# CLH report

# Proposal for Harmonised Classification and Labelling

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

# International Chemical Identification:

# Reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis((2,3-epoxypropoxy)methyl)butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane

**EC Number:** -

**CAS Number:** -

**Index Number:** **603-RST-VW-Y**

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**Version number: 05** **Date: 20 March 2020**

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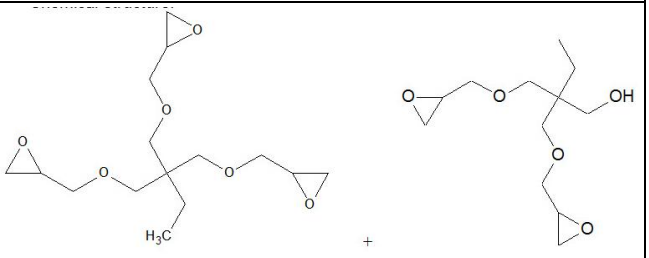
# 1 IDENTITY OF THE SUBSTANCE

## 1.1 Name and other identifiers of the substance

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

| | |
|---|---|
| **Name(s) in the IUPAC nomenclature or other international chemical name(s)** | Reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis((2,3-epoxypropoxy)methyl)butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane |
| **Other names (usual name, trade name, abbreviation)** | 1,3-Propanediol, 2-ethyl-2- (hydroxymethyl)-, oligomeric reaction product with (chloromethyl)oxirane, Denacol EX321, trimethylolpropane triglycidylether, TK30174, Araldite DY-T/CH, |
| **ISO common name (if available and appropriate)** | Not applicable |
| **EC number (if available and appropriate)** | - |
| **EC name (if available and appropriate)** | Reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis ((2,3-epoxypropoxy)methyl) butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane |
| **CAS number (if available)** | - |
| **Other identity code (if available)** | - |
| **Molecular formula of the constituents** | $C_{15}H_{26}O_6$; $C_{12}H_{22}O_5$ |
| **Structural formula of the constituents** |  |
| **SMILES notation (if available)** | Multi-constituent substance |
| **Molecular weight or molecular weight range** | Multi-constituent substance |
| **Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)** | Confidential information |
| **Description of the manufacturing process and identity of the source (for UVCB substances only)** | Not relevant |
| **Degree of purity (%) (if relevant for the entry in Annex VI)** | Not relevant |

## 1.2 Composition of the substance

**Table 2: Constituents (non-confidential information)**

| Constituent (Name and numerical identifier) | Concentration range (% w/w minimum and maximum in multi-constituent substances) | Current CLH in Annex VI Table 3.1 (CLP) | Current self-classification and labelling (CLP) |
|---|---|---|---|
| **1-(2,3-epoxypropoxy)-2,2-bis[(2,3-epoxypropoxy) methyl]butane [$C_{15}H_{26}O_6$]**<br><br>**CAS number: 3454-29-3**<br>**EC number: 222-384-0** | See confidential annex | No harmonised classification available | Skin Irrit. 2 H315<br>Skin Sens. 1 H317<br>Eye Irrit. 2 H319<br>Aquatic Chronic 3 H412<br>(number of notifiers: 45) |
| **1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxy butane [$C_{12}H_{22}O_5$]**<br><br>**CAS number: 18425-64-4**<br>**EC number: -** | See confidential annex | No harmonised classification available | Not listed in ECHA C&L (2019) |

The following self-classification has been provided by the registrant for the reaction mass of 1-(2,3-epoxy-propoxy)-2,2-bis ((2,3-epoxypropoxy)methyl) butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy) methyl)-2-hydroxymethyl butane :

- Skin Corr. 1C (H314: Causes severe skin burns and eye damage)
- Eye Damage 1 (H318: Causes serious eye damage)
- Skin Sens. 1B (H317: May cause an allergic skin reaction)
- Repr. 1B (H360F: May damage fertility or the unborn)
- Muta. 2 (H341: Suspected of causing genetic defects by oral route)
- Aquatic Acute 2 (H401: Toxic to aquatic life)
- Aquatic chronic 2 (H411: Toxic to aquatic life with long lasting effects)

**Table 3: Impurities (non-confidential information) if relevant for the classification of the substance**

| Impurity (Name and numerical identifier) | Concentration range (% w/w minimum and maximum) | Current CLH in Annex VI Table 3.1 (CLP) | Current self-classification and labelling (CLP) | The impurity contributes to the classification and labelling |
|---|---|---|---|---|
| Confidential information | | | | |

**Table 4: Additives (non-confidential information) if relevant for the classification of the substance**

| Additive (Name and numerical identifier) | Function | Concentration range (% w/w minimum and maximum) | Current CLH in Annex VI Table 3.1 (CLP) | Current self-classification and labelling (CLP) | The additive contributes to the classification and labelling |
|---|---|---|---|---|---|
| No information on additives available | | | | | |

**Table 5: Test substances (non-confidential information)**

| Identification of test substance | Purity | Impurities and additives (identity, %, classification if available) | Other information | The study(ies) in which the test substance is used |
|---|---|---|---|---|
| Reaction mass of 1-(2,3-epoxy-propoxy)-2,2-bis((2,3-epoxy-propoxy) methyl)-butane and 1-(2,3-epoxy-propoxy) -2-((2,3-epoxy-propoxy) -methyl)-2-hydroxy-methyl butan | 100% | - | Clear colorless liquid; Test Substance Molecular Weight: 246.3 – 302.37 g/mol (Molecular weight of 302.37 was used for calculation of dose level) | Unnamed (2014a) (ECHA Dissemination, 2019) (OECD 471) |
| Reaction mass of 1-(2,3-epoxy-propoxy)-2,2-bis((2,3-epoxy-propoxy) methyl)-butane and 1-(2,3-epoxy-propoxy) -2-((2,3-epoxy-propoxy) -methyl)-2-hydroxy-methyl butan | 100% | - | Clear colorless liquid; Test Substance Molecular Weight: 246.3 – 302.37 g/mol (Molecular weight of 302.37 was used for calculation of dose level) | Unnamed (2014b) (ECHA Dissemination, 2019) (OECD 473) |
| Reaction mass of 1-(2,3-epoxy-propoxy)-2,2-bis((2,3-epoxy-propoxy) methyl)-butane and 1-(2,3-epoxy-propoxy) -2-((2,3-epoxy-propoxy) -methyl)-2-hydroxy-methyl butan | 100% | - | Clear colorless liquid; Test Substance Molecular Weight: 246.3 – 302.37 g/mol (Molecular weight of 302.37 was used for calculation of dose level) | Unnamed (2014c) (ECHA Dissemination, 2019) (OECD 476) |
| Reaction mass of 1-(2,3-epoxy-propoxy)-2,2-bis((2,3-epoxy-propoxy) methyl)-butane and 1-(2,3-epoxy-propoxy) -2-((2,3-epoxy-propoxy) -methyl)-2-hydroxy-methyl butan | - | - | Liquid | Unnamed (2017) (ECHA Dissemination, 2019) (OECD 489) |
| Reaction mass of 1-(2,3-epoxy-propoxy)-2,2-bis((2,3-epoxy-propoxy) methyl)- | - | Main components: 58% $C_{15}H_{26}O_6$ and 25% $C_{12}H_{22}O_5$ | Clear colorless liquid | Unnamed (2015a) (ECHA Dissemination, 2019) |

| **Identification of test substance** | **Purity** | **Impurities and additives (identity, %, classification if available)** | **Other information** | **The study(ies) in which the test substance is used** |
|---|---|---|---|---|
| butane and 1-(2,3-epoxy-propoxy) -2-((2,3-epoxy-propoxy) -methyl)-2-hydroxy-methyl butan | | | | (OECD 422) |
| Reaction mass of 1-(2,3-epoxy-propoxy)-2,2-bis((2,3-epoxy-propoxy) methyl)-butane and 1-(2,3-epoxy-propoxy) -2-((2,3-epoxy-propoxy) -methyl)-2-hydroxy-methyl butan | - | - | - | Unnamed (2015b)<br>(ECHA Dissemination, 2019)<br>(study on fertility) |

# 2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

## 2.1 Proposed harmonised classification and labelling according to the CLP criteria

**Table 6:**

| | Index No | International Chemical Identification | EC No | CAS No | Classification | | Labelling | | | Specific Conc. Limits, M-factors | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Hazard Class and Category Code(s) | Hazard statement Code(s) | Pictogram, Signal Word Code(s) | Hazard statement Code(s) | Suppl. Hazard statement Code(s) | | |
| Current Annex VI entry | Not applicable | | | | | | | | | | |
| Dossier submitters proposal | 603-RST-VW-Y | Reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis ((2,3-epoxypropoxy) methyl) butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy) methyl)-2-hydroxy-methyl butane | - | - | Mutagenicity Cat. 2<br>Reproductive Toxicity Cat. 1B | H341<br>H360F | GHS08<br>Dgr | H341<br>H360F | | - | - |
| Resulting Annex VI entry if agreed by RAC and COM | 603-RST-VW-Y | Reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis ((2,3-epoxypropoxy) methyl) butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy) methyl)-2-hydroxy-methyl butane | - | - | Mutagenicity Cat. 2<br>Reproductive Toxicity Cat. 1B | H341<br>H360F | GHS08<br>Dgr | H341<br>H360F | | - | - |

**Table 7: Reason for not proposing harmonised classification and status under public consultation**

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

# 3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

There is no harmonised classification and labelling available for the reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis((2,3-epoxypropoxy)methyl)butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane. The substance has not been included in former activities on harmonised classification.

# 4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

There is no requirement for justification that action is needed at Community level.

The substance has CMR properties (reproductive toxicity). Harmonised classification and labelling for CMR is a community-wide action under article 36 of the CLP regulation.

# 5 IDENTIFIED USES

On the ECHA website the use of the reaction mass in inks and toners, in printing and recorded media reproduction as well as in adhesives and sealants is mentioned (ECHA Dissemination, 2019).

# 6 DATA SOURCES

The REACH registration dossier for the reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis((2,3-epoxypropoxy)methyl)butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane (last modified: 3 October 2019) available from ECHA's disseminated database (ECHA Dissemination, 2019) has been analysed for study references, which then have been considered as data sources for this CLH report. Additionally, the original study reports for the genotoxicity studies *in vitro* according to OECD Test Guidelines 471, 473 and 476 and *in vivo* according to OECD Test Guideline 489 as well as the study reports of the Combined Repeat Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test in rats according to OECD 422 and the Investigative Oral (Gavage) Reproduction Study in rats were available for evaluation.

Furthermore, ECHA guidance documents on the application of CLP criteria and on the preparation of dossiers for harmonised classification and labelling were used to compile this report (ECHA, 2014; 2017).

Systematic searches for publications and other relevant data were performed based on the following databases:

- U.S. National Library of Medicine, Pubmed.gov
- TOXNET, ChemIDplus, IPCS, eChemPortal
- Medline, SciSearch, Biosis, PQscitech, Chemical Abstracts (HCA), Embase (at host STN International)

All data sources used in this report are also listed in section 15 or Annex I (references).

# 7 PHYSICOCHEMICAL PROPERTIES

## Table 8: Summary of physicochemical properties

| Property | Value | Reference | Comment (e.g. measured or estimated) |
|---|---|---|---|
| **Physical state at 20°C and 101,3 kPa** | Clear colourless viscous liquid | (ECHA Dissemination, 2019) | Visual observation, at 20 °C and at 101.3 kPa |
| **Melting/freezing point** | < - 20 °C (< 253 K) | (ECHA Dissemination, 2019) | Measured, at 101.3 kPa |
| **Boiling point** | ~350 °C | (ECHA Dissemination, 2019) | Measured, at 101.4 to 101.6 kPa, boiling and/or thermal decomposition observed |
| **Relative density** | 1.12 | (ECHA Dissemination, 2019) | Measured, at 20 °C |
| **Vapour pressure** | 0.01 Pa | (ECHA Dissemination, 2019) | Measured, at 25 °C |
| **Surface tension** | 51.4 mN/m | (ECHA Dissemination, 2019) | Measured, at 1 g/L and 21.8 °C |
| **Water solubility** | 2.73 g/L | (ECHA Dissemination, 2019) | Measured, at 20 °C and pH 7.2 - 7.3 |
| **Partition coefficient n-octanol/water** | 2.93 – 2530 | (ECHA Dissemination, 2019) | Measured |
| **Flash point** | 172 °C | (ECHA Dissemination, 2019) | Measured, at 101.3 kPa |
| **Flammability** | Non-flammable | (ECHA Dissemination, 2019) | Study scientifically not necessary |
| **Explosive properties** | Non explosive | (ECHA Dissemination, 2019) | Waived based on structural assessment of the substance |
| **Self-ignition temperature** | 304 °C | (ECHA Dissemination, 2019) | Measured, at 101.3 kPa |
| **Oxidising properties** | Non oxidising | (ECHA Dissemination, 2019) | Waived based on structural assessment of the substance |
| **Granulometry** | No data | (ECHA Dissemination, 2019) | The substance is a viscous liquid and uses do not generate particles; therefore the study is waived |
| **Stability in organic solvents and identity of relevant degradation products** | No data | (ECHA Dissemination, 2019) | Data waiver: In accordance with Column 1 of REACH, Annex IX the test (required in Section 7.15.) does not need to be conducted based on the findings of the Chemical Safety Assessment and stability of the substance is not considered to be critical. |
| **Dissociation constant** | 14.52 | (ECHA Dissemination, 2019) | Estimated with software |

| Property | Value | Reference | Comment (e.g. measured or estimated) |
|---|---|---|---|
| **Viscosity** | 195 mm²/s | (ECHA Dissemination, 2019) | Measured, at 20 °C |

# 8 EVALUATION OF PHYSICAL HAZARDS

Not performed for this substance.

# 9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

There are no data on toxicokinetics of the reaction mass to be evaluated.

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

In the registration dossier toxicokinetic data for trimethylolpropane phosphate (TMPP; 4-ethyl-1-oxo-2,6,7-trioxa-1-phospho-bicyclo[2.2.2]octane) are reported. The registrant states that TMPP is representative for the registration substance as the substance of toxicological interest of the reaction mass to be evaluated is trimethylolpropane "*and therefore trimethylolpropane phosphate is considered as a suitable surrogate to understand toxicokinetic processes*". No further information was provided to support the statement that trimethylolpropane is the toxicological active metabolite of the reaction mass.

The two constituents of the reaction mass ((1-(2,3-epoxypropoxy)-2,2-bis[(2,3-epoxypropoxy) methyl]butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane)) are bi- or tri-ethers of 1,1,1-trimethylolpropane (2-ethyl-2-(hydroxymethyl)-1,3-propandiol; CAS No. 77-99-6) and glycidol (2,3-epoxypropan-1-ol; CAS No. 556-52-5 (racemate), CAS No. 57044-25-4 (*(R)*-isomer), CAS No. 60456-23-7 (*(S)*-isomer); no information available if the racemate or only one of the isomers was used). The registrants' statement that the substance of toxicological interest is trimethylolpropane implies that the constituents of the reaction mass are hydrolysed under physiological conditions resulting in the formation of 1,1,1-trimethylolpropane (2-ethyl-2-(hydroxymethyl)-1,3-propandiol; CAS No. 77-99-6) and glycidol (2,3-epoxypropan-1-ol). However, there are no experimental data available supporting this hypothesis. Additionally, there is no information where and to what extent the hydrolysis takes part. No information exists if hydrolysis already happens in the gastrointestinal tract or after absorption in the central compartment. Therefore, it remains unknown if and to what extent the postulated hydrolysis products are formed and if they reach (toxicological) relevant concentrations under physiological conditions. As glycidol might be a relevant active metabolite of the reaction mass which is classified *inter alia* as Muta. 2 (H341), Carc. 1B (H350) and Repro. 1B (H360F) (ECHA C&L Inventory, 2019) further investigations on possible metabolites and hydrolysis products of the reaction mass would be desirable.

The results of the kinetic investigations with TMPP could be summarised as following: After a single intraperitoneal application of [14C]TMPP (0.25 mg/kg (1 mCi)) in rats peak blood concentrations of 1.6 mg/ml were reached within 20 minutes after injection. Within 35 minutes after administration rapid clearance was observed resulting in a blood concentration of 0.1 mg/ml. For the the next 5 hr, TMPP concentrations in the blood remained relatively constant, at approximately 0.1 mg/ml.

The highest substance concentrations were measured in the kidney (780 ng/g of wet weight) 30 minutes after administration. Progressively lower concentrations have been detected in liver, spleen, heart, brain and peritoneal fat. The highest concentrations in the brain were found in the cerebellum (420 ±15 ng/g), the differences among brain regions were not statistically significant.

The substance is excreted via urine and faeces. Approximately 20% of the total administered [14C]TMPP dose was recovered from the excreted urine within 30 minutes after administration. Within 30 hr after injection ca. 83% of the total administered TMPP was recovered in the excreted urine and faeces. Within 100 hr after administration >99.5% of the administered TMPP was recovered.

The bioaccumulation potential of TMPP seems to be very low, as no statistically significant differences in TMPP concentrations were detected in any of the analysed tissue compartments of rats sacrificed 24 hr after a single TMPP injection, compared with those sacrificed 24 hr after the series of five daily injections.

After a single oral gavage administration of [14C]TMPP (1mCi) in rats a concentration of 100 mg TMPP/ml of blood was reached within 15 min after oral gavage, with a mean concentration that remained relatively constant throughout the next 6 hr. 99.5% of the TMPP dose was recovered in the excreted urine and faeces within 72 hr after gavage.

No *in vivo* metabolic transformation has been observed. In urine, faeces and bile of TMPP-treated rats, and in *in vitro* incubations of TMPP with microsomes, only unchanged TMPP was detected (ECHA Dissemination, 2019; Rossi, et al., 1998).

The relevance of the TMPP kinetic data for the reaction mass to be evaluated is unclear. TMPP is judged by the registrant to be similar to the metabolite of toxicological interest, 1,1,1-trimethylolpropane. However, the reaction mass to be evaluated also consists of larger molecules, glycidylethers of trimethylolpropane. The different sizes might influence the absorption parameters. Assuming that hydrolysis of the reaction mass constituents already takes place in relevant amounts in the gastrointestinal tract and taking the data on TMPP as a worst-case scenario, complete and rapid absorption of the reaction mass to be evaluated via oral route can be assumed. Further, no bioaccumulation potential has been assumed in the registration dossier, on basis of the TMPP data, which revealed that 99.5% of the TMPP dose was recovered in the excreted urine and faeces within 72 hr after gavage. Under these assumptions the bioaccumulation potential of the reaction mass also seems to be low. However, in the absence of relevant information on the extent of hydrolysis and the

amount and relevance of the possible metabolite glycidol there remain some uncertainties on the toxicokinetics of the reaction mass.

# 10 EVALUATION OF HEALTH HAZARDS

## Acute toxicity

### 10.1 Acute toxicity - oral route

Evaluation not performed for this substance.

### 10.2 Acute toxicity - dermal route

Evaluation not performed for this substance.

### 10.3 Acute toxicity - inhalation route

Evaluation not performed for this substance.

### 10.4 Skin corrosion/irritation

Evaluation not performed for this substance.

### 10.5 Serious eye damage/eye irritation

Evaluation not performed for this substance.

### 10.6 Respiratory sensitisation

Evaluation not performed for this substance.

### 10.7 Skin sensitisation

Evaluation not performed for this substance.

### 10.8 Germ cell mutagenicity

**Table 9: Summary table of mutagenicity/genotoxicity tests *in vitro***

| Method, guideline, deviations if any | Test substance, | Relevant information about the study including rationale for dose selection (as applicable) | Observations | Reference |
|---|---|---|---|---|
| Bacterial gene mutation<br>OECD TG 471<br>Deviations: | Reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis((2,3-epoxypropoxy) methyl) butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy) | Salmonella typhimurium TA 1535, TA1537, TA 98, TA 100 and E. coli WP2 uvrA<br>Plate incorporation - Initial toxicity-mutation assay (n=2): 1.5, 5.0, 15, 50, 150, 500, 1500 and 5000 µg/plate with or without S9-mix | Positive in strains TA 100 and TA 1535 (+/- S9 mix) and in strain WP2 uvrA in the presence of S9 mix: positive results ranging from 4.3- to 68.6-fold maximum | Unnamed (2014a)<br>(ECHA Dissemination, 2019) |

| Method, guideline, deviations if any | Test substance, | Relevant information about the study including rationale for dose selection (as applicable) | Observations | Reference |
|---|---|---|---|---|
| no<br>Ames Test<br>GLP: yes<br>RL1[#] (according to registration dossier and the authors of this document) | methyl)-2-hydroxymethyl butane (Purity: 100%) | Plate incorporation – confirmation assay (all strains; n=3): 50, 150, 500, 1500 and 5000 µg/plate with and without S9-mix<br>Tested up to limit concentration<br>+/- S9 mix from from Aroclor 1254 induced rat liver<br>Positive controls: yes<br>Vehicle: DMSO | increases and ranging from 4.2- to 93.9-fold maximum increases in the initial toxicity mutation assay and the confirmatory assay, respectively. Neither precipitate nor toxicity was observed (no further details provided in the public available registration dossier). | |
| Chromosome aberration study in mammalian cells<br>OECD TG 473<br>Deviations: no<br>GLP: yes<br>RL1 (according to registration dossier and the authors of this document) | Reaction mass of 1-(2,3-epoxy-propoxy)-2,2-bis((2,3-epoxy-propoxy) methyl)-butane and 1-(2,3-epoxy-propoxy) -2-((2,3-epoxy-propoxy) -methyl)-2-hydroxy-methyl butane (Purity: 100%) | Chinese hamster ovary (CHO-K1) cells<br>Preliminary toxicity assay: 0.302 to 3020 µg/mL (10 mM))<br>Assay 1:<br>4-h treatment with and without S9-mix, 20 h fixation time:<br>concentrations: 15 to 150 µg/mL without MA[##]; 50 to 350 µg/mL with MA;<br>Assay 2:<br>20-h treatment without S9-mix, 20 h fixation time:<br>concentrations: 5 to 50 µg/mL<br>+/- S9 mix from Aroclor induced rat liver<br>Positive controls: yes<br>Concentrations for Assay 1 and Assay 2 selected on basis of the cytotoxicity assay (no details provided)<br>Vehicle: DMSO | Positive (+/- S9 mix):<br>statistically significant and dose-dependent increases in structural aberrations in treatment groups with or without S9-mix.<br>Number of polyploid cells and cells with endoreduplicated chromosomes not affected. | Unnamed (2014b)<br>(ECHA Dissemination, 2019) |
| Gene mutation study in mammalian cells<br>OECD TG 476<br>Deviations: yes | Reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis((2,3-epoxy-propoxy)-methyl)-butane and 1-(2,3-epoxy-propoxy)-2-((2,3-epoxy-propoxy)-methyl)-2-hydroxy-methyl butane (Purity: | Chinese hamster ovary (CHO) cells (CHO-K1-BH4 cells)<br>Target gene: HPRT locus<br>Preliminary toxicity assay: no details provided<br>Assay 1:<br>(treatment (duration confidential) with MA): 50.0, **100, 200, 300, 350**, 400, | Positive (+/- S9 mix).<br>The average relative survival was 25.72 and 15.88% at concentrations of 350 µg/mL with S9 and 40.0 µg/mL without S9, respectively. Significant increases in mutant frequency, | Unnamed (2014c)<br>(ECHA Dissemination, 2019) |

| Method, guideline, deviations if any | Test substance, | Relevant information about the study including rationale for dose selection (as applicable) | Observations | Reference |
|---|---|---|---|---|
| GLP: yes<br>RL1 (according to registration dossier and the authors of this document ) | 100%) | 450 and 500 µg/mL<br>Assay 2:<br>**5.00, 10.0, 20.0,** 25.0, **30.0**, 35.0, **40.0** and 50.0 µg/mL without MA<br>(concentrations marked in bold were evaluated)<br>Vehicle: DMSO<br>No visible precipitate was observed at the beginning or end of treatment.<br>+/- S9 mix from Aroclor 1254 induced rat liver | as compared to the concurrent vehicle controls, were observed at the highest acceptable dose level with and without S9 ($p < 0.05$). These increases were dose-dependent, and they also exceeded the 95% confidence limit for the historical vehicle control data. | |

[#] RL = Klimisch reliability score

[##] MA = metabolic activation

## Table 10: Summary table of mutagenicity/genotoxicity tests in mammalian somatic or germ cells *in vivo*

| Method, guideline, deviations if any | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| *In vivo* Mammalian Alkaline Comet Assay<br>OECD TG 489<br>Deviations: yes<br>GLP: yes<br>RL1 (according to registration dossier and the authors of this document) | Reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis((2,3-epoxypropoxy)methyl)butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane (Purity: confidential) | Animals: Sprague Dawley rats (males and females in DRF; only males in main test)<br>Exposure: oral by gavage on two consecutive days; second dose 21 hours after the first dose (DRF: 3 animals per sex per dose; Main study: 6 males per dose)<br>Positive control: ethyl methanesulfonate (EMS).<br>Doses: 0, 500, 1000, 2000 mg/kg bw/d (dose volume: 10 ml/kg bw/d)<br>Vehicle: Polyethyene glycol 400 (PEG 400)<br>Organs investigated: liver, glandular stomach and duodenum; preparation of 3 slides/wells per organ per animal, 50 cells per slide evaluated<br>Deviations from guideline:<br>In the Dose Range Finding Assay was the interval between | Positive in liver in the mid and high dose group; positive in duodenum in high dose group. No effects in stomach observed. No histopathologically visible cytotoxicity in any organ.<br>Details:<br>Dose responsive, statistically significant increase in % tail DNA in the 1000 and 2000 mg/kg/day dose of the liver samples; the 2000 mg/kg/day increase was outside current historical control and 95% confidence range.<br>Dose responsive, statistically significant increase in % tail DNA in the 2000 mg/kg/day dose of the duodenal samples;<br>No increases in % tail | Unnamed (2017)<br>(ECHA Dissemination, 2019) |

| Method, guideline, deviations if any | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| | | first and second dosing ca. 24-25 hours instead of 21 hours; during electrophoresis the buffer temperature at the end of electrophoresis was 11.2°C, which is outside the protocol range of 2 to 10°C; both deviations were not regarded to impact the study validity | DNA in the stomach samples.<br>The vehicle and positive control % tail DNA values were within expected ranges for all three organs. All valid assay criteria were met. | |

**Table 11: Summary table of human data relevant for germ cell mutagenicity**

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| No data available | | | | |

### 10.8.1 Short summary and overall relevance of the provided information on germ cell mutagenicity

Genotoxicity of the reaction mass to be evaluated has been investigated in three *in vitro* assays and one *in vivo* study. *In vitro* data are available from a Bacterial Reverse Mutation Assay (Ames Test according to OECD TG 471), a Mammalian Chromosome Aberration Assay in Chinese Hamster Ovary according to OECD TG 473 and a Mammalian Cell Forward Gene Mutation (CHO/HPRT) Assay according to OECD TG 476.

In the Ames Assay clearly positive results were observed in the presence and absence of the metabolic activating rat liver S9 mix in the strains TA 100 and TA 1535 and in the presence of metabolic activation in E.coli WP2 uvrA. Results in these strains were clearly positive, revertants were increased from about 4-fold to up to 69- or 94-fold in the first and confirmatory assay, depending on the strain. In the Chromosome Aberration assay statistically significant and dose-dependent increases in structural aberrations in treatment groups with or without S9-mix were observed. No effects on polyploid cells and cells with endoreduplicated chromosomes were recorded. Clearly positive and dose-dependent results were also observed in the mammalian cells gene mutation assay in a concentration range, which was still acceptable for the test but already caused clear cytotoxicity in the cell. These clearly positive results *in vitro* were confirmed by an *in vivo* comet assay in mice. Positive results were observed in liver of mid and high dose animals and in duodenum of high dose animals, pointing to the possibility of the test material to induce DNA strand breaks after administration via a relevant route (oral gavage). No effects were observed in stomach. Histopathological investigations did not reveal visible signs of cytotoxicity in any organ.

In summary, all three *in vitro* assays and the *in vivo* assay, which were reliable and relevant, provided consistently positive results.

### 10.8.2 Comparison with the CLP criteria

There are no epidemiological data investigating heritable mutations in the germ cells of humans to support classification of the reaction mass in Category 1A.

There are neither experimental data from *in vivo* heritable germ cell mutagenicity tests in mammals nor positive results from *in vivo* somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells to support classification of the reaction mass

in Category 1B. Additionally, there is no information that the substance or its metabolites is able to interact with the genetic material of germ cells and no evidence that the substance shows mutagenic effects in the germ cells of humans supporting a classification of the reaction mass in Category 1B.

However, the existing data consistently provide evidence that the reaction mass under evaluation induces mutagenicity in common *in vitro* assays. Due to the different types of *in vitro* tests it can reasonably be assumed that the substance induces both, gene mutations and chromosome mutations. These findings are supported by the induction of DNA strand breaks in liver and duodenum in an *in vivo* comet assay in mice, which strengthen the *evidence for* the induction of chromosome mutations.

Whether the substance could reach the germ cells remains currently unclear. Results of an OECD 422 study which revealed effects on male fertility provides some suspicion that the substance reaches male germ cells. However, these data do not unequivocally show that the substance causes genetic damage in the germ cells, as the mechanism underlying the effects on fertility is unclear.

Together, the positive *in vitro* findings and the positive effects in somatic cells in mammals *in vivo* cause concern that the reaction mass, which reaches the systemic blood circulation, may induce heritable mutations in germ cells of humans. However, there are no human data which report genetic damage to germ cells in exposed humans. Based on these findings a classification for germ cell mutagenicity Category 2 is suggested.

### 10.8.3 Conclusion on classification and labelling for germ cell mutagenicity

As outlined in section 10.8.1 consistently positive results were obtained in available *in vitro* assays with the reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis ((2,3-epoxypropoxy)methyl) butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane. Additionally, positive results were also obtained in an *in vivo* Comet Assay after gavage application of the test item to mice. However, toxicokinetic data which unequivocally show that the substance reaches the germ cells and interacts with the genetic information of the germ cells are missing. Therefore, the criteria for classification for germ cell mutagenicity Category 2 are fulfilled.

**Therefore, classification as germ cell mutagen Category 2 is proposed for the reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis ((2,3-epoxypropoxy)methyl) butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane.**

## 10.9 Carcinogenicity

There are no carcinogenicity studies for the reaction mass to be evaluated available.

Evaluation not performed for this substance.

## 10.10 Reproductive toxicity

### 10.10.1 Adverse effects on sexual function and fertility

**Table 12: Summary table of animal studies on adverse effects on sexual function and fertility**

| Method, guideline, deviations if any, species, strain, sex, no/group | Test substance, dose levels duration of exposure | Results | Reference |
|---|---|---|---|
| Combined Repeated Dose Toxicity Study with the Reproduction/Developmental | Reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis((2,3-epoxypropoxy)methyl)butane | Parental animals: NOAEL (fertility): 100 mg/kg bw/d (no effects on mating performance, gestation length (tendency | Unnamed (2015a) (ECHA |

| **Method, guideline, deviations if any, species, strain, sex, no/group** | **Test substance, dose levels duration of exposure** | **Results** | **Reference** |
|---|---|---|---|
| Toxicity Screening Test<br>According to OECD TG 422<br>Deviations: yes<br>GLP: yes<br>Male and female Wistar Han™:RccHan™:WIST strain rats (12 animals per sex per dose)<br>RL1 (according to registration dossier and the authors of this document) | and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane (Concentrations of constituents: 58% C15H26O6 and 25% C12H22O5)<br>Doses: 0, 30, 100, 300 mg/kg bw/d (two week pre-pairing phase, pairing, gestation and early lactation for females)<br>On Day 15 (Day 16 for male 25 and female 37), animals were paired on a 1 male: 1 female basis within each dose group for a maximum of fourteen days.<br>Adult males were sacrificed on Day 43 or 44; adult females were sacrificed on Day 5 post partum or Day 25 post coitum for females at 300 mg/kg bw/d<br>Application via gavage<br>Vehicle: polyethylene glycol 400 | to increase gestation length in LD and MD, but within the lab's control range). None of the females of the HD became pregnant<br>NOAEL (systemic toxicity): 300 mg/kg bw/d (no effects on functional observations and sensory reactivity assessment, no adverse findings during necropsy, no relevant findings on hematology and clinical chemistry)<br>HD: males and females showed increased salivation after dosing; males revealed slightly lower body weight gain during last week of treatment, which was not toxicological relevant; none of the females became pregnant despite normal mating performance; therefore no comparison with control group with respect to e.g. food consumption, body weight gain; higher glucose, calcium and inorganic phosphorus levels attained statistical significance compared to control; in two animals glucose values and inorganic phosphorus values exceeded the historical control, all other values were within this historical range; no histopathological effects on testes (sperm parameters) observed<br>MD: one male showed incidences of pilo-erection on two separate occasions (not observed in HD group); effects on hematological parameters without histological correlates;<br>LD: one female sacrificed for animal welfare on Day 2 (dark swollen eye, not regarded as substance related), replaced by a new female); no effects on functional observations and sensory reactivity assessment, effects on hematological parameters without histological correlates;<br>Offspring: NOAEL: 100 mg/kg bw/d (highest dose, as no offspring in 300 mg/kg bw/d group) (no adverse effect of treatment on the corpora lutea count, pre-implantation loss, numbers of implantations, post-implantation loss, litter size at birth/Day 1 and subsequent offspring survival to Day 4; on surface righting or visible during necropsy. At 100 mg/kg bw/day, offspring body | Dissemination, 2019) |

| Method, guideline, deviations if any, species, strain, sex, no/group | Test substance, dose levels duration of exposure | Results | Reference |
|---|---|---|---|
| | | weights were slightly higher than control on Day 1 of age, with differences for males attaining statistical significance. These differences were considered to reflect the slightly longer gestation period observed for parent females at this dosage rather than any treatment related effect on pre-natal/early post-natal growth).<br><br>Deviations: some procedures were performed on Day 25 or 26 post coitum rather than post partum, as HD females failed to achieve pregnancy | |
| Investigation of effects on fertility (further investigation of effects observed in OECD 422), no guideline followed<br><br>GLP: yes<br><br>Male and female Wistar Han™:RccHan™:WIST strain rats (12 animals per sex per dose)<br><br>RL1 (according to registration dossier)<br><br>RL2 (according to the authors of this document due to reduced investigation depth) | Reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis((2,3-epoxypropoxy)methyl)butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane (Purity: confidential)<br><br>Doses: 300 mg/kg bw/d (two week pre-pairing phase, pairing, gestation and early lactation for females)<br><br>Males were dosed for 38 consecutive days and females dosed for at least 4 weeks (including a two-week pre-pairing phase, pairing and then to Day 13 of gestation.<br><br>On Day 15 animals were paired on a 1 male: 1 female basis within each dose group for a maximum of fourteen days.<br><br>Control males were paired with females receiving 300 mg/kg bw/day and 300 mg/kg bw/day males were paired with control females to separately assess possible effects on fertility for each sex.<br><br>Application via gavage<br><br>Vehicle: polyethylene glycol 400 | <u>Fertility:</u><br><br>(equivocal) NOAEL females: 300 mg/kg bw/d; litter data available for treated females did not indicate any obvious adverse effect of treatment; however, two mated treated females (paired with control males) failed to achieve pregnancy (unclear whether treatment-related effect) and one treated female failed to mate, but this was considered to reflect poor fertility of the control male (indicated by male reproductive organ weight and sperm analysis).<br><br>LOAEL males: 300 mg/kg bw/d (all control females (paired with treated males) failed to achieve pregnancy, mating performance was not affected; treated males: absolute and body weight relative left epididymal weights were lower than control with differences attaining statistical significance; sperm analysis: for treated males, mean homogenisation resistant spermatid count from the cauda epididymis was lower than control, with differences attaining statistical significance. No similar decrease was observed for mean homogenisation resistant spermatid count from the testis of treated male; assessment of sperm concentration and motility at necropsy and subsequent sperm morphology did not indicate any obvious effect of treatment.)<br><br><u>Systemic toxicity:</u><br><br>NOAEL males/females: 300 mg/kg bw/d (no mortality, increased post-dosing salivation for both sexes, statistically significant reduced body | Unnamed (2015b)<br><br>(ECHA Dissemination, 2019) |

| Method, guideline, deviations if any, species, strain, sex, no/group | Test substance, dose levels duration of exposure | Results | Reference |
|---|---|---|---|
| | | weight gain in males only during the first two weeks of treatment accompanied by reduced food consumption) | |

**Table 13: Summary table of human data on adverse effects on sexual function and fertility**

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| No data available | | | | |

**Table 14: Summary table of other studies relevant for toxicity on sexual function and fertility**

| Type of study/data | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| No data available | | | | |

### 10.10.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

There is a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test in rats according to OECD TG 422 available, which showed clear effect on fertility at the highest dose group of 300 mg/kg bw/d. None of the females of this dose group became pregnant, whereas no effects on fertility were observed at the lower dose groups of 30 and 100 mg/kg bw/d. Histopathological investigations of reproductive organs did not reveal any adverse effects. No effects on functional observations and sensory reactivity assessment, mating performance, and gestation length were observed. No other relevant systemic toxicity findings were recorded.

An additional study was performed to further investigate the effects on fertility observed in the OECD TG 422 study. Males and females were treated with test material at doses of 300 mg/kg bw/d. Treated males were paired with control females and treated females with control males to separately assess possible effects on fertility for each sex. There were no treatment-related effects on mating performance as assessed by pre-coital interval. The evidence of mating (sperm in vaginal smear, numbers of copulation plugs) appeared similar in both groups. However, all control females mated with treated males failed to achieve pregnancy whereas two out of 12 treated females, which were mated with control males failed to achieve pregnancy. For treated males, absolute and relative left epididymal weights were statistically significantly lower than control. Also, mean homogenisation resistant spermatid count from the cauda epididymis was statistically significantly lower than control. No similar decrease was observed for mean homogenisation resistant spermatid count from the testis. No obvious effect of treatment was evident on sperm concentration or motility or on sperm morphology.

Also, no effects on testes histopathology in high dose group males (only high dose group and control group investigated), oestrus cycle status and thyroid hormone level (TSH, T4 and T3) was observed in a sub-chronic 90-d study.

In summary, the available studies clearly revealed an effect on male fertility which was obvious in the absence of any other relevant systemic toxic effects. The underlying mechanism of action is unclear. Whether the two non-pregnant females of the group of treated females, which were paired with non-treated males also point to effects on female fertility or are only representing biological variability remains unclear. Histopathological investigations did not indicate any effects on female reproductive organs.

### 10.10.3 Comparison with the CLP criteria

There are no epidemiological data to support classification of the reaction mass under evaluation in Category 1A.

There is clear evidence from experimental studies with rats showing effects on male fertility in the absence of relevant systemic toxicity. Effects on female fertility could not be excluded with certainty, as it remains unclear if the effects observed in two of 12 females are treatment-related or representing biological variability. No effects on sexual function were observed. Whereas there is some evidence for effects on spermatid count in cauda epididymis, no such effect was observed in testis. Additionally, no histopathologically visible effects were observed in female reproductive organs. Therefore, mechanisms underlying the effects on fertility are unclear.

Due to the very limited database for the substance there is no additional information on possible effects on fertility available.

There is no information on a possible mode of action underlying the observed effects. In the absence of any information on a species-specific mode of action the effects are regarded as relevant for humans.

There is only information from two toxicological studies available. But due to the severity of effects and assuming relevance of the underlying mode of action for humans in the absence of any other information, classification for effects on fertility in Category 1B is proposed.

### 10.10.4 Adverse effects on development

**Table 15: Summary table of animal studies on adverse effects on development**

| Method, guideline, deviations if any, species, strain, sex, no/group | Test substance, dose levels duration of exposure | Results | Reference |
|---|---|---|---|
| Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test<br><br>According to OECD TG 422<br><br>Deviations: yes<br><br>GLP: yes<br><br>Male and female Wistar Han™:RccHan™:WIST strain rats (12 animals per sex per dose)<br><br>RL1 (according to registration dossier and the | Reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis((2,3-epoxypropoxy)methyl)butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane (Concentrations of constituents: 58% C15H26O6 and 25% C12H22O5)<br><br>Doses: 0, 30, 100, 300 mg/kg bw/d (two week pre-pairing phase, pairing, gestation and early lactation for females)<br><br>On Day 15 (Day 16 for male | <u>Parental animals:</u> NOAEL: 100 mg/kg bw/d (for details see section 10.10.1);<br><br><u>Offspring:</u> NOAEL: 100 mg/kg bw/d (highest dose, as no offspring in 300 mg/kg bw/d group): no adverse effect of treatment on the corpora lutea count, pre-implantation loss, numbers of implantations, post-implantation loss, litter size at birth/Day 1 and subsequent offspring survival to Day 4; on surface righting or visible during necropsy. At 100 mg/kg bw/day, offspring body weights were slightly higher than control on Day 1 of age, with differences for males attaining statistical | Unnamed (2015a)<br><br>(ECHA Dissemination, 2019) |

| Method, guideline, deviations if any, species, strain, sex, no/group | Test substance, dose levels duration of exposure | Results | Reference |
|---|---|---|---|
| authors of this document) | 25 and female 37), animals were paired on a 1 male: 1 female basis within each dose group for a maximum of fourteen days.<br>Adult males were sacrificed on Day 43 or 44; adult females were sacrificed on Day 5 post partum or Day 25 post coitum for females at 300 mg/kg bw/d.<br>Application via gavage<br>Vehicle: polyethylene glycol 400 | significance. These differences were considered to reflect the slightly longer gestation period observed for parent females at this dosage rather than any treatment related effect on pre-natal/early post-natal growth.<br>Deviations: some procedures were performed on Day 25 or 26 post coitum rather than post partum, as HD females failed to achieve pregnancy | |

**Table 16: Summary table of human data on adverse effects on development**

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| No data available | | | | |

**Table 17: Summary table of other studies relevant for developmental toxicity**

| Type of study/data | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| No data available | | | | |

### 10.10.5 Short summary and overall relevance of the provided information on adverse effects on development

There is no multi-generation study available for the reaction mass under evaluation. Results of a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test in rats did not indicate any adverse effects on development of pups up to PND 4 up to 100 mg/kg bw/d. No offspring were born in the highest dose group of 300 mg/kg bw/d as none of the females of this dose group became pregnant. Additionally, a developmental toxicity study in rats is available. Rats were exposed from GD 5 to GD 19 to three different doses up to 180 mg/kg bw/d. Up to the highest dose, neither effects on maternal toxicity nor developmental effects were observed. Based on this study, no conclusions on possible effects of the test substance on developmental effects could be drawn as only doses without any toxic effects were investigated.

### 10.10.6 Comparison with the CLP criteria

Limited available animal data do not point to effects of the reaction mass on developmental effects. However, in the absence of a relevant and reliable developmental toxicity study this endpoint cannot be assessed.

### 10.10.7 Adverse effects on or via lactation

**Table 18: Summary table of animal studies on effects on or via lactation**

| Method, guideline, deviations if any, species, strain, sex, no/group | Test substance, dose levels duration of exposure | Results | Reference |
|---|---|---|---|
| No data available | | | |

**Table 19: Summary table of human data on effects on or via lactation**

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| No data available | | | | |

**Table 20: Summary table of other studies relevant for effects on or via lactation**

| Type of study/data | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---|---|---|---|---|
| No data available | | | | |

### 10.10.8 Short summary and overall relevance of the provided information on effects on or via lactation

There are no human or experimental data available with respect to effects via lactation.

### 10.10.9 Comparison with the CLP criteria

In the absence of any data on possible effects on or via lactation this endpoint cannot be assessed.

### 10.10.10 Conclusion on classification and labelling for reproductive toxicity

Available information from a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test in rats in combination with a study investigating possible effects on fertility for each sex clearly revealed that the substance under evaluation impairs male fertility in the absence of systemic toxic effects. Based on these clear-cut experimental data and in the

absence of human data classification of the reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis((2,3-epoxypropoxy)methyl)butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane for effects on fertility Cat. 1B is suggested.

**Therefore, classification for effects on fertility category 1B is proposed for reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis((2,3-epoxypropoxy)methyl)butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane.**

In the absence of relevant and reliable studies no classification is proposed for effects of the reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis((2,3-epoxypropoxy)methyl)butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane on developmental toxicity.

**Therefore, no classification for effects on development is warranted for reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis((2,3-epoxypropoxy)methyl)butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane.**

In the absence of relevant and reliable studies no classification is proposed for effects of the reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis((2,3-epoxypropoxy)methyl)butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane on or via lactation.

**Therefore, no classification for effects on or via lactation is warranted for reaction mass of 1-(2,3-epoxypropoxy)-2,2-bis((2,3-epoxypropoxy)methyl)butane and 1-(2,3-epoxypropoxy)-2-((2,3-epoxypropoxy)methyl)-2-hydroxymethyl butane.**

### 10.11 Specific target organ toxicity-single exposure

Evaluation not performed for this substance.

### 10.12 Specific target organ toxicity-repeated exposure

Evaluation not performed for this substance.

### 10.13 Aspiration hazard

Evaluation not performed for this substance.

## 11 EVALUATION OF ENVIRONMENTAL HAZARDS

Evaluation not performed for this substance.

## 12 EVALUATION OF ADDITIONAL HAZARDS

Evaluation not performed for this substance.

## 13 ADDITIONAL LABELLING

Not applicable for this evaluation.

## 14 ANNEXES

Please see separate documents for non-confidential and confidential Annex I.

## 15 REFERENCES

ECHA, European Chemicals Agency (2014): Guidance on the preparation of dossiers for harmonised classification and labelling. Version 2.0. August 2014, http://publications.europa.eu/en/publication-detail/-/publication/3102d5d7-e68b-11e5-8a50-01aa75ed71a1/language-en

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