CLH-O-0000002824-72-02/A1

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**

**11 September 2013**

# CLH report

# Proposal for Harmonised Classification and Labelling

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

# Substance Name: 1,2-epoxybutane

**EC Number:** **203-438-2**

**CAS Number:** **106-88-7**

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**Version number:** **1.0**

**Date:** **April 2012**

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# Part A.

## 1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

### 1.1 Substance

**Table 1: Substance identity**

| | |
|---|---|
| **Substance name:** | *1,2-epoxybutane* |
| **EC number:** | *203-438-2* |
| **CAS number:** | *106-88-7* |
| **Annex VI Index number:** | *603-102-00-9* |
| **Degree of purity:** | *> 99.5%* |

### 1.2 Harmonised classification and labelling proposal

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

| | **Regulation (EC) No 1272/2008 (2nd ATP)** | **Directive 67/548/EEC (Dangerous Substances Directive; DSD)** |
|---|---|---|
| **Current entry in Annex VI, CLP Regulation** | Flam. Liq. 2; H225<br>Carc. 2; H351<br>Acute Tox. 4; H332<br>Acute Tox. 4; H312<br>Acute Tox. 4; H302<br>Eye Irrit. 2; H319<br>STOT SE 3; H335<br>Skin Irrit. 2; H315<br>Aquatic Chronic 3; H412 | F; R11<br>Carc. Cat. 3; R40<br>Xn; R20/21/22<br>Xi; R36/37/38<br>R52-53 |
| **Current proposal for consideration by RAC** | Removal of<br>Aquatic Chronic 3; H412 | Removal of<br>R52-53 |
| **Resulting harmonised classification (future entry in Annex VI, CLP Regulation)** | Flam. Liq. 2; H225<br>Carc. 2; H351<br>Acute Tox. 4; H332<br>Acute Tox. 4; H312<br>Acute Tox. 4; H302<br>Eye Irrit. 2; H319<br>STOT SE 3; H335<br>Skin Irrit. 2; H315 | F; R11<br>Carc. Cat. 3; R40<br>Xn; R20/21/22<br>Xi; R36/37/38 |

## 1.3 Proposed harmonised classification based on CLP Regulation and/or DSD criteria

According 67/548/EEC Annex I, the substance meets the criteria for classification as harmful to aquatic organisms, which may cause long-term adverse effects in the aquatic environment (R52-53). The main argument for the classification was the lack of data on biodegradation.

Since new experimental results show that 1,2-epoxybutane is readily biodegradable, the data gap on biodegradability of 1,2-epoxybutane is closed. Hence the database for the classification of 1,2-epoxybutane is conclusive. The hazard assessment of 1,2-epoxybutane reveals no need to classify the substance as dangerous for the environment.

**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 | | | | Conclusive but not sufficient for classification |
| **2.2.** | Flammable gases | | | | Conclusive but not sufficient for classification |
| **2.3.** | Flammable aerosols | | | | Conclusive but not sufficient for classification |
| **2.4.** | Oxidising gases | | | | Conclusive but not sufficient for classification |
| **2.5.** | Gases under pressure | | | | Conclusive but not sufficient for classification |
| **2.6.** | Flammable liquids | Flam. Liquid 2 | | Flam. Liquid 2 | |
| **2.7.** | Flammable solids | | | | Conclusive but not sufficient for classification |
| **2.8.** | Self-reactive substances and mixtures | | | | Conclusive but not sufficient for classification |
| **2.9.** | Pyrophoric liquids | | | | Conclusive but not sufficient for classification |
| **2.10.** | Pyrophoric solids | | | | Conclusive but not sufficient for classification |
| **2.11.** | Self-heating substances and mixtures | | | | Conclusive but not sufficient for classification |
| **2.12.** | Substances and mixtures which in contact with water emit flammable gases | | | | Conclusive but not sufficient for classification |
| **2.13.** | Oxidising liquids | | | | Conclusive but not sufficient for classification |
| **2.14.** | Oxidising solids | | | | Conclusive but not sufficient for classification |
| **2.15.** | Organic peroxides | | | | Conclusive but not sufficient for classification |
| **2.16.** | Substance and mixtures corrosive to metals | | | | Conclusive but not sufficient for classification |
| **3.1.** | Acute toxicity - oral | Acute Tox. 4 | | Acute Tox. 4 | |

| | | | | | |
|---|---|---|---|---|---|
| | Acute toxicity - dermal | Acute Tox. 4 | | Acute Tox. 4 | |
| | Acute toxicity - inhalation | Acute Tox. 4 | | Acute Tox. 4 | |
| **3.2.** | Skin corrosion / irritation | Skin Irrit. 2 | | Skin Irrit. 2 | |
| **3.3.** | Serious eye damage / eye irritation | Eye Irrit. 2A | | Eye Irrit. 2A | |
| **3.4.** | Respiratory sensitisation | | | | Data lacking |
| **3.4.** | Skin sensitisation | | | | Conclusive but not sufficient for classification |
| **3.5.** | Germ cell mutagenicity | | | | Conclusive but not sufficient for classification |
| **3.6.** | Carcinogenicity | Carc. Cat. 2 | | Carc. Cat. 2 | |
| **3.7.** | Reproductive toxicity | | | | Conclusive but not sufficient for classification |
| **3.8.** | Specific target organ toxicity –single exposure | STOT SE 3 | | STOT SE 3 | |
| **3.9.** | Specific target organ toxicity – repeated exposure | | | | Conclusive but not sufficient for classification |
| **3.10.** | Aspiration hazard | | | | Conclusive but not sufficient for classification |
| **4.1.** | Hazardous to the aquatic environment | none | | Aquatic Chronic 3; H412 | Conclusive but not sufficient for classification |
| **5.1.** | Hazardous to the ozone layer | | | | Data lacking |

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

**Table 4: Proposed classification according to DSD**

| Hazardous property | Proposed classification | Proposed SCLs | Current classification [1)] | Reason for no classification [2)] |
|---|---|---|---|---|
| Explosiveness | | | | Conclusive but not sufficient for classification |
| Oxidising properties | | | | Conclusive but not sufficient for classification |
| Flammability | F; R11 | | F; R11 | |
| Thermal stability | | | | Conclusive but not sufficient for classification |
| Acute toxicity | Xn; R20/21/22 | | Xn; R20/21/22 | |
| Acute toxicity – irreversible damage after single exposure | | | | Conclusive but not sufficient for classification |
| Repeated dose toxicity | | | | Conclusive but not sufficient for classification |
| Irritation / Corrosion | Xi; R36/37/38 | | Xi; R36/37/38 | |
| Sensitisation | | | | Conclusive but not sufficient for classification |
| Carcinogenicity | Carc. Cat. 3; R40 | | Carc. Cat. 3; R40 | |
| Mutagenicity – Genetic toxicity | | | | Conclusive but not sufficient for classification |
| Toxicity to reproduction – fertility | | | | Conclusive but not sufficient for classification |
| Toxicity to reproduction – development | | | | Conclusive but not sufficient for classification |
| Toxicity to reproduction – breastfed babies. Effects on or via lactation | | | | Data lacking |
| Environment | none | | R52-53 | Conclusive but not sufficient for classification |

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

# 2 BACKGROUND TO THE CLH PROPOSAL

This proposal has been prepared by BASF SE in accordance with Article 37(6) of CLP Regulation and submitted by the DE-MSCA.

REACH registrations available on 12/03/2012 have been considered by the MSCA.

## 2.1 History of the previous classification and labelling

The existing classification R 52/53 has been added to Annex I of Directive 67/548/EEC in 1998 by the 25th ATP. The classification was discussed at the TC C&L meeting held from 10th-12th September 1997 (ECBI/48/97- Rev.1). The main argument for the classification was the lack of data on biodegradation.

## 2.2 Short summary of the scientific justification for the CLH proposal

Since new experimental results show that 1,2-epoxybutane is readily biodegradable, the data gap on biodegradability of 1,2-epoxybutane is closed. Hence the database for the classification of 1,2-epoxybutane is conclusive. The hazard assessment of 1,2-epoxybutane reveals no need to classify the substance as dangerous for the environment.

## 2.3 Current harmonised classification and labelling

**Table 5:** Current classification in Annex VI, Table 3.1 in the CLP Regulation

| Index number | Classification | | Labelling | | |
|---|---|---|---|---|---|
| | **Hazard Class and Category Code(s)** | **Hazard Statement Code(s)** | **Pictogram, Signal Word Code(s)** | **Hazard statement Code(s)** | **Suppl. Hazard statement Code(s)** |
| 603-102-00-9 | Flam. Liq. 2<br>Carc. 2<br>Acute Tox. 4 *<br>Acute Tox. 4 *<br>Acute Tox. 4 *<br>Eye Irrit. 2<br>STOT SE 3<br>Skin Irrit. 2<br>Aquatic Chronic 3 | H225<br>H351<br>H332<br>H312<br>H302<br>H319<br>H335<br>H315<br>H412 | GHS02<br>GHS08<br>GHS07<br>**Dgr** | H225<br>H351<br>H332<br>H312<br>H302<br>H319<br>H335<br>H315<br>H412 | |

**Table 6: Current classification in Annex VI, Table 3.2 in the CLP Regulation**

| Index number | Classification | Labelling |
|---|---|---|
| 603-102-00-9 | F; R11<br>Carc. Cat. 3; R40<br>Xn; R20/21/22<br>Xi; R36/37/38<br>R52-53 | F; Xn<br>R: 11-20/21/22-36/37/38-40-52/53<br>S: (2-)9-16-29-36/37-61 |

# 3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

According to 67/548/EEC Annex I, the substance meets the criteria for classification as harmful to aquatic organisms, which may cause long-term adverse effects in the aquatic environment (R52-53). The main argument for the classification was the lack of data on biodegradation. Since new experimental results show that 1,2-epoxybutane is readily biodegradable, the data gap on biodegradability of 1,2-epoxybutane is closed. Hence the database for the classification of 1,2-epoxybutane is conclusive. The hazard assessment of 1,2-epoxybutane reveals no need to classify the substance as dangerous for the environment.

# Part B.

## SCIENTIFIC EVALUATION OF THE DATA

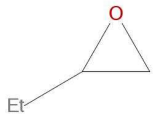
## 1 IDENTITY OF THE SUBSTANCE

### 1.1 Name and other identifiers of the substance

**Table 7: Substance identity**

| | |
|---|---|
| **EC number:** | 203-438-2 |
| **EC name:** | 1,2-epoxybutane |
| **CAS number:** | 106-88-7 |
| **CAS name:** | Oxirane, ethyl- |
| **IUPAC name:** | 2-ethyloxirane |
| **CLP Annex VI Index number:** | 603-102-00-9 |
| **Molecular formula:** | C4H8O |
| **Molecular weight range:** | 72.1057 g/mol |

**Structural formula:**



## 1.2 Composition of the substance

### Table 8: Constituents

| Constituent | Typical concentration | Concentration range | Remarks |
|---|---|---|---|
| 1,2-epoxybutane<br>EC No: 203-438-2 | See confidential annex | See confidential annex | |

### Table 9: Impurities

| Impurity | Typical concentration | Concentration range | Remarks |
|---|---|---|---|
| See confidential annex | | | |

### Table 10: Additives

| Additive | Function | Typical concentration | Concentration range | Remarks |
|---|---|---|---|---|
| See confidential annex | | | | |

## 1.3 Physico-chemical properties

**Table 11: 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 | [16] GESTIS (2008) | literature |
| Melting/freezing point | - 129.5 °C | [1] BASF AG (1976) | measured |
| Boiling point | 63.4 °C | [2] BASF AG (1986) | measured |
| Relative density | 0.83 g/cm3 | [3] BASF AG (1986) | measured |
| Vapour pressure | 227 hPa | [4] BASF AG (1986) | measured |
| Surface tension | not surface active | | expert judgement |
| Water solubility | 86.8 g/L at 25 °C | [5] BASF AG (1981) | measured |
| Partition coefficient n-octanol/water | 0.68 at 25 °C | [6] BASF AG (1988) | measured |
| Flash point | -25.5 °C | [7] BASF AG (1974) | measured |
| Flammability | highly flammable | | expert judgement |
| Explosive properties | non explosive | | expert judgement |
| Self-ignition temperature | 370°C | [7] BASF AG (1974) | |
| Oxidising properties | no oxidising properties | | expert judgement |
| Granulometry | Substance is marketed or used in a non solid or granular form. | | expert judgement |
| Stability in organic solvents and identity of relevant degradation products | The stability of the substance is not considered as critical. | | expert judgement |
| Dissociation constant | The substance does not contain any ionic structure. | | expert judgement |
| Viscosity | 0.42 mPa_s at 20°C | | estimated |

# 2 MANUFACTURE AND USES

## 2.1 Manufacture

Confidential Information

## 2.2 Identified uses

Production of 1,2-epoxybutane

Mixing into a formulation

Industrial use as intermediate for the synthesis of other substances

Industrial use as monomer in a polymerization process

Industrial use as monomer in a polymerization process of down stream users

# 3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Not relevant for this dossier.

# 4 HUMAN HEALTH HAZARD ASSESSMENT

Not relevant for this dossier.

# 5 ENVIRONMENTAL HAZARD ASSESSMENT

## 5.1 Degradation

**Table 12: Summary of relevant information on degradation**

| Method | Results | Remarks | Reference |
|---|---|---|---|
| Photodegradation (EPIWin, AOP v1.92) | degraded slowly by photochemical processes | | [8] BASF AG (2007) |
| Hydrolyses (measured) | hydrolyse slowly | | [9] Gervasi et al. (1985) |
| Biodegradation (ISO 14593) | readily biodegradable (80-90 % CO2 evolution) | | [10] BASF AG (2000) |
| Biodegradation (OECD 301 C) | Readily biodegradable (>= 100 % O2 consumption) | | [15] MITI (1997) |
| Biodegradation (OECD 301A) | readily biodegradable, but missing the 10 day window (90 % DOC removal) | | [11] Dow Chemical Company (1999) |

### 5.1.1 Stability

After evaporation or exposure to the atmosphere, the substance is expected to photodegrade by reaction with OH-radicals with a half-life of about 8.8 days (EPIWin, AOP v1.92) [8]. In contact with water the substance will hydrolyse slowly [9].

### 5.1.2 Biodegradation

#### 5.1.2.1 Biodegradation estimation

#### 5.1.2.2 Screening tests

The biodegradability of 1,2-epoxybutane was investigated in several studies. 1,2-epoxybutane is readily biodegradable in a headspace test according to ISO guideline 14593 and in a MITI test according to OECD guideline 301C. After 28 days the measured degradation was 80 - 90 % carbon dioxide evolution and ca. 100 % oxygen consumption respectively [10, 15]. Additionally the substance was readily biodegradable in a DOC-Die-Away test, but missing the 10 day window [11].

#### 5.1.2.3 Simulation tests

No data available.

### 5.1.3 Summary and discussion of degradation

The substance is readily biodegradable according to OECD-criteria.

## 5.2 Environmental distribution

Not relevant for this dossier.

## 5.3 Aquatic Bioaccumulation

### 5.3.1 Aquatic bioaccumulation

Not relevant for this dossier.

### 5.3.2 Summary and discussion of aquatic bioaccumulation

Regarding the 1-octanol/water partition coefficient, accumulation of the test substance in organisms is not to be expected.

## 5.4 Aquatic toxicity

**Table 13: Summary of relevant information on aquatic toxicity**

| Method | Results | Remarks | Reference |
|---|---|---|---|
| Short-term toxicity to fish (DIN 38412) | LC50 (96h) > 100 mg/L | | [12] BASF AG (1988) |
| Short-term toxicity to aquatic invertebrates (EU Directive 84/449/EEC, C2) | EC50 (48h) = 70 mg/L | | [13] BASF AG (1988) |
| Toxicity to aquatic algae (DIN 38412) | EC50 (72h) > 500 mg/L | | [14] BASF AG (1989) |

### 5.4.1 Fish

#### 5.4.1.1 Short-term toxicity to fish

In an acute fish test according to German national standards (DIN 38412), the LC50 (96h) for *Leuciscus idus* was determined to be > 100 mg/L 1,2-epoxybutane [12].

#### 5.4.1.2 Long-term toxicity to fish

No data available.

### 5.4.2 Aquatic invertebrates

#### 5.4.2.1 Short-term toxicity to aquatic invertebrates

The toxicity of 1,2-epoxybutane on *Daphnia magna* was tested in an acute toxicity test [13]. The EC50 (48h) determined to be 70 mg/L.

#### 5.4.2.2 Long-term toxicity to aquatic invertebrates

No data available.

### 5.4.3 Algae and aquatic plants

The toxicity of 1,2-epoxybutane on the green algae *Selenastrum capricornutum* was measured in a test according to German national standards (DIN38412) [14]. The EC50 (72h) for the growth rate determined to be > 500 mg/L.

### 5.4.4 Other aquatic organisms (including sediment)

No data available.

## 5.5 Comparison with criteria for environmental hazards (sections 5.1 – 5.4)

1,2-Epoxybutane was found to be rapidly degradable, not bioaccumulative and acute toxic to aquatic invertebrates (EC50 (48h) > 10 ≤ 100 mg/L). No chronic toxicity data were available.

## 5.6 Conclusions on classification and labelling for environmental hazards (sections 5.1 – 5.4)

1,2-Epoxybutane does not fulfil the criteria for environmental hazards (according to DSD and CLP Regulation). The existing classification, Aquatic Chronic 3 (R52/53), should be removed.

**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 25$^{th}$ 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* | DIN 38412, Part | static | $ECr_{50}$ 72h>500 |

| | | | |
|---|---|---|---|
| *subspicatus* | 9, cell multiplication inhibitory test , non-GLP | | 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.

## Additional key elements

Aquatic toxicity

The DS submitted QSAR estimates on acute toxicity and one MS provided calculations on chronic endpoints. The calculations were updated with the most current version of the program by the RAC.
The ECOSAR v1.11 (in EPIWIN v4.11) gives the following class specific estimates to 1,2-epoxybutane:

| | Organism | Duration | End point | mg/L (ppm) | N (x+y)** | $r^{2***}$ |
|---|---|---|---|---|---|---|
| Epoxides, mono | Fish | 96-hr | LC50 | 30.124 | 7+2 | 0.9457 |
| Epoxides, mono | Daphnid | 48-hr | LC50 | 106.794 | 4+2 | 0.9677 |
| Epoxides, mono | Green algae | 96-hr | EC50 | 154.647 | 3+1 | 0.9784 |
| Epoxides, mono | Fish | | ChV | 0.012 | 2+1 | 0.847 |
| Epoxides, mono | Daphnid | | ChV | 10.551(* | 0+2 | |
| Epoxides, mono | Green algae | | ChV | 70.560 | 1+1 | N/A |

*estimation through application of acute-to-chronic ratio
** x= number of studies used in actual equation development y= neutral organic cut off data point and/or SAR Data not included in Regression Equation
*** Coefficient of Determination

The QSAR Methodology used in the opinion is ECOSAR v.1.11 Class-specific Estimations (U.S.EPA). The SARs in ECOSAR express correlations between a compound's physicochemical properties and its toxicity within specific chemical classes. SARs are based on measured toxicity data.

1,2-epoxybutane is a directly acting electrophile. Due to this property, 1,2-epoxybutane is likely to be toxic at lower concentrations than chemicals that act by narcosis and consequently QSARs based on neutral organic SAR are not suitable for the substance. The ECOSAR QSAR Class used for this substance is Epoxides, mono. The SAR equations used to estimate toxicity are based on measured toxicity data on substances of the same chemical class.

In Deneer et al. (1988) a QSAR equation combining log P (octanol-water coefficient) and log $k_1$ (pseudo first-order reaction rate constant towards 4-nitrobenzylpyridine ($day^{-1}$)) was tested (N=12, R=0.945, s (standard error of estimate) = 0.27). The 14 day $LC_{50}$ calculated using this equation was 23.9 mg/L. The tested 14-day semi-static $LC_{50}$ to the guppy was 33.0 mg/L. This equation gives an estimate of the same magnitude as the ECOSAR Epoxides, mono equation estimate showing that the electrophilic nature of the substance is taken into account also in the ECOSAR estimation.

For acute toxicity there are more data points to derive the equation than for chronic toxicity. Also the coefficient of determination (r) for acute toxicity for fish, daphnia and algae are much higher than for chronic toxicity for fish. For chronic toxicity to daphnia and algae no coefficient of determination could even be determined. Since there are only two studies on which to base the chronic fish equation, and since the properties of the substance tested (molecular weight 330, log $K_{ow}$ 2.8) are different from the properties of 1,2-epoxybutane (molecular weight 72.11, log $K_{ow}$ 0.86), it is unlikely that the equation used would be suitable for 1,2-epoxybutane.

References:
Deneer, J.W., Sinnige, T.L., Seinen, W. & Hermens, J.L.M. 1988. A quantitative structure-activity relationship for the acute toxicity of some epoxy compounds to the guppy. Aquatic Toxicology, 13(1988) 195-204.

Methodology Document for the ECOlogical Structure-Activity Relationship Model (ECOSAR) Class Program. MS-Windows Version 1.11. May 2012. http://www.epa.gov/oppt/newchems/tools/ecosartechfinal.pdf

Biodegradation

Additional information provided by the DS on the OECD 301C (MITI I) test:

Amount of test substance: 100 mg/L
Amount of reference substance: 100 mg/L
Activated sludge: 30 mg/L
Kinetic based on oxygen consumption:

| | Degradation % (BOD) | | | |
|---|---|---|---|---|
| | day 7 | day 14 | day 21 | day 28 |
| reference control (1): sludge + aniline | 69.1 | 101.5 | 111.7 | 112.1 |
| sterile control (2): water + test substance | 0 | 0 | 0 | 0 |
| test vessel (3): sludge + test substance | 5.4 | 38.8 | 68.5 | 88.9 |
| test vessel (4): sludge + test substance | 12.0 | 39.0 | 69.6 | 89.7 |
| test vessel (5): sludge + test substance | 12.4 | 40.6 | 70.9 | 91.5 |
| control blank (6) | 3.3 | 6.7 | 9.4 | 10.7 |

The degradation curve can be seen in the RCOM.

## 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 ($10 < L(E)C50 \leq 100$ 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 $10 < L(E)C50 \leq 100$ 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.

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