Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

2,3-epoxypropyl neodecanoate

EC Number: 247-979-2
CAS Number: 26761-45-5

CLH-O-0000007104-83-01/F

Adopted

18 March 2022

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 2,3-EPOXYPROPYL NEODECANOATE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: 2,3-epoxypropyl neodecanoate
EC number: 247-979-2
CAS number: 26761-45-5
Dossier submitter: Denmark

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2021	Germany		MemberState	1
Comment received				
In Table 1, section 1.1 it is not clear why the substance is a UVCB substance. The IUPAC name "(oxiran-2-yl)methyl 2,2-dimethyloctanoate)" and structural formula refer to only one isomer. DECA suggests adding an explanation that the branching of the C10 chain is highly variable which causes the UVCB nature of the substance. Additional exemplary or general structural formulas (similar to the one in the registered substances factsheet on ECHA website) would be beneficial. Moreover, the substance is classified as Muta. 2 (H341). According to the CLP Regulation this classification requires an allocation of the hazard pictogram GHS08. Thus, in Section 2.1 of the CLP dossier "Proposed harmonised classification and labelling according to the CLP criteria" Table 2 - line „Dossier submitters proposal" / column „Labelling/ Pictogram, Signal Word Code(s)" and - line „Resulting Annex VI entry if agreed by RAC and COM" / column „Labelling/ Pictogram, Signal Word Code(s)" the coding of the hazard pictogram "GHS08" has to be added.				
Dossier Submitter's Response				
Thank you for the comments. The DS agrees completely. It is right that the IUPAC name and structural formula refers to only one isomer. However, the registration report (CSR) defines around 37 different isomers and constituents, each in concentrations from 0% to about 20%. The branching of the chain is highly variable and causes the UVCB nature of the substance. It is not possible to describe all the different isomers and their individual concentration ranges here in the RCOM because of confidentiality.				

The pictogram GHS08 will be added in the final report.
RAC's response
Thank you very much for your comments. Noted.

Date	Country	Organisation	Type of Organisation	Comment number
04.08.2021	France		MemberState	2
Comment received				
The substance is an UVCB. Three constituents are listed in section 1.2. Could you please specify their levels in EPDA if non-confidential data or clarify if they have an impact on the proposed classification.				
Dossier Submitter's Response				
Thank you for your comment. The three constituents; 1,3-dichloropropan-2-ol and; 1-chloro-3-(propan-2-yloxy)propan-2-ol and the last; 2,2'-oxybis(methylene)]bisoxirane are only present at concentration ranges that would have no influence of the classification of the UVCB.				
RAC's response				
Thank you very much for your comments. Noted.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
30.07.2021	Germany		MemberState	3
Comment received				
DE-CA supports the proposal for classification as Muta. 2 (H341). The classification as Muta. 2 is considered warranted because of positive evidences for induction of gene mutations in somatic cells in an adequate mammalian vivo mutagenicity test (oral TGR according to OECD 488; positive in liver, kidney and bone marrow). Furthermore, the available data in germ cells are not considered to be sufficient to support a Muta. 1B classification. DE-CA agrees with the DS that the biological relevance of the results of the available transgenic animal mutagenicity assay performed in germ cells according to OECD TG 488 using the appropriate dosing and sampling times are unclear. This is based on the following arguments: • No statistically significant difference was detected in the mean mutation frequency values between controls and the 7 treated animals. • The mutation frequency values of all animals (also the 3 with pfu below 125,000) fell within the laboratory's historical control data. • Statistically significant difference between controls and treated animals was detected only if animals with pfu < 125,000 were excluded from the data set (2 control and 1 treated animals). However, whereas the mean mutation frequency of the remaining 6 treated animals (pfu > 125,000) was similar and even lower compared to the mean mutation frequency of all 7 treated animals (52.76 versus 53.18), the mean mutation frequency of the vehicle controls group was lower if the 2 control animals with pfu < 125,000 were excluded (39.59 versus 46.16). Thus, the biological relevance of this estimated significant difference is considered to be highly questionable. Moreover, the				

detected increase was marginal (1.33-fold) and the mean mutation frequency of all treated animals were not outside the historical control data.
Thus, from the available data no clear evidence for induction of mutations in germ cells can be derived.

Dossier Submitter's Response

The DS thank you for your support.

RAC's response

Thank you very much for your comments. Noted.

Date	Country	Organisation	Type of Organisation	Comment number
04.08.2021	France		MemberState	4

Comment received

This is a borderline case between Muta 2 or no classification.

Negative result obtained in germ cells from a TGR study and one equivocal result of questionable toxicological relevance in germ cells in another TGR would not be in favour to classification.

In contrast, we note that consistent findings were observed for induction of gene mutations from in vitro studies (3 Ames tests) and in vivo studies with positive results for various somatic cells in a TGR study by intraperitoneal injection. These results can support a classification as Muta 2 according to CLP guidance:
Positive evidence obtained from experiments in mammals and/or in some cases from in vitro experiments, obtained from:
– Somatic cell mutagenicity tests in vivo, in mammals; or
– Other in vivo somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays.

We have some questions which may help for concluding:
• Could you please clarify if the TGR (2012) was performed by oral or IP route? (page 19: oral route is noted but page 27 refers to ip injection)
• Do you have any indication that germ cells were actually reached in the TGR studies? If not, is there any additional information from other studies (such as repeated dose toxicity studies) that can suggest that the substance can reach the germ cells?

Dossier Submitter's Response

The DS does not agree that this is a borderline case between Muta 2 or no classification. According to the CLP criteria, positive results in somatic tissues are sufficient for Muta 2 classification, whereas results obtained in germ cells are only relevant when considering a Muta 1 classification:

The classification in Category 2 is based on:

— positive evidence obtained from experiments in mammals and/or in some cases from in vitro experiments, obtained from:
— somatic cell mutagenicity tests in vivo, in mammals; or
— other in vivo somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays (Source: CLP regulation (EC) No 1272/2008).

Therefore, the consistent findings observed for induction of gene mutations in *in vitro* studies and *in vivo* studies with positive results for various somatic tissue in a TGR study (2012) is supportive of a classification as Muta 2 according to the CLP criteria.

It should be noted that the 2012 TGR study should not be taken in to account when considering germ cell mutagenicity, as this is a 28 + 3d study. According to the guideline (TG 488), this time scheme (28+3) cannot be used to assess germ cell mutagenicity, which is also why another TGR study was requested and conducted in 2019. To sum up, there is only one reliable germ cell study available, and that study was equivocal.

Answers to questions raised by France:
EPDA was administered by gavage in the 2012 TGR study whereas the positive control used was ethylnitrosourea (ENU) and this substance was administered by intraperitoneal injection.

We have no indications of whether the germ cells were reached in the TGR study or indications otherwise from other studies such as repeated dose toxicity studies.

RAC's response

Thank you very much for your comments. Noted.

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
04.08.2021	France		MemberState	5

Comment received

Based on experimental data, classification as Skin. Sens. 1A is clearly fulfilled. In contrast, human data do not indicate a high level of skin sensitisation based on clinical cases (only 2 positive among 9 clinical cases) and data on selected patients (all negative), when using the substance at doses of 0.25% or 1% in the patch tests.
Based on experimental studies, FR supports the classification as Skin Sens.1A.

Concerning the SCL, we agree that one experimental study concludes to extreme potency of the substance for skin sensitisation. However, other experimental studies suggest lower potency or cannot be used for concluding on potency. Considering also the rather negative human data, we question if the GCL for strong potency (0.1%) would not be more appropriate than the proposed SCL of 0.001%

Dossier Submitter's Response

Thank you for your support on for the classification in Skin Sens 1A, and the considerations on the rather few human data. With respect to the animal data, the DS would stress that 2,3-epoxypropyl neodecanoate is an UVCB, thus that variations in composition may influence the sensitising potential of the substance on the marked and also contribute to disparity in studies results. The DS considers that the more severe results should be given more weight in the evaluation of the relevant SCLs for 2,3-epoxypropyl neodecanoate. The SCL will be discussed in the RAC.

RAC's response

Thank you very much for your comments. Noted.

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Date	Country	Organisation	Type of Organisation	Comment number
30.07.2021	Germany		MemberState	6
Comment received				
DE-CA agrees to the classification of 2,3-epoxypropyl neodecanoate as Skin Sens. 1 A with the corresponding concentration limits. The reported human evidences show that sensitisation is possible. Two GMPT-studies clearly prove that 2,3-epoxypropyl neodecanoate is a potent sensitiser. A third study does not prove the classification as Skin Sens. 1A, but also does not contradict it. However, it is viewed critically that one study (Unpublished report, 1998) is evaluated in the dossier as "do not contradict this conclusion" (p. 12), because it is considered actually not to support a classification as sub-category 1A. Rather, the limitations of this study should be discussed which would include the unspecified composition of the test substance. The nature of the substance as a UVCB with varying composition may also help to explain the inconsistent study results.				
Dossier Submitter's Response				
Thank you for the support to the classification in category 1A. The DS agrees that the GPMT from 1998 fulfils the subcategorization in category 1B due to the dose used and the response achieved and not sub-category 1A. The sensitising response to EPDA thus differs across the available studies. As you point to, constituent variation of the UVCB may lead different affinity to receptor (e.g. different structural configuration of constituents) may contribute to variation in the results. The DS considers that the more severe results should be given more weight in the evaluation of the relevant SCLs for 2,3-epoxypropyl neodecanoate.				
RAC's response				
Thank you very much for your comments. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
06.08.2021	United States of America	Hexion VAD	Company-Manufacturer	7
Comment received				
Dear ECHA, In regards to the harmonization of classification and labelling of 2,3-epoxypropyl neodecanoate (EC# 247-979-2, CAS# 26761-45-5), particularly sensitization, it is our expert judgment that the studies available are not sufficient to determine the level of specific concentration limit of 0.001%. While we would agree that the evidence would support a category level of 1A we believe the correct SCL is uncertain. The Danish authority states that the evidence does not rule it out this SCL, however, the data does not mandate it either. The early OECD 406 Guinea Pig Maximization test is qualitative in nature and is poor at determining a qualitative sensitization response. We, therefore, propose to initiate a series of in silico, in vitro and/or in vivo studies including but not limited to the following: OECD 442C In Chemico Skin Sensitisation OECD 442D ARE-Nrf2 Luciferase Test Method OECD 442A Local Lymph Node Assay: DA OECD 442B Local Lymph Node Assay: BrdU-ELISA or –FCM				

OECD 429 mouse Local Lymph Node Assay
GARDskin1
GARDpotency1
The details of the studies and the timings will need to be coordinated with validated and reliable CROs to determine the most appropriate protocols. The in vitro and in silico studies would be relatively rapid to complete and clarity on the correct SCL would be obtained. We propose to complete these studies before the harmonization of the classification and labelling is finalized.

1: GARDskin and GARDpotency included in OECD Test Guideline Program [TGP no. 4.106]
GARDskin: Published in Johansson et al. [2019], Validation of the GARDTMskin assay for assessment of chemical skin sensitizers — ring trial results of predictive performance and reproducibility. Toxicological Sciences.
GARDpotency: Published in Gradin et al. [2020]. The GARDTMpotency Assay for Potency—Associated Subclassification of Chemical Skin Sensitizers — Rationale, Method Development and Ring Trial Results of Predictive Performance and Reproducibility. Toxicological Sciences.

Dossier Submitter's Response

Thank you for the support to classify 2,3-epoxypropyl neodecanoate (EPDA) as a skin sensitiser in category 1A. The SCL setting will be discussed in the RAC.
The DS appreciates the proposal to investigate the skin sensitising potential of EPDA further in an extensive *in chemico, in vitro* and *in vivo* test battery. However, as the available *in vivo* animal data were deemed sufficient by the registrant to fulfil the requirements under REACH registration they are considered sufficient for classification purposes. This was confirmed by the Member State Committee in relation to substance evaluation on EPDA in 2016, leading to the deletion of a testing requirement for skin sensitisation from the substance evaluation decision. As EPDA appears to be a potent sensitiser, a harmonised classification should not be postponed further. The DS prefers not to put the process of classification on hold awaiting the projected experimental data. If substantial new data are provided, a revision of the classification could be initiated.

RAC's response

Thank you very much for your comments. Noted.