CLH report

Proposal for Harmonised Classification and Labelling

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

Chemical name: 2,3-epoxypropyl o-tolyl ether

EC Number: 218-645-3

CAS Number: 2210-79-9

Index Number: 603-056-00-X

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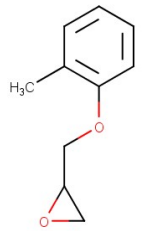
CONTENTS

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)	2-[(2-methylphenoxy)methyl]oxirane
Other names (usual name, trade name, abbreviation)	2,3-epoxypropyl o-tolyl ether Cresyl glycidyl ether o-Cresol glycidyl ether (o-CGE) EPOTE ARALDITE® DY 023 ARALDITE® DY-K D.E.R.(TM) 723 Epoxy Diluent EPOTEC RD 105
ISO common name (if available and appropriate)	-
EC number (if available and appropriate)	218-645-3
EC name (if available and appropriate)	2,3-epoxypropyl o-tolyl ether
CAS number (if available)	2210-79-9
Other identity code (if available)	-
Molecular formula	C10H12O2

Structural formula	
SMILES notation (if available)	Cc1ccccc1OCC1CO1
Molecular weight or molecular weight range	164.2 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	-
Description of the manufacturing process and identity of the source (for UVCB substances only)	-
Degree of purity (%) (if relevant for the entry in Annex VI)	Not relevant

1.2 Composition of the substance

The chemical structure of EPOTE contains one chiral carbon atom and shows stereochemistry. The name and numerical identifiers of the substance do not refer to stereochemistry but include both stereoisomers. Therefore, EPOTE is regarded as a multi-constituent substance.

Table 2: Constituent

Constituent	Typical concentration	Concentration range
2,3-epoxypropyl o-tolyl ether EC no.: 218-645-3	Approx. 85.5 % (w/w)	>=80 - <=100 % (w/w)

Table 3: Impurities

Constituent

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 4: Proposed harmonised classification and labelling according to the CLP criteria

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATEs	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	603-056-00-X	2,3-epoxypropyl o-tolyl ether	218-645-3	2210-79-9	Skin Irrit. 2 Skin Sens. 1 Muta. 2 Aquatic Chronic 2	H315 H317 H341 H411	GHS09 GHS08 GHS07 Wng	H315 H317 H341 H411			Note C
Dossier submitters (DS) proposal	603-RST-VW-Y	2,3-epoxypropyl o-tolyl ether	218-645-3	2210-79-9	**Modify** Skin Sens. 1A	**Retain** H317		**Retain** H317			
Resulting Annex VI entry if agreed by RAC and COM	603-RST-VW-Y	2,3-epoxypropyl o-tolyl ether	218-645-3	2210-79-9	Skin Irrit. 2 Skin Sens. 1A Muta. 2 Aquatic Chronic 2	H315 H317 H341 H411	GHS09 GHS08 GHS07 Wng	H315 H317 H341 H411			Note C

Table 5: Reason for not proposing harmonised classification and status under consultation

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

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

The substance EPOTE (Cas no. 2210-79-9) has the current harmonised classification in Annex VI of the CLP regulation, entry 603-056-00-X: Skin Irrit. 2, Skin Sens. 1, Muta. 2 and Aquatic Chronic 2.

All 523 notifiers self-classify EPOTE as a skin sensitiser, but only 63 notifiers classify as category 1A.

Entry 603-056-00-X includes also other substances than EPOTE. Therefore, a new substance specific entry will need to be created if the current proposal for updating the harmonized classification of EPOTE is accepted.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Justification that action is needed at Community level is required.

With respect to the endpoint of skin sensitisation, the substance falls under article 36 (3). The Dose submitter (DS) wishes for an update of the existing entry due to new data.

Further detail on need of action at Community level

The DS' evaluation shows that the available data on skin sensitisation fulfil the criteria for classification as a strong skin sensitiser. Thus, EPOTE should be classified as Skin Sens. category 1A with the generic concentration limit (GCL) of 0.1%.

Since only 63 of the notifiers self-classify the substance as category 1A, an update of the harmonised classification is necessary to secure that European users of EPOTE receive sufficient information through labelling and the Safety Data Sheet (SDS) to take relevant precautions in the handling of mixtures containing EPOTE at a concentration that may entail sensitisation.

5 IDENTIFIED USES

EPOTE is an epoxy substance used in products for building, renovation and construction work such as adhesives, sealants, coatings, fillers, puttie, floorings etc. It is also used in the manufacture of plastic products, fabricated metal products, electrical, electronic and optical equipment, machinery and vehicles, rubber products and mineral products. The use of the substance is mainly professional but according to the Nordic product register (SPIN database: http://www.spin2000.net/spinmyphp/) there are indications of consumer use.

6 DATA SOURCES

The DS has scrutinised all available data relevant to the endpoint of skin sensitisation including data from a literature search in the open scientific literature. On that basis, the DS has prepared the present proposal for a harmonised classification for EPOTE as Skin Sens. cat 1A.

The primary source of information is the publicly available part of the REACH registration dossier for EPOTE (ECHA webpage, October 2021), the REACH registration dossier (October 2021), and the conclusion document of the SEv published in January 2022 (ECHA, 2022). Furthermore, reports published by FOBIG (2012), Health Canada (2018) and NICNAS (2015) were also consulted.

In addition, a search in peer-reviewed scientific literature databases and websites (grey literature) was conducted. The searches included literature databases such as Google Scholar, PubMed, Web of Science as well as searches in sources such as OECD SIDS and IPCS INCHEM. For identification of information from grey literature, the OpenGrey database was checked. General searches via Google have also been carried out.

7 PHYSICOCHEMICAL PROPERTIES

Table 6: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Colourless liquid	REACH registration dossier	
Melting/freezing point	Freezing point < -69°C (OECD TG 102)	REACH registration dossier	
Boiling point	260 +/- 0.29 °C (OECD TG 103)	REACH registration dossier	
Relative density	1.09 (OECD TG 109)	REACH registration dossier	
Vapour pressure	0.514 Pascal at 20°C and 0.822 Pascal at 25°C(OECD TG 104)	REACH registration dossier	
Surface tension	Data waived		
Water solubility	Appr. 0.84 g/L , moderately soluble (100-1000 mg/L) (OECD TG 107)	REACH registration dossier	
Partition coefficient n-octanol/water	2.50 +/- 0.062. (OECD TG 107)	REACH registration dossier	
Flash point	123.4 +/- 2.14 °C at 30.0 mmHg. (EU test method A9)	REACH registration dossier	
Flammability	Data waived		
Explosive properties	Data waived		
Self-ignition temperature	436°C at 1013 hP	REACH registration dossier	
Oxidising properties	Data waived		
Granulometry	Data waived		
Stability in organic solvents and identity of relevant degradation	Data waived		

Property	Value	Reference	Comment (e.g. measured or estimated)
products			
Dissociation constant	Data waived		
Viscosity	9.64 cSt +/- 0.03 cSt at 20 °C and 4.72 cSt +/- 0.01 cSt at 40 °C. (OECD TG 114)	REACH registration dossier	

8 EVALUATION OF PHYSICAL HAZARD

Hazard class not assessed in this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Toxicokinetics has not been assessed in this dossier.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

Hazard class not assessed in this dossier.

10.2 Acute toxicity - dermal route

Hazard class not assessed in this dossier.

10.3 Acute toxicity - inhalation route

Hazard class not assessed in this dossier.

10.4 Skin corrosion/irritation

Hazard class not assessed in this dossier.

10.5 Serious eye damage/eye irritation

Hazard class not assessed in this dossier.

10.6 Respiratory sensitisation

Hazard class not assessed in this dossier.

10.7 Skin sensitisation

10.7.1.1 Animal data

Table 7: Summary table of animal studies on skin sensitisation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results	Reference
Guinea pig maximisation test (GPMT) according to OECD TG 406 (version 1981) Klimisch 2	Guinea pig, Pirbright White Strain (Tif: DHP), 10 male and 10 female guinea pigs in each group	TK 10410 OP-WMO 366U, ARALDIT DY 023	10% (Induction dose) 3% (challenge dose)	20/20; 100%	Unpublished report, 1989
Guinea pig maximisation test (GPMT) according to OECD TG 406 (version 1981) Klimisch 2	10 male and 10 female Albino Guinea pigs were used in the test group and 5 male and 5 female in the control group	o-cresyl-glycidyl-ether (purity 98.9%)	Induction phase 1: 5% (intradermal injections) Induction phase 2: 10% (epidermal) Challenge phase: 1%	14/20; 70%	Unpublished report, 1991
Guinea pig maximisation test (GPMT) (conducted prier to OECD TG, not considered reliable by the DS: Klimisch 3	10 male and 10 female Pirbright white strain Guinea pigs in each group. A total of 10 animals in the positive controle group	TK 10410 (No information on purity)	Induction phase 1: 0.1% (intradermal injection) Induction phase 2: 50% (intracutaneously) Challenge phase: 0.1%	3/20; 15%	Unpublished report, 1976
Local Lymph Node Assay (LLNA) (OECD TG 429, version 2010) Klimisch 1	Mice CBA/CaOlaHsd strain 4 female mice in each group	2,3-epoxypropylo-tolylether (purity approximately 90%	Three test groups: 0.5 %, 1 % and 2.5 %	SI: 1.58 (0.5%), 2.09 (1%) and 6.34 (2.5%) EC3 value: 1.3%	Unpublished report, 2019

Guinea pig maximisation test (1989)

A Guinea pig maximisation test was performed in 1989 according to OECD TG 406 (version 1981) with GLP compliance. The test substance was only identified by trade name (not chemical name or CAS Number), but assumed to be EPOTE, as the study was included in the registration. No information regarding composition or purity was available in the study report (unpublished report, 1989).

The induction was done in two stages. Intradermal injections were performed in the neck region of 20 test animals and succeeded by closed patch occlusive epicutaneous exposure over the injection sites one week later. Induction stage 1: Three pairs of intradermal injections (of 0.1 ml per injection) were made into the neck (shaved) as follows: Adjuvant/saline mixture 1:1 (v/v), test substance in sesame oil (w/v) and the test substance in the adjuvant saline mixture (w/v). The dose level used was 3%.

Induction stage 2: The epidermal induction phase was conducted one week later with the test substance (vaseline was used as the vehicle (w/w)) applied on filter paper to the neck of the animals (patch 2x4 -cm; approx. 0.4 g paste/patch; occluded administration for 48 hours). The concentration used was 10%.

Challenge phase: Two weeks after the epidermal induction application. Animals were tested on the flank with the test substance in vaseline (w/w) and the vehicle alone (patch 2x2 cm; approx. 0.2 g paste per patch; occluded administration for 24 hours). The dose level used was 3%. The challenge reactions were graded after 24 hours and 48 hours according to the Draize scoring scale.

The control group were only treated with adjuvant and the vehicle during the induction periods. During the challenge period the group was treated with the vehicle and with the test substance.

All (20/20) of the tested animals (100%) demonstrated positive dermal reactions when compared with the control group (0/20 positive dermal reactions). The test substance was concluded by the study authors to be an extreme skin sensitiser under the conditions of this study, but due to the relatively high concentration used for the induction phase, in combination with the high incidence of sensitised animals, the CLP criteria are not directly applicable for sub-categorisation of the substance. The DS has evaluated this study as reliable with restrictions, Klimisch 2.

Guinea pig maximisation test (1991)

Another Guinea pig maximisation test was performed in 1991 according to OECD TG 406 (version 1981) with GLP compliance. The test substance was described as o-cresyl-glycidyl-ether (identical to 2,3-epoxypropyl o-tolyl ether) (purity 98.9%, no further information on the chemical identity of impurities was available). The highest non-irritating test article concentration used for the challenge phase was 1%. 10 male and 10 female guinea pigs were used in the test group and 5 male and 5 female guinea pigs in the control group (Unpublished report, 1991).

Induction stage 1: Three pairs of intradermal injections (of 0.1 ml per injection) were made into the back of the animals: Freund’s complete adjuvant 1:1 with bi-distilled water, test article diluted to 5 % with oleum arachides and the test substance (dose 5%) emulsified in a 1:1 mixture of Freund’s complete adjuvant and oleum arachides.

Induction stage 2: The epidermal induction was conducted one week after the intradermal injections: A patch of filter paper was saturated with the test substance (10% in vaseline) and placed

over the injection sites of the test animals. The patches were left in place for approximately 48 hours.

Challenge phase: Two weeks after the epidermal induction application, the animals were tested on the flank with the test substance in vaseline (w/w) and the vehicle alone (patch 2x2 cm; approx. 0.2 g paste per patch; occluded administration for 24 hours). The concentration used was 1%. The challenge reactions were graded after 24 hours and 48 hours (14 positive of 20 animals (70%)) according to the Draize scoring scale.

Results: Positive reactions to the challenge 24 hours after treated with the test substance were seen in 16 of 20 animals (80%) and 14 positive reactions were seen 48 hours after challenge (70%). In the negative control group, no positive reactions were observed (0/10). The test substance was considered to be a "strong" dermal sensitiser by the authors of the study under the conditions of the experiment. The DS has evaluated this study as reliable with restrictions, Klimisch 2.

Non-guideline study similar to the Guinea pig maximisation test (1976)

A non-guideline study like the Guinea pig maximisation test was performed in 1976 (unpublished report, 1976). The test substance was defined by trade name only (not identified by chemical name or CAS Number and no information was available about purity or chemical identity of impurities). 10 male and 10 female guinea pigs were tested in each group. For the positive control group, a total of 10 animals were tested.

Induction phase: Volumes of 0.1 ml of the test substance (0.1%) in saline without adjuvant were injected intradermally three days during week 1. The test substance was mixed with adjuvant in a 1: 1 ratio. A total of 6 sensitising doses of 0.1 mL were injected intracutaneously into the skin of the neck during the second and third week of induction.

Challenge phase: Two weeks after the last sensitising treatment with the adjuvant mixture, 0.1 mL of the test substance (0.1%) in saline without adjuvant was injected intradermally on the previously untreated flank. The reaction sites were evaluated 24 hours after the challenge by skin-fold thickness determined with a skin—fold gauge: length and height of erythema was recorded and compared to the length, width and height of erythema that occurred after the first week of induction.

In the test group 3 animals out of 20 elicited an erythematous reaction. No erythematous reactions were observed in the negative control group. Dermal reaction scores according to the Magnusson and Kligman scale criteria were not recorded in this study. The DS has evaluated this study as not reliable, Klimisch 3.

Local Lymph Node Assay (LLNA) (2019)

A Local Lymph Node Assay (LLNA) (OECD TG 429) was requested in a SEv final decision in January 2018 (Unpublished study, 2019). It was argued that it is not possible to establish the skin sensitising potency of the Substance EPOTE based on the available GPMT data, and hence a new *in vivo* study on skin sensitisation was needed. The requested LLNA study was performed in 2019 according to OECD TG 429 (version 2010) with GLP compliance (unpublished report, 2019). The test substance was described as 2,3-epoxypropylo-tolylether (purity approximately 90%, no further information on the chemical impurities was available). The highest non-irritant test concentration with no signs of systemic toxicity was identified to be 2.5% in a pre-test. Thus, the assay was performed using test concentrations of 0.5, 1, and 2.5% in vehicle acetone: olive oil (4:1, v/v) (AOO 4:1 v/v) with a vehicle control group.

The choice of vehicle is not further justified in the study report. However, since acetone: olive oil is one of the recommended vehicles in the guideline, the DS finds this sufficient.

Preparations of test formulations were made freshly before each application to ensure maximal exposure to unreacted EPOTE. In the ECHA draft decision from January 2018, it was required that homogenecity and stability of the test formulations were analysed and documented in the study report. No such documentation is given in the study report, however, since preparations were freshly made prior to each application, the DS finds this sufficient to ensure adequate EPOTE exposure.

Four female mice of the CBA/CaOlaHsd strain (age 8-13 weeks) were randomly distributed to each group. Each test group was treated by topical application to the dorsal surface of the ear, with 25 µl of the respective test concentrations in AOO (4:1, v/v) on each ear once daily for three consecutive days. The vehicle control group was treated with the equivalent volume of the vehicle alone.

Five days after the first application all animals were injected with ^{3}H-methyl-thymidine (^{3}HTdR) in a phosphate-buffered saline via the tail vein. Approximately five hours after the treatment all animals were euthanized and the lymph nodes were harvested, and the animals were sacrificed.

Single cell suspensions of pooled lymph node cells were prepared, and the cellular proliferation were determined by measuring ^{3}HTdR in a β-scintillation counter, expressing ^{3}HTdR incorporation as the number of radioactive disintegrations per minute (DPM). Background levels of ^{3}HTdR were measured. The proliferative response of the lymph node cells is expressed as DPM per lymph node (mean values) of test animals relative to control animals (Stimulation Index; SI) adjusted for background levels.

If the test concentration results in a 3-fold increase or greater in ^{3}HTdR incorporation (SI of 3) and data has a dose-response relationship, the test is considered positive. The Estimated Concentration of the test substance required to produce a SI of 3 (EC3) was calculated.

Two deviations from the study plan are mentioned in the study report. The age of the mice were 8 to 13 weeks instead of 8 to 12 weeks. The relative humidity in the environment where the mice were kept was for a few hours between approximately 13-45% instead of 45-65%. The authors consider that the deviations did not affect the validity of the study.

A periodic positive control study with α-hexyl cinnamaldehyde was performed using CBA/CaOlaHsd mice in October 2019.
No signs of systemic toxicity or local skin irritation at the ears were observed during the study period. From days 2 and 3 the animals showed an erythema of the ear skin corresponding to score 1 of the test guideline.

The test concentrations of 0.5, 1, and 2.5% resulted in a SI of 1.58, 2.09, and 6.34, respectively. The test concentration of 2.5% resulted in a SI of 6.34 with data having a dose-response relationship, thus EPOTE tested positive for skin sensitising effects. The EC3 value was calculated to be 1.3%, showing that EPOTE is a strong skin sensitiser. The DS has evaluated the study to be reliable without restrictions, Klimisch 1.

10.7.1.2 Human data

Table 8: Summary table of human data on skin sensitisation

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Clinical case study	Cresyl glycidyl ether	The focus in the study was on epoxy hardeners, but patch tests performed with epoxy substances in the patients were also reported. Hence, it is not clear how many patients that were tested for Cresyl glycidylether all together, but only one is reported.	1 patient was positive for Cresyl glycidyl ether	Aalto-Korte et al., 2014
Clinical patch tests of selected patients	o-cresylglycidyl ether. Concentration: 0.25%	Patch tests on selected patients.	3 out of 146 patients (2.1%) showed allergic reactions.	Kanerva et al, 1997
Clinical patch tests of known exposed patients suspected of occupational contact dermatitis and airborne contact dermatitis	o-cresyl glycidyl ether	Patch tests conducted on 22 marble workers handling a bicomponent resin, based on epoxy resin and ortho-cresyl glycidyl ether (CGE). Within 20 days to 2 months of exposure, 10 out of the 22 marble workers had developed contact dermatitis and airborne contact dermatitis.	10 out of 22 exposed workers were positive (45%)	Angelini et al., 1996
Clinical patch tests of selected patients with skin disease	o-cresylglycidyl ether Concentration: 0.25%	Patch tests conducted in the years 1985 to 1992	1 out of 343 patients were positive (0.25%)	Tarvainen et al., 1995
Clinical patch tests of selected patients suspected of occupational skin disease	o-cresylglycidyl ether. Concentration: 0.25%	Patch testing was performed in the years 1984 to 1988	8 out of the 140 patients responded positively (5.7%).	Jolanki et al., 1990

Review reports

The sensitising properties of the substance EPOTE have been assessed in the report 'Ranking of components of epoxy resin systems on the basis of their sensitising potency' from the German Forschungs- und Beratungsinstitut Gefahrstoffe (FOBIG, 2012). The report from 2012 is a thorough

evaluation of the use, experimental and human data on the sensitising capacity of epoxy chemicals. In this report studies of occupational exposure showing contact allergy against o-cresyl glycidyl ethers, usually with simultaneous reaction to phenylglycidyl ether, were described and the authors concluded that EPOTE can be categorised as having a high sensitising potency.

Health Canada has also assessed the skin sensitising properties of EPOTE in a report published in 2020. In this report, it was concluded that available data from human studies and case reports in occupational settings support the potential for skin sensitisation. This is based on several published reports showing positive path tests (0.25% (w/w) of o-CGE) on previously diagnosed patients suffering from allergic contact dermatitis or other skin conditions (Health Canada, 2018). This is in line with the conclusion that that EPOTE can be considered a skin sensitiser in humans by NICNAS (the National Industrial Chemicals Notification and Assessment Scheme) (NICNAS, 2015).

Patch test data
In a study by Jolanki and colleagues (Jolanki et al., 1990), patch testing was performed in the years 1984 to 1988 on a total of 140 patients suspected of occupational skin disease. Of these, 8 responded positively (5.7%) to a concentration of 0.25% o-cresylglycidyl ether. Details about cross-reactions of individual exposures or of the clinical relevance of the reactions in the patients with a positive response to o-cresylglycidyl ether are only available for one of the eight patients (Jolanki et al., 1990, reviewed in FOBIG 2012).

In 1997, Kanerva et al. published the results of a patch test study (no further details) including 50 substances from a plastic and glue test series. For EPOTE, 3 out of 146 patients (2.1%) showed allergic reactions to a concentration of 0.25% o-cresylglycidyl ether. Details from the study were not available (Kanerva et al., 1997, reviewed in FOBIG 2012).

A study by Tarvainen reported results of patch testing with a plastic and glue test series, conducted in the years 1985 to 1992. Only one of 343 patients had a positive reaction to o-cresylglycidyl ether (0.25%). However, the clinical relevance of this reaction could not be established (Tarvainen 1995, reviewed in FOBIG 2012).

In 1996 Angelini et al. reported a case of contact dermatitis to o-cresyl glycidyl ether in marble workers. 10/22 workers handling a bicomponent resin, based on epoxy resin and o-cresyl glycidyl ether developed contact dermatitis and airborne contact dermatitis within 20 days to 2 months of exposure. When patch tested, the 10 symptomatic subjects were all positive to the reactive diluent o-cresyl glycidyl ether and 4 of them also to epoxy resin. Phenyl glycidyl ether also yielded positive responses (in 7/10 cases).

In a publication about contact allergy to epoxy hardeners, patch tests were also performed with epoxy substances. It is not clear how many patients that were tested for Cresyl Glycidyl ether all together, but it is reported that one patient was positive to the substance (Aalto-Korte et al., 1997).

10.7.2 Short summary and overall relevance of the provided information on skin sensitisation

Two reliable Guinea pig maximisation tests have been performed according to OECD TG 406. The results of these studies show that EPOTE is a skin sensitiser, fulfilling the criteria for category 1 according to CLP. The studies were however not considered to be sufficient for subcategorising the

substance as Skin Sens 1A or 1B. Therefore, an LLNA study was requested and conducted in 2018 according to OECD TG 429, to evaluate the skin sensitising potency of EPOTE. Here, a dose-response relationship with an EC3 of 1.3% was found.

In addition to animal data, contact allergy in humans against o-cresyl glycidyl ethers including EPOTE have been repeatedly described in patch test studies of occupational exposure confirming the sensitising properties of EPOTE.

10.7.3 Comparison with the CLP criteria

Classification as a skin sensitiser is warranted when there is evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons or if there are positive results from an appropriate animal test. The information should be considered in a weight of evidence approach.

There is solid evidence that EPOTE is sensitising in animals as well as in humans. Animal data include positive, reliable guinea pig maximisation tests and an LLNA test. In addition, contact allergy against o-cresyl glycidyl ethers including EPOTE has been repeatedly described in patch test studies of occupational exposure, confirming the sensitising properties of EPOTE. Thereby the substance fulfils the criteria for skin sensitiser category 1, according to the CLP criteria.

Classification for skin sensitisation should further include subcategorization in subcategory 1A or 1B when data fulfil cut-offs indicated in the CLP criteria.

For subcategorising as 1A, the substance must show a high frequency of occurrence in humans and/or a high potency in animals to be presumed to have the potential to produce significant sensitisation in humans, whereas the substance most show low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals for subcategorising as 1B. Severity of reaction may also be considered.

The datasets from human patch tests with EPOTE do not include information of exposure levels to the substance at the workplace. Thus, the suggested subcategorisation of EPOTE in this CLH report is based on the available animal studies.

The criteria for subcategorisation in 1A on the basis of results from GPMT are:

≥ 30 % responding at ≤ 0.1 % intradermal induction dose or

≥ 60 % responding at an intradermal induction dose between 0.1 < and ≤ 1 %

The induction concentration used in the two reliable GPMT studies of EPOTE that are available were 5% and 3% respectively, and therefore, the induction concentration of these studies were too high to allow for subcategorization of the substance. On the other hand, the studies do not exclude the possibility of subcategorising as 1A.

The criteria for subcategorisation in 1A on the basis of results from LLNA are:

EC3 values ≤ 2%

In the LLNA from 2018 conducted according to OECD TG 429, a dose-response relationship with an EC3 of 1.3% was found. Thus, according to the CLP criteria, the LLNA points to classification of EPOTE as a strong sensitiser, category 1A.

Taken together, the available positive patch test studies in humans, the positive reliable GPMT studies and the LLNA study suggest that EPOTE should be subcategorised as a Skin Sensitiser category 1A.

10.7.4 Conclusion on classification and labelling for skin sensitisation

According to the CLP criteria as descried above, EPOTE should be classified as Skin sens. 1A;H317: May cause an allergic skin reaction.

No scientific information has been identified to set a specific concentration limit (SCL) and the generic concentration limits of the sub-category 1A (0.1 % w/v) should be used.

10.8 Germ cell mutagenicity

Hazard class not assessed in this dossier.

10.9 Carcinogenicity

Hazard class not assessed in this dossier.

10.10 Reproductive toxicity

Hazard class not assessed in this dossier.

10.11 Specific target organ toxicity-single exposure

Hazard class not assessed in this dossier.

10.12 Specific target organ toxicity-repeated exposure

Hazard class not assessed in this dossier.

10.13 Aspiration hazard

Hazard class not assessed in this dossier.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Hazard class not assessed in this dossier.

12 EVALUATION OF ADDITIONAL HAZARDS

12.1 Hazardous to the ozone layer

Hazard class not assessed in this dossier.

13 ADDITIONAL LABELLING

Skin sensitisers, sub-category 1A, has the generic concentration limit triggering classification of a mixture of ≥ 0.1 %. To protect individuals who are already sensitised to the substance, a lower concentration limit for elicitation is used. According to CLP Table 3.4.6., mixtures containing ≥ 0.01 % of a skin sensitiser in category 1A should be subject to the specific labelling requirements of section 2.8 of Annex II.

A mixture containing ≥ 0.01 % EPOTE should therefore use the statement:

EUH208 – 'Contains 2,3-epoxypropyl o-tolyl ether. May produce an allergic reaction'

14 REFERENCES

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15 ANNEXES

Not relevant