Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

2,3-epoxypropyl *o*-tolyl ether

EC Number: 218-645-3
CAS Number: 2210-79-9

CLH-O-0000007343-77-01/F

Adopted

14 September 2023

14 September 2023

CLH-O-0000007343-77-01/F

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

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted on **14 September 2023** by **consensus** an opinion on the proposal for harmonised classification and labelling (CLH) of:

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

EC Number: **218-645-3**

CAS Number: **2210-79-9**

Rapporteur, appointed by RAC: **Beata Pęczkowska**

Administrative information on the opinion

Denmark has submitted on **1 October 2022** a CLH dossier containing a proposal together with the justification and background information documented in a CLH report.

The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **14 November 2022**.

Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **13 January 2023**.

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The following table provides a summary of the Current Annex VI entry, Dossier submitter proposal, RAC opinion and potential Annex VI entry if agreed by the Commission.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	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	GHS07 GHS08 GHS09 Wng	H315 H317 H341 H411			Note C
Dossier submitters 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			
RAC opinion	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 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	GHS07 GHS08 GHS09 Wng	H315 H317 H341 H411			Note C

GROUNDS FOR ADOPTION OF THE OPINION

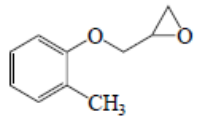
RAC general comment

2,3-epoxypropyl *o*-tolyl ether is a reactive diluent, belonging to glycidyl ethers, used to reduce viscosity and improve polymerisation, and hardeners, particularly amines in epoxy resins.

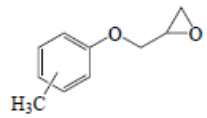
Synonyms of 2,3-epoxypropyl *o*-tolyl ether include o-cresyl glycidyl ether (o-CGE), glycidyl o-tolyl ether, [(o-tolyloxy)methyl]oxirane and 2-[(2-methylphenoxy)methyl]-oxirane.

In two GMPT studies (Unpublished reports, 1989 and 1976) and one clinical case study (Aalto-Korte *et al.,* 2014) included in the CLH report for 2,3-epoxypropyl *o*-tolyl ether, cresyl glycidyl ether (CGE; CAS no.: 26447-14-3) was probably used as test material, although only the trade names for the test substance are available. CGE is the isomer mixture of ortho-, meta- and para-cresyl glycidyl ethers, and is considered as an appropriate analogue for the assessment of the skin sensitising potential of o-cresyl glycidyl ether, as o-CGE and CGE have identical active chemical groups.

Structural formula of o-cresyl glycidyl ether:



Structural formula of cresyl glycidyl ether:



HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

Based on the available data, the Dossier Submitter (DS) proposed to modify the harmonised classification for skin sensitisation from Skin Sens. 1 to Skin Sens. 1A, with the generic concentration limit (GCL) of 0.1%.

Animal data

***Table**: Summary 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**
Local Lymph Node Assay (LLNA) (OECD TG 429, version 2010) GLP Klimisch 1	Mice CBA/CaOlaHsd strain 4 female mice in each group	2,3-epoxypropyl *o*-tolyl ether (purity approximately 90%) Vehicle: acetone/ olive oil (4:1, v/v) Positive Control: α-hexyl cinnamaldehyde dissolved in acetone/olive oil (4:1 v/v)	Three test groups: 0.5%, 1% and 2.5% (the highest non-irritant concentration in pre-test)	**Positive** **Dose-dependent proliferation of lymphocytes,** SI: 1.58 (at 0.5%), 2.09 (1%) and 6.34 (2.5%) **EC3 value: 1.3%**	Unpublished report, 2019
Guinea pig maximisation test (GPMT) according to OECD TG 406 (version 1981) GLP 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 (trade names; composition and purity not reported) Vehicle: vaseline	3% (intradermal induction dose) 10% (topical induction dose) 3% (challenge dose, non-irritating)	**Positive** 20/20 (100%; 24h, 48h after challenge) Control group: 0/20	Unpublished report, 1989
Guinea pig maximisation test (GPMT) according to OECD TG 406 (version 1981) GLP Klimisch 2	10 male and 10 female 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%) Vehicle: vaseline	Induction phase 1: 5% (intradermal injections) Induction phase 2: 10% (epidermal) Challenge phase: 1% (as non-irritating)	**Positive** 24h -16/20 (80%) 48h -14/20 (70%) Control group: 0/10	Unpublished report, 1991
Guinea pig maximisation test (GPMT) (conducted prior to OECD TG, not considered reliable by the DS: Klimisch 3 Non-GLP	10 male and 10 female Pirbright white strain Guinea pigs in each group. A total of 10 animals in the positive control group	TK 10410 (trade name; no information on purity) Vehicle: saline	Induction phase: 0.1% (intradermal injection) Challenge phase: 0.1% injected intradermally on the previously untreated flank	24h -3/20 (15%) the reaction sites were evaluated by skin-fold thickness determined with a skin-fold gauge	Unpublished report, 1976

Human data

Table: *Summary 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 (CGE, CAS no.: 26447-14-3) Concentration: 0.25%[1]	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 glycidyl ether altogether, 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-cresyl glycidyl 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 concentration: 0.25% in petrolatum	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-cresyl glycidyl 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-cresyl glycidyl 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

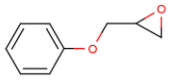
Review reports

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), studies of occupational exposure showing contact allergy against o-cresyl glycidyl ether, usually with simultaneous positive reaction to phenyl glycidyl ether (a structurally analogous substance)[2], were described and the authors concluded that o-CGE can be categorised as having a high sensitising potency.

Health Canada assessed the skin sensitising properties of o-CGE 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 patch 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 o-CGE can be considered a skin sensitiser in humans by

[1] Based on the publication by Aalto-Korte *et al.,* (2015), where the same case was reported.

[2] Phenyl glycidyl ether (CAS no.: 122-60-1), structural formula:



NICNAS (the Australian National Industrial Chemicals Notification and Assessment Scheme[3]) (NICNAS, 2015).

Comments received during consultation

There were two comments submitted by Member States (MS). Both MSs supported the proposal to modify the classification from Skin Sens. 1 to Skin Sens. 1A with a GCL of 0.1% (w/v). One MS pointed out that the purity of substance used in the LLNA study were approximately 90%. The dose calculation was not adjusted to the purity, and it is not clear whether the results obtained can be attributed to 2,3-epoxypropyl *o*-tolyl ether or the impurity(-ies).

The DS's responded that the LLNA study was included in the registration dossier for 2,3-epoxypropyl *o*-tolyl ether (EC 218-645-3) and therefore the tested substance is considered to be similar to the registered one. Furter, they considered it unlikely that the impurities in the registered o-CGE contribute to the skin sensitising properties of the substance.

The two commenting MS's asked for clarification on substance identification (impurities contribution to the proposed classification, stereochemistry). The DS responded that none of the impurities of 2,3-epoxypropyl *o*-tolyl ether (as declared in the registration dossier) carry a notification or harmonised classification. In addition, QSAR analysis performed by the DS did not reveal any concerns in regard to skin sensitisation. In relation to the stereoisomerism of 2,3-epoxypropyl o-tolyl ether, information on the ratio of the stereoisomers is not available.

Assessment and comparison with the classification criteria

Animal data

Two GPMT studies, (1989, 1991) performed according to OECD TG 406 and GLP are available for 2,3-epoxypropyl *o*-tolyl ether (o-CGE). In the first GPMT (1989) the dose level used for intradermal induction was 3%. All of the tested animals (100%) demonstrated positive dermal reactions when compared with the control group (0/20 positive dermal reactions) at 24 hours and 48 hours after challenge. In the second GPMT study (1991), the dose level used for intradermal induction was 5%. The tested animals showed positive dermal reactions: 80% and 70%, 24 hours and 48 hours after challenge, respectively, when compared to the control group (0/10 positive dermal reactions). The results of both GPMT fulfil the criteria for classification in Sub-Category 1B (≥30% responding at >1% intradermal induction dose). O-CGE was not tested at ≤1% intradermal induction dose in the guinea pig maximisation tests (above), therefore, a classification in Sub-Category 1A cannot be excluded.

In the third GPMT study (1976), an intradermal induction concentration of the test substance (identified by trade name only) of 0.1% was tested, with positive response in 15% animals at 24 hours after challenge. However, this study is considered as not reliable as it was not performed according to OECD or similar test guidelines and it is a non-GLP study.

The new LLNA study was conducted in 2019 according to OECD TG 429, to evaluate the skin sensitising potency of o-CGE. A dose-response relationship with an EC3 of 1.3% was found and

[3] NICNAS is the statutory scheme regulating importing and manufacturing of industrial chemicals that are new to Australia (REACH-like regulation and registration). After July 1st, 2020, NICNAS was replaced by a new scheme called Australian Industrial Chemicals Introduction Scheme (AICIS).

thus the criteria for a classification for skin sensitisation in Sub-category 1A (EC3 values ≤2%) are met on the basis of this study.

Human data

Contact allergy against glycidyl ethers, including o-CGE, has been repeatedly described in patch test studies of occupational exposure, confirming the sensitising properties of o-CGE (Aalto-Korte *et al.,* 2014; Kanerva *et al,* 1997; Angelini *et al.,* 1996; Tarvainen *et al.,* 1995; Jolanki *et al.,* 1990). Thereby, the substance fulfils the criteria for a classification for skin sensitisation, according to the CLP criteria, i.e.: "substance shall be classified as skin sensitiser (category 1) if there is evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons".

In the available positive clinical patch tests of selected patients, the positive response to a concentration of 0.25% o-cresyl glycidyl ether was 2.1% and 5.7%, respectively (Kanerva *et al.,* 1997 and Jolanki *et al., 1990*). Therefore, a high frequency of occurrence of skin sensitisation (>2%) is demonstrated according to the Guidance on the Application of the CLP Criteria (Section 3.4.2.2.3.1., Table 3.2). However, the datasets from human patch tests with o-CGE do not include information of exposure levels to the substance at the workplace and the exposure index could not be achieved (according to the Guidance on the Application of the CLP Criteria, Section 3.4.2.2.3.1., Table 3.3) thus sub-categorisation of skin sensitisation, based on human data, is not possible. The study by Angelini et al., (1996), showed that o-CGE gave positive responses in all 10 symptomatic marble workers handling a bicomponent resin when the workers were patch tested simultaneously with other reactive diluents. On this basis, o-CGE can be categorised as having a high sensitising potency.

Overall, based on animal data (GPMT studies from 1989, 1991) and human data, 2,3-epoxypropyl *o*-tolyl ether fulfils the criteria for a classification for skin sensitisation in Category 1, according to the CLP criteria. Further, the results of the LLNA study (2019) with o-CGE allow for a classification for skin sensitisation in Sub-category 1A based on the EC3 value of 1.3%

In conclusion, RAC considers that 2,3-epoxypropyl *o*-tolyl ether **warrants a classification as Skin Sens. 1A, H317, with the generic concentration limit (GCL) of 0.1%** (in agreement with the DS).

Additional references

Aalto-Korte K., Pesonen M. and Suuronen K. Occupational allergic contact dermatitis caused by epoxy chemicals: occupations, sensitizing products, and diagnosis, Contact Dermatitis. 2015 July, 73, 336–342 doi:10.1111/cod.12445

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter and additional information (if applicable).

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