Ministry of Environment of Denmark
Environmental Protection Agency

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

2,3-epoxypropyl neodecanoate

EC No 247-979-2

CAS No 26761-45-5

Evaluating Member State: Denmark

Dated: 25 January 2021

Evaluating Member State Competent Authority

MSCA name: Danish Environmental Protection Agency

Contact information:
Tolderlundsvej 5
5000, Odense C
Denmark
Tel: +45 72 54 40 00
Email: mst@mst.dk
Contact person: Nellie Anne Martin
Tel: +45 21 77 34 87
Email: neama@mst.dk

Year of evaluation in CoRAP: 2015

Before concluding the substance evaluation a Decision to request further information was issued on: 01 March 2017.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

2,3-epoxypropyl neodecanoate was originally selected for substance evaluation in order to clarify concerns about:

- Suspected Sensitiser (Skin sensitisation)
- Suspected CMR (Mutagenicity, Carcinogenicity)
- Exposure (workers, high (aggregated) tonnage, wide dispersive use)

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

The eMSCA has submitted a classification proposal for Skin Sens cat 1A and Muta cat 2 in December 2020.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION Conclusions	Tick box
Need for follow-up regulatory action at EU level	X
Harmonised Classification and Labelling	X
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

4.1.1. Harmonised Classification and Labelling

Sensitisation

The eMSCA has evaluated that the available data on skin sensitisation of 2,3-epoxypropyl neodecanoate (EPDA) fulfil the criteria for classification as an extreme skin sensitiser. EPDA thus should be classified as Skin Sens category 1A with a specific concentration limit (SCL) of 0.001%.
The substance has no harmonised classification in Annex VI of the CLP regulation. Amongst notifications of self-classification, only one group of 44 notifiers (total number of notifiers is around 1200) has proposed to classify EPDA as Skin Sens category 1A, with the general

concentration limit (GCL) of 0.1%. A total of 1138 notifiers (10 groups), including the registration holder, classify as Skin Sens 1 (GCL 1%).

Harmonisation of the classification for skin sensitisation as Skin Sens 1A with an SCL of 0.001% is proposed with the aim of securing that European users of EPDA receive sufficient information through the label and through the Safety Data Sheet (SDS) to take relevant precautions in the handling of mixtures containing EPDA.

Mutagenicity

In vitro and *in vivo* data demonstrate that EDPA is a somatic cell mutagen in various tissues, whereas a concern for germ cell mutagenicity is not likely. Consequently, the eMSCA finds that EPDA meets the requirements for a harmonized classification as Muta cat. 2.

Amongst notification of self-classification, 293 notifiers out of around 1200 notificers have proposed to classify EPDA as Muta 2. Harmonisation of the classification for Muta 2 is therefore necessary to secure that European users of EPDA receive sufficient information through the label and through the safety Data Sheet (SDS) to take relevant precautions in handling of mixtures containing EPDA.

4.1.2. Conclusion on other initial concerns

Carcinogenicity

The available *in vivo* and *in vitro* data show that EPDA might be a genotoxic, non-threshold carcinogen. This concern is further supported by the positive predictions for carcinogenicity in the Danish (Q)SAR Database. Furthermore, glycidyl alcohol, which has a harmonized classification for carcinogenicity (CARC 1B) is predicted to be a metabolite of EPDA.

Based on these observations, the draft decision originally contained a request for a carcinogenicity study (OECD 451). Following the comments from the registrant, this request was removed from the final decision. It was, however, specified in the final decision that the concern for carcinogenicity had not been clarified, but that the eMSCA considered that the process for clarification of this concern would benefit from the clarification of the concern for mutagenicity in the follow up phase. As mentioned above, the eMSCA concludes that EPDA is a somatic mutagen. The next regulatory step was the submission of a Muta 2 classification proposal in December 2020.

According to REACH Annex X, a carcinogenicity study may be required if the substance has wide dispersive use and is classified as Muta 2. Therefore, should a harmonised classification as Muta 2 be adopted, further information on carcinogenicity may be requested in a subsequent compliance check.

Exposure

Based on information in the registration report and in the report from the Danish LOUS project (Danish EPA, 2015) there is sufficient evidence to conclude on possible frequent and/or long-term human exposure to EPDA due to very high tonnage, widespread use, the wide range of end uses of EPDA, as well as the many uses in products of which some are available for consumers. Reports on skin sensitisation in workers also corroborate the potential for exposure.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

- Not relevant

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Indication of a tentative plan is not a formal commitment by the evaluating Member State. A commitment to prepare a REACH Annex XV dossier (SVHC, restrictions) and/or CLP Annex VI dossier should be made via the Registry of Intentions.

Table 2

FOLLOW-UP		
Follow-up action	Date for intention	Actor
CLP classification proposal for Skin Sens 1A and Muta 2	*18 December 2020*	*DK EPA*

Following up on conclusions of the present substance evaluation the Danish EPA has filed a registry of intention, and subsequently, in December 2020, a classification proposal for the endpoints Skin Sens cat 1A and Muta cat 2 under CLP. The proposal is currently being reviewed by ECHA.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

2,3-epoxypropyl neodecanoate was originally selected for substance evaluation in order to clarify concerns about:

- Suspected Sensitiser (Skin sensitisation)
- Suspected CMR (Mutagenicity, Carcinogenicity)
- Exposure (workers, high (aggregated) tonnage, wide dispersive use)

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	Outcome/conclusion
Skin sensitisation	*Follow up action: CLP proposal for Skin Sens 1A classification*
Mutagenicity	*Follow up action: CLP proposal for Muta 2 classification*
Carcinogenicity	*Ambiguous but currently no further action – please see section 7.9.6*
Exposure	*Ambiguous but currently no further action – please see section 7.12*

7.2. Procedure

EPDA (2,3-epoxypropyl neodecanoate; EC No 247-979-2, CAS No 26761-45-5) was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2015. The initial concerns for EPDA leading to enrolment in CoRAP were human health mutagenicity; skin sensitisation; carcinogenicity and exposure due to wide dispersive use, consumer use, high (aggregated) tonnage.

The Competent Authority of Denmark (hereafter called the evaluating MSCA (eMSCA)) was appointed to carry out the evaluation pursuant to Article 45(4) of the REACH Regulation. The eMSCA concluded that further information was required to clarify the concerns. Therefore, a draft decision pursuant to Article 46(1) of the REACH Regulation was prepared to request further information. The draft decision was submitted to ECHA 17 March 2016 and the decision making followed the procedure of Articles 50 and 52 of the REACH Regulation.

ECHA notified the registrant of the draft decision and comments from the registrants were received within the commenting period. In addition, the registrant updated their dossier in June 2016 with regard to exposure. These comments and updates were taken into account in the preparation of the final decision.

In the final decision, published in March 2017, a transgenic rodent somatic and germ cell assay (OECD 488) in mice was requested to clarify the mutagenicity concern.

Originally, the draft decision also contained a request for a carcinogenicity study (OECD 451). Although this request was removed in the final decision, it was specified that the

concern for carcinogenicity had not been clarified but that this concern would be revisited in the follow up phase once the information requested by the decision was available.

Likewise, a request on skin sensitisation was deleted from the final decision, as the MSC considered that the studies included in the registration dossier were valid and could be relied upon for classification. No further studies for skin sensitisation were thus requested.

In the end of May 2019, the registrant(s) updated the registration dossier in response to the substance evaluation decision, including the requested full report from the OECD TG 488 study. Due to a number of discrepancies in the study protocol from the decision request, the eMSCA asked the registrant for justification for these deviations. Supplemental information was provided 20 September 2019, allowing the eMSCA to initiate the follow-up evaluation of the substance.

Overall, the eMSCA considers the available data on mutagenicity sufficient to conclude that EPDA is mutagenic in somatic cells and that it is unlikely that further testing would clarify the significance of the findings on mature sperm seen in the TGR from 2019.

As a consequence of the conclusions for the endpoints skin sens and mutagenicity obtained in this substance evaluation, the eMSCA filed a classification proposal for Skin Sens 1A and Muta 2 in December 2020.

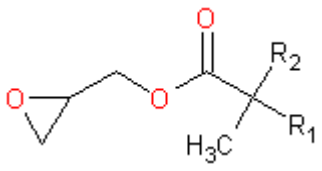
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	2,3-epoxypropyl neodecanoate (EPDA)
EC number:	247-979-2
CAS number:	26761-45-5
Index number in Annex VI of the CLP Regulation:	
Molecular formula:	C13H24O3
Molecular weight range:	~200-300 g/mol
Synonyms:	• Glycidyl neodecanoate • Neodecanoic acid, oxiranylmethyl ester • oxiran-2-ylmethyl 2,2-dimethyloctanoate • Oxiran-2-ylmethyl 2-ethyl-2,5-dimethylhexanoate

Type of substance ☐ Mono-constituent ☐ Multi-constituent ☒ UVCB

Structural formula:



Multiconstituent/UVCB substance/others

Constituents

A list of up to 37 constituents is available in the publicly available registration dossier on ECHA website. Concentration ranges are claimed confidential.

7.4. Physico-chemical properties

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	Value
Physical state at 20°C and 101.3 kPa	Liquid
Vapour pressure	1.5 - 15 Pa @ 20 - 25 °C
Water solubility	70 mg/L @ 20 °C and pH 5.3
Partition coefficient n-octanol/water (Log Kow)	The Log Pow for 2,3-epoxypropyl neodecanoate was measured experimentally by the "Shake-Flask" HPLC method and estimated by QSAR modeling. Log Pow values ranged from approximately 2.6 to 4.4
Flammability	Not technically Feasible
Explosive properties	No explosive functional groups and oxygen balance less than -200
Oxidising properties	*Data waived*
Granulometry	*Data waived*
Stability in organic solvents and identity of relevant degradation products	*Data waived*
Dissociation constant	*Data waived*

7.5. Manufacture and uses

7.5.1. Quantities

Table 6

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☒ 10 – 100 t	☒ 100 – 1000 t	☒ 1000- 10,000 t	☒ 10,000-50,000 t
☒ 50,000 – 100,000 t	☒ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☒ > 1000,000 t	☐ Confidential

7.5.2. Overview of uses

Table 7

USES	
	Use(s)
Manufacture: Synthesis	Environment release categories (ERCs) ERC 1: Manufacture of substances Process categories (PROCs) PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 15: Use as laboratory reagent
Uses as intermediate	Environmental release categories (ERCs) ERC 6a: Industrial use resulting in manufacture of another substance (use of intermediates) Process categories (PROCs) PROC 3: Use in closed batch process (synthesis or formulation) PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 15: Use as laboratory reagent Product Categories PC 0: Other: PC 19: Intermediate
Uses at industrial sites	Industrial Blending (pure substance use) Preparation of substance for epoxy flooring. pure substance used. Technical function of the substance: Intermediate Environmental release categories (ERCs) ERC2: Formulation of preparations Process categories (PROCs) PROC 3: Use in closed batch process (synthesis or formulation) PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) Product categories PC1: Adhesives, sealants Industrial blending (<20% EPDA) Epoxy flooring. Formulated resin processing. Environmental release category (ERC) ERC 4: Industrial use of processing aids in processes and products, not becoming part of

	articles Process categories (PROCs) PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 15: Use as laboratory reagent Product categories: PC1: adhesives, sealants Automotive and Industrial coatings – Resin manufacturing Technical function of the substance during formulation: Intermediates Environmental release categories (ERCs) ERC 6a: Industrial use resulting in manufacture of another substance (use of intermediates) Process categories (PROCs): PROC 3: Use in closed batch process (synthesis or formulation) PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 15: Use as laboratory reagent Product Categories PC 9a: Coatings and paints, thinners, paint removes Paint manufacturing/formulation <1% EPDA Technical function of the substance during formulation: Intermediates Environmental release categories (ERCs) ERC 6a: Industrial use resulting in manufacture of another substance (use of intermediates) Process categories (PROCs) PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) Product Categories used PC 9a: Coatings and paints, thinners, paint removes
Uses by professional workers	Professional application of Epoxy flooring with <20% substance Building and construction work

	Environmental release categories (ERCs) ERC 8f: Wide dispersive outdoor use resulting in inclusion into or onto a matrix ERC 8c: Wide dispersive indoor use resulting in inclusion into or onto a matrix Process categories (PROC) PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 10: Roller application or brushing Product Categories PC 1: Adhesives, sealants
Consumer Uses	All consumer use in products, substances and mixtures is advised against by the registrant. However, according to 'Survey of 2,3-epoxypropyl-neodecanoate. A report under the LOUS review project' Danish EPA (Environmental project No. 1713, 2015) exposure to consumers cannot be excluded as coating products are available to consumers according to information from safety data sheets. This is supported by information in the Nordic product registers (SPIN database: http://www.spin2000.net/spinmyphp/) indicating that one or several uses very probably leads to consumer exposure.
Article service life	Not evaluated by eMSCA. Not relevant according to the registrant.

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Not available

7.6.2. Self-classification

In the registration(s):

Aquatic Chronic 2, H411
Skin Sens. 1, H317
Muta. 2, H340

In addition the following hazard classes are notified among the aggregated self-classifications in the C&L Inventory:

Skin Irrit. 2, H315
Muta. 2, H341
Carc. 1B, H350
Aquatic Chronic 2, H413
Eye Irrit. 2, H319
STOT SE 3, H335

7.7. Environmental fate properties

Not evaluated

7.8. Environmental hazard assessment

Not evaluated

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

The predominant pathway of detoxication of EPDA was found to be epoxide hydrolase and carboxylesterase hydrolysis. To a lesser extent EPDA was metabolised by glutathione conjugation.

Data from *in vitro* studies using diffusion cell technology with skin samples from rats, mice and humans demonstrated that an EPDA-isomer was metabolised in skin samples from rat, mouse and humans and that rat skin was most permeable to the test substance isomer. The degree of metabolism was not stated. Human skin samples were approximately one order of magnitude less permeable to the EPDA-isomer than rodent skin (REACH registration data, 2014).

7.9.1.1. QSAR Predictions of metabolism of EPDA

Predicted metabolism of EPDA by carboxylesterase hydrolysis results in the generation of glycidyl alcohol (CAS no.: 556-52-5), which has a harmonised classification of Muta cat 2 and Carc cat 1B. Predicted metabolism of EPDA by carboxylesterase hydrolysis results in the generation of glycidyl alcohol. The metabolic site predictor Metaprint 2D (previously available from Cambridge University, but no longer available) which indicate the relative likelihood of metabolism occurring at a particular site in the molecule, report the likelihood of some constituents of EPDA being hydrolyzed to yield glycidyl alcohol to be between 66-100%.The MultiCASE META mammalian metabolism rule-based (Q)SAR system was applied to predict if, according to the program, glycidyl alcohol would be formed from the Neodecanoic acid, 2-oxiranylmethyl ester constituents, and if so in which concentration. For a number of constituents formation of glycidyl alcohol is predicted with a yield between 0.9% and 11.5%.

7.9.2. Acute toxicity and Corrosion / Irritation

Information from the registration dossier on the above end-points are included for information. The eMSCA has not evaluated the data presented by the registrant.

No acute toxicity of EPDA has been observed in studies with oral, dermal and inhalation doses of EPDA to rats (REACH registration data, 2014).

In an acute oral toxicity study according to OECD TG 420, no adverse findings attributed to the test substance administration were observed. Single oral administration of EPDA at a dose level of 2000 mg/kg caused no death in a group of ten fasted rats. The acute median lethal oral dose level (LD50) was found to exceed 2000 mg/kg body weight (REACH registration data, 2014).

Inhalation exposure of rats to a saturated vapour concentration of EPDA of approximately 240 mg/m^3 (26 ppm) performed according to a non-guideline standard method resulted in no mortalities. Therefore, the acute 4 hr LC50 value for EPDA is > 240 mg/m^3 (26 ppm) (REACH registration data, 2014).

The acute dermal toxicity of EPDA to male and female rats was assessed in an OECD TG 402 study. No mortalities or significant adverse clinical signs were observed. The slight erythematous reactions observed proved to be transient. The acute median lethal dermal dose level (LD50) for the test substance was found to exceed 2000 mg/kg body weight (REACH registration data, 2014).

Under the conditions of an OECD TG 404 study undiluted EPDA was not irritating to rabbit skin following four hours of exposure (REACH registration data, 2014).

The conclusion in the registration on studies on skin and eye irritation is that EPDA is not an irritant (REACH registration data, 2014).

EPDA was investigated for eye irritation potential in an OECD TG405. Instillation of 0.1 mL EPDA into the conjunctival sac of three rabbits caused transient conjunctival changes that resolved within 24 hours. The iris and cornea were overtly unaffected by instillation of the test article. Therefore, under the conditions of this study, EPDA was considered by the registrant to be non-irritant to the rabbit eye (REACH registration data, 2014).

7.9.3. Sensitisation

7.9.3.1.1. Animal data

Four animal tests on skin sensitisation performed with EPDA have been identified. Two tests using Guinea pigs were performed in 1977 prior to the establishment of the first OECD guidelines. Two other more recent GPM tests were OECD compliant. The eMSCA notes that the MSC during discussion on the draft decision on EPDA in December 2016 considered the three studies from 1977 and 1998 described below valid and sufficient for classification purposes.

A study in Guinea pigs using adjuvant (Unpublished report, 1977a) reports sensitisation response at challenge in 19/20 animals (95 %) following an intradermal induction concentration of 0.5 % EPDA in corn oil, followed by topical application using a patch. The challenge concentration was 50 %. The study design is comparable with the OECD TG 406 and reporting clear, and the study is assessed to be reliable with restrictions (Klim. 2).

In another Guinea pig study (Unpublished report, 1977b), 13/20 animals (65%) reacted at first reading 24 hours post challenge. The intradermal induction concentration was 0.05 % using adjuvant and subsequent topical application under patch, and the challenge dose was 50 %. The test substance has undergone a “stripping” process with nitrogen at 120 °C to remove contaminants, resulting in a total weight loss of 1% of the tested substance. The vehicle used was corn oil. The method description and reporting is clear. The study is assessed as reliable with restrictions (Klim. 2).

A Guinea pig maximisation test (Unpublished report, 1998a) was performed in 1998 according to OECD TG 406 (OECD TG as revised in 1992), following a preliminary test to establish relevant dosing for the induction and challenge concentration in the main test. The main test included intradermal induction with 25% EPDA, topical induction (using a chamber) and challenge with 25 and 50% EPDA, at the anterior and posterior part of the back of the guinea pigs. Sodium Lauryl Sulphate was used to create a mild skin irritation prior to topical induction. Alembicol D, a fractionated coconut oil, was used as vehicle. As some irritation in the controls was seen at challenge, the reactions in the treated animals were regarded as positive when they were more marked or more persistent than in the controls. The author reported that 9 out of 20 Dunkin-Hartley guinea pigs (45 %) showed

a positive reaction (well defined erythema and/or induration) at 48 hours post-challenge at the challenge concentration 50 %. At 25% challenge concentration, 6/20 animals have positive reactions, 2 of which are reported to be doubtful. The study is assessed as reliable with restrictions as there are some unclarities in the reporting with respect to the scoring criteria of the responses (Klim. 2).

Another Guinea Pig Maximisation test was performed in 2003 (Unpublished summary, 2003). The study was only available as a summary, corresponding to a Klimish 4 scoring, although it is stated to be OECD 406 and GLP compliant. Following an induction concentration of 5 % skin reactions were reported in 17 out of 20 animals (85%) at 48 hrs after application of a challenge concentration of 50 %. The study concluded that "2,3 - epoxypropyl neodecanoate is a strong to extreme skin sensitiser under the conditions of the study".

Overall, the available animal studies on EPDA show that EPDA has elicited moderate to extreme sensitising reactions in four skin sensitisation tests in Guinea pigs.

Human data

A severe case of dermatitis was reported in 16-year old male working for 9 days with undiluted epoxy resins. He showed a positive patch test to 0.01 % EPDA (Cardura E10) in acetone and to 0.001 % epoxy resin of the bisphenol A type. He tested negative to isophoronediamine, triethylhexamethylenediamine, N-ethyl o- and p-toluene sulphonamide, and to three different modified polyamidoamine hardeners. (Dahlquist et. al., 1979)

Another case of sensitisation to Cardura E10 alone was reported in 33-year old man who had been working 6 to 7 days with epoxy resin in an open tank with Cardura E10 and other reactive diluents and fillers. 4 other workers at the plant were patch tested. Of these 2 were tested positive to epoxy resin, but none were tested positive to Cardura E10. Cardura E10 tested negative in 10 unexposed subjects (Lovell et. al., 1984).

A third study reported negative patch tests using 0.25 % EPDA in three female workers in a brush factory who were sensitised to other resin components and 1,4-butanediol diglycidyl ether (BDDGE) at the workplace (Jolanki et. al., 1987).

In another study on selected patients with contact dermatitis 87 persons were patch tested with EPDA. Two had an ambiguous reaction (not positive or negative) and 85 tested negative. The test group consisted of patients who had an occupational or non-occupational exposure to epoxy resin systems, which may have included EPDA, but details on exposure to EPDA specifically were not reported. The authors state that the concentration used for patch testing, 0.25% EPDA, may have been too low to trigger a response (Geier et.al., 2004).

In a recent retrospective study a total of 39 selected patients with contact dermatitis occupationally exposed to resins were patch tested with EPDA at a concentration of 0.25%. A further 215 selected patients were patch tested with a concentration of 1% EPDA. No patients in the study reacted to the substance No details were available on the occupational exposure levels of EPDA. (Alto-Korte et. al., 2015).

The information from human data on the sensitising potential of EPDA are overall negative, with only two positive cases specifically related to EPDA reported. Although the substance is included in standard mixtures for testing for sensitisation to resins at the workplace, reported data on testing of EPDA alone are scarce. Further, information on the exposure levels to EPDA at the workplaces is lacking. Overall, the information from these data in humans is insufficient to conclude on the sensitising potency of EPDA.

Conclusion on skin sensitisation

Information on the skin sensitising potential of EPDA from humans is limited. In contrast, results from four positive Guinea pig maximisation tests support classification of EPDA as

a skin sensitiser. Two of the animal tests point to categorisation of EPDA as a strong/extreme sensitiser, whilst the remaining two studies do not contradict this conclusion. The results from one GPMT study (Unpublished Study report, 1977b) fulfils the criteria under CLP for the potency category "Extreme skin sensitiser", as an intradermal induction concentration of 0.05% (<<0.1%) resulted in 65% sensitised animals (≥60%). Considering the high percentage of positive reactions (95%) in another GPMT study (Unpublished Study report, 1977a), extreme sensitising potency of EPDA cannot be excluded, although the intradermal induction concentration of 0.5% is 5 times above the criteria for the category of extreme sensitisers. The GPMTs from 1998 and 2003, respectively, both use too high induction concentrations to permit evaluation of strong/extreme potency, and the results suggest EPDA to be of moderate skin sensitising potency.
Overall, the eMSCA considers that the evidence on skin sensitisation on EPDA supports a classification as an extreme sensitiser and should be classified as Skin sens cat. 1A with an SCL of 0.001%.

7.9.4. Repeated dose toxicity

Not evaluated

7.9.5. Mutagenicity

EPDA was included in CoRAP with a concern on mutagenicity. This was based on positive results of some *in vitro* assays and on *in vivo* gene mutations reported in somatic cells in a transgenic rodent assay.

7.9.5.1. Description of the available data on mutagenicity

A review of the available studies on mutagenicity has been performed under this substance evaluation. Unless otherwise stated all evaluated studies were part of the registration dossier. During the follow up period, a structured data search for the toxicological endpoint of mutagenicity was performed for the period 2016-2020 using public available databases (PubMed) as well as commercial databases (STN). The data search was performed to identify peer-reviewed and original literature for EPDA. In addition, a screening of expert opinions/risk assessments performed by regulatory bodies or other relevant reports for the period of 2016-2020 was performed. No data on mutagenicity of EPDA were retrieved in the data search.

Gene mutations in bacteria:

EPDA induced gene-mutations in Ames/Salmonella tester strains TA 1535, TA 1537, TA98 and TA 100 with metabolic activation, but not without (OECD 471), (eMSCA: Reliable (Klim. 1)). Two other studies similar to OECD 471 also yielded positive results in the same strains. In one study EPDA was positive with metabolic activation, but not without (eMSCA: Reliable (Klim. 2)) and in the other study EPDA was only positive without metabolic activation (eMSCA: Reliable (Klim. 2) (unpublished report 1998b)).

Gene mutations in yeast and mammalian cells

A negative result was observed in a yeast cytogenetic assay (corresponding to OECD 481) both with and without metabolic activation. (Klim. 2) (1979).
No studies on gene mutations in mammalian cells were reported.

Chromosomal aberrations:

A negative result was obtained in a guideline *in vitro* mammalian chromosome aberration test using CHO cells (OECD 473). Cells were tested for 4 hours with metabolic activation (at 1-35 µg/ml) as well as without metabolic activation (at 5-40 µg/ml). Cells were also

treated for 20 hours without metabolic activation (at 5-40 µg/ml). Cells were harvested approximately 20 hours after the beginning of treatment (eMSCA: Reliable (Klim 2) (2011). A non-guideline *in vitro* mammalian chromosome aberration study using an epithelial—type cell line, designated RL1, derived from rat liver (with inherent metabolic capability) yielded an ambiguous result. Final concentrations for separate experiments were 12.5-50 ug/ml or 7.5-30 ug/ml. In both cases, occasional chromatid aberrations were seen after 6 hours and 24 hours. Although the incidence of chromatid aberrations was very small, they occurred consistently in each of the experiments (eMSCA: Reliable (Klim 2) (1979)).

In vitro cell transformation Assay (genome mutation):

A negative result was obtained in an *in vitro* mammalian cell transformation assay from 1981 using Syrian hamster fibroblast kidney cells (BHK) with metabolic activation. The validity of the performance of the BHK cell line for rodent carcinogenicity is unknown (e.g. the number of rodent carcinogens and non carcinogens included in a validation exercise, its inter- and intra-laboratory variability and its sensitivity, specificity, positive and negative predictive values) as this study was conducted as a non-guidance study at the time. It is therefore not possible to draw a conclusion as to what the alleged negative result means in relation to the potential of EPDA for rodent carcinogenicity (eMSCA: Not reliable (Klim. 3)).

In vivo:

In vivo Genotoxicity

Genotoxicity of EPDA was investigated in a non-guideline alkaline filter elution assay in 1981, which assesses single strand breaks and alkaline labile sites in DNA. EPDA did not induce DNA damage *in vivo* in a rat alkaline elution study 6 hours after a single dose of 4850 mg/kg of body weight. Two males and two females were tested per group. Methyl methanesulphonate was administered in DMSO as a positive control. This is not a guideline study, group size was too small and only one dose was tested. No protease was used in the lysing solution, so it is possible that single strand breaks could still be adducted to proteins, which would mask a positive result (eMSCA Klim. 3 not reliable).

An Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells *in vivo* (OECD 486) yielded a negative result. Four male rats (Harlan Sprague-Dawley) per dose and time interval were administered EPDA in corn oil by oral gavage at the final dose levels of 0, 500, 1000, and 2000 mg/kg of body weight. The duration of exposure was 2 to 4 hr and 12 to 16 hr per dose group. Dimethylnitrosamine at 35 mg/kg of body weight was used as a positive control. No significant increase in mean Net Nuclear Grain Counts (NNGC) or percent liver cells in DNA repair (UDS) was obtained. (eMSCA: Reliable (Klim. 2)).

Gene mutations *in vivo*

In 2012 a Transgenic Rodent Somatic and Germ Cell Gene Mutation Assay was conducted in a MutaMouse (CD_2-lacZ80/HazfBR), whose DNA bearing cells each contain a transgenic lambda g10 vector with the bacterial lacZ gene. Exposure by oral gavage yielded a positive result in all somatic tissues tested. The study was conducted according to OECD 488 (2011) with GLP compliance and test substance concentration verification (eMSCA Klim 1).
Seven male animals were tested per group. The animals were dosed with EPDA in corn oil once per day on each of 42 consecutive days (Days 1-42) and sacrificed on Day 45, i.e. 3 days after the final administration. A dose volume of up to 10 mL/kg of body was used. Dose volumes were based on individual body weight. Dose concentrations used were 0, 250, 500 and 1000 mg/kg body weight per day. Tissues tested were liver, kidney, bone marrow and developing sperm cells from seminiferous tubules. The positive control used was Ethylnitrosourea (ENU) at 100 mg/kg bw/d by intraperitoneal injection for all tissues sampled. Statistical analyses were done using ANOVA, Dunnett's test and Levene's test. Plaque forming units (pfu) for each sample on any packaging occasion exceeded 30000 for the majority of samples. In a few cases pfu's between 10000 and 30000 were accepted.
EPDA was shown to be a gene-mutagen in liver, kidney and bone marrow of the MutaMouse demonstrating that the test substance is a systemic gene mutagen in mice by the oral

route of exposure. In the liver at the high dose level (1000 mg/kg bw/d) the group mean mutant frequency was 3.1 -fold the mean concurrent vehicle control value. Although lower doses did not induce a significant increase in mutation frequency, an increase in group mean mutation frequency compared to the vehicle control was observed and a significant linear trend was also observed.
For the kidney, a statistically significant increase in mutant frequency was observed at all dose levels, a significant linear trend was also observed.
For bone marrow statistically significant increases in mutation frequency were observed at 500 and 1000 mg/kg bw/day. No increase was observed for 250 mg/kg/day, however, a significant linear trend was observed.
Mutation analysis of developing sperm cell from the seminiferous tubules showed no statistically significant increase in mutation frequency at any dose level and no significant linear trend was observed. All individual animals had mutation frequencies that were comparable with the concurrent vehicle control.
Vas deferens tissue containing mature sperm cells was collected in the study, but was not analysed but rather only stored.

TGR study in mature germ cells

In response to the request in the ECHA decision of March 2017 a TransGenicRecombinant Assay was performed in 2019. As requested in the decision EPDA was tested for its ability to induce gene mutation in the *lacZ* transgene in mature sperm from male Muta™Mice (CD2-*lacZ*80/HazfBR strain) in a 28 + 49 day regime. In the MSC decision, it was further specified that the preparations of the formulations should be freshly made daily no later than 20 minutes before administration of each dosage and that analyses of homogeneity and stability of the test formulations should also be performed.

The TGR study included 4-7 male animals per group. The animals were dosed with EPDA in corn oil by oral gavage once per day on each of 28 consecutive days (Days 1-28) and sacrificed on Day 78, i.e. 50 days after the final administration. The study was conducted using a limit dose of 1000 mg/kg bw/day EPDA (CARDURA™ E10P), bilateral vas deferens and cauda epididymis were dissected from each animal and mature sperm was retrieved according to established protocols. The positive control used was Ethylnitrosourea (ENU) at 150 mg/kg bw/d.

Formulation and dosing of test material

The test article formulations were prepared weekly by formulating CARDURA™ E10P in corn oil. Although it was stated in the final decision that preparations of test formulations should be freshly made daily, the eMSCA is of the opinion that the stability of the test formulation for the purpose of this study has been adequately demonstrated based on the information on homogeneity and stability provided by the registrant upon request during the follow-up evaluation period.

DNA packaging and transfection of host bacteria

7.5 µg DNA per animal was packaged into bacteriophage heads using Agilent Transpack packaging reagents. For each animal bacteriophages along with a suspension of *E. coli* C $lac^{-}galE^{-}Kan^{r}$ ($galE^{+}$ Amp^{r}) were added to titration plates without phenyl-galactose (P-Gal) to determine the total number of plaque-forming units (pfus) and to selection plates containing P-Gal to determine the number of mutants.

The pfu for each sample on any packaging occasion exceeded 30,000, although in the event of a poorly packaging sample data were accepted if the pfu fell between 10,000 and 30,000. Packaging reactions were in the range of 3-5.
The laboratory's acceptance criteria for number of pfus is a total of at least 200,000 pfu from at least three packaging reactions were obtained per animal. According to the study director it was not possible to obtain data from 200,000 pfu for some animals due to poor packaging. Furthermore, because of limited amounts of viable DNA remaining, it was not possible to perform any further packaging. 4 of 7 animals in the vehicle control group and animals 6 of 7 animals in the test group fell below the 200,000 pfu cut off. According to

the study director the mutant frequencies (MF) for these animals were highly consistent with the data from the animals which did achieve 200,000 pfu, and as at least 1 million pfu were obtained for each group, the low pfu values were considered to not adversely affect data interpretation.

Positive controls

Tissues from 4 appropriate positive control treated animals (treated independently in the current study with 150 mg/kg N-ethyl-N-nitrosourea (ENU)) were used to provide DNA that were analyzed alongside the DNA from animals in this study, to confirm the correct functioning of the packaging reactions and platings in accordance with OECD TG 488. For two out of four animals in the positive control group pfus far below 200,000 was obtained (21,344 and 52,693 pfus respectively). The packaging reactions were in the range of 1-6. Although two out of four animals had very low pfus in the ENU positive control group, the increase in MF was high and in the expected range, which indicates that the assay has worked as expected.

Determination of mutant frequency

Mutant frequency is determined by dividing the number of plaques/plasmids containing mutations in the transgene by the total number of plaques/plasmids recovered from the same DNA sample. No statistically significant increases in mutant frequency (MF) were observed in the mature sperm of treated male MutaMice. The MF of all individual animals were considered to be comparable with the concurrent vehicle control group and the MF of all animals fell within the laboratory's historical control data (41.07±42.06; based on 20 animals, range 13.82-188.17).

Table 8

Group	Treatment (dose)	Mutant frequency Group Mean MF (x 10^{-6})	Standard deviation	P-value
Vehicle control group (7 animals)	corn oil	46.16	14.91	-
Test group (7 animals)	EPDA 1000 mg/kg/d	53.18	9.32	0.1560 (NS)
Positive control (4 animals)	ENU 150 mg/kg	339.86	48.85	<.0001 (P≤0.001)

Statistical analyses

According to the study director both ANOVA and a t-test were performed at the 5% level. The study director compared the vehicle control group to the treated group using a two-sample t-test. The t-test was interpreted with a one-sided risk for increasing response. The Levene's test for equality of variances between the groups was also performed and where this showed evidence of heterogeneity (P≤0.01), the data were rank-transformed prior to analysis. The positive control data were also compared to Group 1 as described above. Levene's test for equality of variances across the groups was also performed. In all cases there was no evidence of heterogeneity (P>0.01).

The eMSCA repeated the statistical analysis excluding the 3 animals which fell below the 125,000 pfu limit described in the TG 488 guideline. When the one-sided t-test was

repeated (using SigmaStat) without these 3 animals the increase in MF in the test group was statistically significant. Each group still included at least 5 animals (the minimum number of animals per group according to the test guideline). Data without the 3 low pfu animals passed the Normality test (Shapiro-Wilk test (P=0.109)) and the Equal variance test (P=0.621).

Table 9 t-test recalculated by eMSCA

Group	Treatment (dose)	Mutant frequency Group Mean MF (x 10^{-6})	Standard deviation	P-value
Vehicle control group (5 animals)	corn oil	39.59	11.02	-
Test group (6 animals)	EPDA 1000 mg/kg/d	52.76	10.14	P= 0.035 (P≤0.05)

The increase in MF in the test group compared to the vehicle group was very slight (1.33-fold), and even though the increase in MF is statistically significant, the biological relevance is unclear.
Furthermore, the fact that the data passed the normality and the equal variance test may be an indication that the two groups are not different from each other. Data from the TGR assay are generally not normally distributed (O'Brien 2014) and when there is a significant response, it is rare to have equal variance, which is why non parametric tests (or appropriate data transformation) are normally used in TGR statistical analyses.
The total number of pfus for some animals was below the limit recommended in the OECD test guideline, which leads to a lower reliability on the results of the study. As a result, the eMSCA has given the study a Klimisch 2 score (reliable with restrictions).
In conclusion, the result of the TGR study is equivocal due to the statistically significant response but unclear biological relevance of the very slight increase after removal of the animals with pfus below the limit recommended in the guideline.

7.9.5.2. Conclusion on Mutagenicity

EPDA induced gene mutations in multiple *in vitro* Ames tests assays in salmonella strains TA 1535, TA 1537, TA98 and TA 100 (OECD TG 471 or similar) with or without activation.

In an *in vivo* Transgenic Rodent Somatic and Germ Cell Gene Mutation Assay OECD (TG 488) in MutaMouse in the EPDA was found to be mutagenic in bone-marrow, kidney and liver tissue when exposed at up to 1000 mg/kg/day for 42 days and sampled 3 days later. The mutation frequency was not increased above the level of controls when germ cells from the seminiferous tubules were exposed and sampled under the same conditions.
Another TGR study from 2019, which analyzed mature germ cells from MutaMouse exposed at 1000 mg/kg/day for 28 days and analyzed 49 days later, was made available to the eMSCA in 2019. This study yielded an equivocal result.
The 28 + 49 day test strategy for sampling mature sperm cells (from cauda epididymis/vas deferens) targets the stem cell stage and was until recently considered the golden standard of germ cell testing. However, according to the recently published modelling of spermatogenesis (Marchetti et al 2018), cells which have entered the spermatogonial stage are more sensitive than stem cells because they divide more rapidly. Consequently, based on the results in germ cells obtained from the two available TGR studies, it is the opinion of the eMSCA that a concern for germ cell mutagenicity for EPDA is not likely.

Based on the available *in vitro* and in *vivo* data, the eMSCA finds that EPDA meets the requirements for classification as Muta 2, under CLP. The eMSCA has submitted a proposal for harmonised classification.

7.9.6. Carcinogenicity

The Concern(s) Identified
EPDA is listed on CoRAP with a concern for carcinogenicity, as the substance is clearly positive for gene mutations in somatic tissues *in vivo* in all tissues tested (liver, kidney, bone marrow), supporting a classification as muta cat 2. Given the strong correlation between *in vivo* mutagenicity and carcinogenicity there is a clear concern that EPDA may be a genotoxic carcinogen. However, no *in vivo* studies on carcinogenicity are available.
This is supported by positive QSAR predictions within the applicability domain of several of the carcinogenicity models from the Danish (Q)SAR database (http://qsardb.food.dtu.dk/database/index.html): Predictions were made for all constituents of EPDA in a commercial MultiCASE CASE Ultra FDA cancer suite consisting of seven models for cancer in male rat, female rat, male mouse, female mouse, rats, mice and rodents, respectively. The majority of the constituents of EPDA were predicted positive in multiple cancer models in at least six out of the seven models. Furthermore, a so-called ricinus communis agglutinin (RCA) algorithm was applied based on predictions in 4 individual models for male rat, female rat, male mouse and female mouse carcinogenicity, which gives an overall call for cancer. Positive overall calls were obtained for mostconstituents of EPDA, except for a few which all lack the epoxy group and which are typically present in low levels.
Predicted metabolism of EPDA by carboxylesterase hydrolysis results in the generation of glycidyl alcohol (CAS no.: 556-52-5), which has a harmonised classification of MUTA cat 2 and CARC cat 1B. The metabolic site predictor Metaprint 2D (previously available from Cambridge University, but no longer available) which indicates the relative likelihood of metabolism occurring at a particular site in the molecule assuming it is metabolised, report the likelihood of some constituents of EPDA being hydrolyzed to yield glycidyl alcohol to be between 66-100%. The MultiCASE META mammalian metabolism rule-based (Q)SAR system was applied to predict if, according to the program, glycidyl alcohol would be formed from the Neodecanoic acid, 2-oxiranylmethyl ester constituents, and if so, in which concentration. For a number of constituents formation of glycidyl alcohol is predicted with a yield between 0.9% and 11.5%. (see Appendix 1 for details).

7.9.6.1. Conclusion on Carcinogenicity

The positive results obtained in an *in vivo* gene mutagenicity test in several somatic tissues in the OECD 488 TGR assay indicate that EPDA may be a genotoxic, non-threshold carcinogen. This concern is further supported by the positive predictions for carcinogenicity in the Danish (Q)SAR Database. No carcinogenicity assay on EPDA is available. The eMSCA noted that glycidyl alcohol, a predicted metabolite of EPDA has a harmonised classification for carcinogenicity (CARC 1B).

Based on the above mentioned observations, the draft decision originally contained a request for a carcinogenicity study (OECD 451). However, this request was deleted from the final decision, pending the conclusion on mutagenicity. A classification proposal for Muta 2 was submitted in December 2020. According to REACH Annex X point 9.8.1 column 2 a carcinogenicity study may be required if the substance has wide dispersive use and is classified as Muta 2. Therefore, a compliance check may be initiated depending on the outcome of the classification process.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

Not evaluated

7.9.8. Hazard assessment of physico-chemical properties

Not evaluated

7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

Not evaluated

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

With respect to the end-point of concern on skin sensitisation the eMSCA concludes that the available data in animals and humans on 2,3-epoxypropyl neodecanoate (EPDA) fulfil the criteria for classification as an extreme skin sensitiser as Skin Sens. category 1A with a specific concentration limit (SCL) of 0.001%.

The eMSCA's conclusion on the endpoint of mutagenicity is that *in vitro* and *in vivo* data demonstrate that EDPA is a somatic cell mutagen in various tissues, whereas a potential for germ cell mutagenicity is not likely. Consequently, the eMSCA finds that EPDA meets the requirements for a harmonised classification as Muta cat. 2.
Evidence from QSAR and mutagenicity assays support the concern on carcinogenicity.
However, the eMSCA will await the outcome on classification to conclude on this endpoint, as a harmonised classification as Muta 2 may trigger the criteria in REACH, Annex X on the endpoint of carcinogenicity.

7.10. Assessment of endocrine disrupting (ED) properties

Not evaluated

7.10.1. Endocrine disruption – Environment

Not evaluated

7.10.2. Endocrine disruption - Human health

Not evaluated

7.10.3. Conclusion on endocrine disrupting properties (combined/separate)

Not evaluated

7.11. PBT and VPVB assessment

Not evaluated

7.12. Exposure assessment

7.12.1. Exposure data required in the LOUS review project

In addition to data given on exposure in the registration dossier, the data from the project "Survey of 2,3-epoxypropyl-neodecanoate, A report under the LOUS review project" conducted by the eMSCA (Danish EPA, 2015) have been included in the evaluation of this

end-point. The following section in grey is a citation from the above mentioned LOUS report. Table and figure labelling is in consistency with the LOUS report.

“ The structure of EPDA holds an epoxy group, which is very reactive. It reacts with molecules containing reactive hydrogen such as amines, acids, acid anhydrides, phenols, alcohols and thiols by opening of the O-ring. This makes EPDA useful in a range of applications. EPDA is used to produce resins or as epoxy resin diluent and is mainly used in coatings, paints and dyes such as two-component systems consisting of resins and hardeners. EPDA may also occur in solvents for these systems. […] EPDA is an organic epoxy compound and is mostly used as curing agent and binder in epoxy paint systems, varnishes, adhesives and construction materials within the industrial sector and by professional users. The uses registered under REACH are representing a wide range of end use sectors. Consumer use is not registered under REACH. However, available material safety data sheets as well as the responses from the questionnaire part of the project conducted by the eMSCA indicated that EPDA is applied in coating products for consumers. […] This is supported by information from the SPIN database indicating that one or several uses very probably leads to consumer exposure.”

“A google search was performed in order to identify uses of EPDA as well as EPDA-containing products and suppliers. The table below presents some of the products identified based on information in safety data sheets (SDSs). It is emphasised that the data do not necessarily cover all product types and uses. The results indicate that the substance is applied mainly in products for industrial and professional uses. However, some coating products may also be applied by consumers. The reported percentage of EPDA within the products varies and is up to 35%.

TABLE 10
IDENTIFIED PRODUCTS CONTAINING 2,3-EPOXYPROPYLNEODECANOATE (CAS: 26761-45-5) BASED ON GOOGLE SEARCH

Product name	Company	% EPDA in the product	Stated use	Typical application	Reference
Sigma mortar primer 2K EP hardener	PPG Coatings AC EMEA	25-<35	Hardener, coating	Coatings, consumer and professional use	Safety data sheet 00346617 2013.04.24
DELTA EP System H (Härter)	CD-Color GmbH & Co. KG	15-25	Hardener	Not stated	Safety data sheet 120648DE 2010.07.29
Sigma mortar primer 2K EP base	PPG Coatings AC EMEA	2.5-< 25	Base, coating	Coatings, consumer and professional use	Safety data sheet 00346616 2013.04.24
HEMPADUR MULTI-STRENGTH 35539	Hempel A/S	2.5 - < 25	Primer	Industrial application	Hempel Safety Data sheet version 0.01 31 January 2014
HEMPEL'S CURING AGENT 97382	Hempel A/S	2.5 - < 25	Curing agent	Industrial application	Hempel Safety Data sheet version 0.03 31 January 2014
EPIKOTE™ Resin 816 MV	Momentive	15-20	Epoxy resin	Industrial application	Momentive Safety data sheet 01/02/2013
EPIKOTE 255	Albion Chemical Group	10-20	NA	NA	Safety Data Sheet EPIKOTE 255 14/02/2008.
StoJet IHS Komp. A	Sto Danmark A/S	≥ 10 - < 20	Injection resin	Industrial and professional use	Safety data sheet MA10002357 2014.01.23

Product name	Company	% EPDA in the product	Stated use	Typical application	Reference
Catalyst 0656 13058	Esbjerg Farve- & Lakfabrik A/S	2.50 - 10	Paint	Surface treatment of metal	Safety data sheet 0656 13058 2014.03.31
Tremco CS175A	Tremco Illbruck	5 - <10	Epoxy resin – primer/sub-coating	NA	Tremco Illbruck Safety data sheet version 1 21/02/2013
StoPox WHG Grund 100 Komp. A	Sto Danmark A/S	≥ 2,5 - < 10	Coating material	Industrial and professional use	Safety data sheet 130000005679/E 2014.01.31
Tremco CS100 A	Tremco Illbruck	1 -<5	Epoxy resin – primer/sub-coating	NA	Tremco Illbruck Safety data sheet version 1 13/02/2013
MASTERTOP TC 473,T.A RAL 7035	BASF	≥ 0.5 - ≤2.5	Product applied in construction chemicals	Professional	Safety data sheet , MASTERTOP TC 473,T.A RAL 7035 (Version 1.0) 2010.08.17
StoPox Mörtel fein Komp. A	Sto Danmark A/S	≥ 1 - < 2.5	Mortar	Industrial and professional use	Safety data sheet MA10004006 2013.03.12
PercoTop ® 531 CS912	Axalta Coating Systems Germany GmbH	0.10 - < 0.20	Binder	Industrial and professional use	Safety data sheet 1250066027 v11.24 2014.02.05
EV350 IMRON® INDUSTRY PUR MATT BINDER	Dupont	0.10 - < 0.20	Paint	Painting of vehicles by professional painter	Safety data sheet, EV350 2010.11.26
Permaflex Iron Mica Binder Series 510 IM 510	Spies Hecker	0.10 - < 0.20	Binder	Industrial and professional use	Safety data sheet 4025331708780 v8.0 2011-01-07
Cardura E 10P	Momentive	NA	Reactive diluent for epoxy resins	Compositions for the building and civil engineering industries (e.g. flooring compounds, adhesives, mortars and grouts), for laminating binders, solvent-free and high solids coatings.	Product bulletin Cardura E 10P (2011)
CC6600 CROMAX ® PRO STAR CLEAR	Dupont	0.10 - < 0.20	SU 3, SU 22 PC9a, PC9b	Industrial and professional use	Safety data sheet, CC6600 2011.05.05

NA: NOT AVAILABLE

As part of this survey the Danish Chemical Industry, which is part of the Danish Chamber of Commerce was asked about the use and import of EPDA by its members, but no responses were received from the members. Furthermore a questionnaire was prepared and sent to the European organisations CEPE (European Council of the Paint, Printing Ink

and Artists) and FEICA (The European Adhesive and Sealant Industry), as well as the Danish Coatings and Adhesives Association.

A total of 20 responses were received of which 11 companies responded that they do not use EDPA. The responses to the questionnaires are summarised in the table below. One of the companies is importing the products containing EPDA from outside EU. According to the results from the questionnaires, EPDA is used in products for industrial and professional uses and in formulation of articles or treatment of articles. The products are described as raw material for polymer production (epoxy resin), epoxy resins, epoxy paint, binders and primers for epoxy paint, coatings and catalysts. The responses from the questionnaires indicated that products are available for consumer use.

According to the responses from the questionnaires, EPDA is reacting chemically during the use in the epoxy paint. However, for some end products, the presence of EPDA is reported. This is the case for treated products such as enamels and coated steel and aluminium sheet.

TABLE 11
IDENTIFIED USES OF 2,3-EPOXYPROPYLNEODECANOATE BASED ON ANSWERS TO QUESTIONNAIRE.

Company	Type of use (sector)	Product type and content of EPDA	Concentration of EDPA in the end product
1	Industrial/Professional Formulation/mixing	Binder for paint (0.7%) Paint (0.3%)	No information
2	Industrial/Professional Formulation/mixing	Epoxy resin (10-20%) Base components, primers (1.5-6%)	Reacted in final product
4	Industrial Formulation/mixing	Catalyst (5%)	0.075-0.15 % in products Bound in the material
8	Industrial	Catalyst (<5%)	0.12% in enamels
3	Industrial/Professional	Epoxy resin (18-30%)	No information
5	Industrial/Professional	Epoxy resin (12.5-15%) Primers (<2%) Vehicle refinish products (>2.5%)	No information
7	Industrial/Professional	Raw material for polymer production (100%) Formulated paint (<30%)	Bound in the paint matrix. Up to 5% in epoxy based paints
9	Industrial/Professional	Coatings: Professional (< 0.05%) Industrial (0.4-14%)	Bound in the paint matrix <0.0004% in coated steel and aluminium sheet
6	Professional	Formulated paint (2-16%)	Reacted into the paint matrix

Use in the Nordic countries

The Nordic SPIN database (“Substances in Preparations in the Nordic Countries”) is the result of a common Nordic initiative to gather non-confidential data. The database summarized information from the Nordic product registers on the common use of chemical substances in different types of products and industrial areas. Information of use volumes and information on the tonnage of substances in preparation in the Nordic countries has been retrieved (SPIN database, 2014).

Figure 3.1 below displays the numbers of preparations in which EPDA is applied in the Nordic countries. For Sweden, Finland and Norway there has been a marked increase in the numbers of preparations containing EPDA during the period from 2006 to 2012, whereas the number of preparations in Denmark has been almost constant.

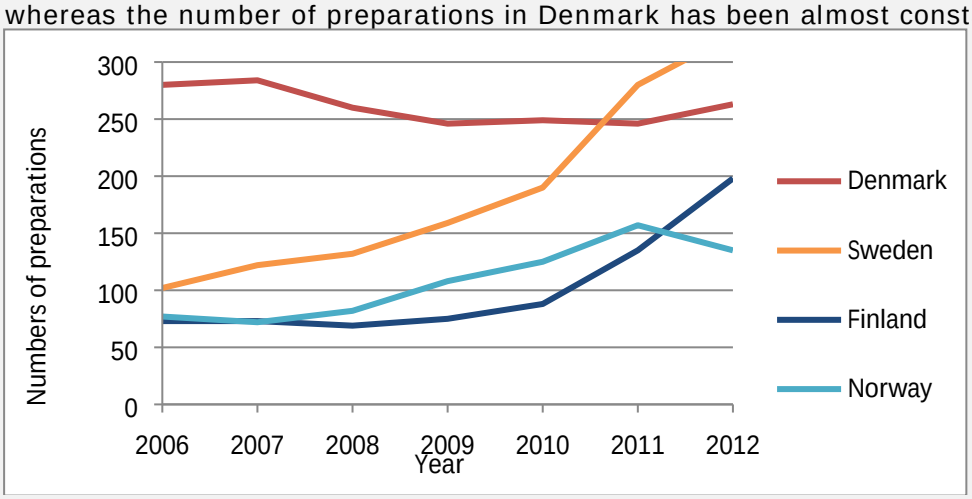


FIGURE 1
NUMBERS OF PREPARATIONS IN WHICH 2,3-EPOXYPROPYLNEODECANOATE (CAS: 26761-45-5) IS APPLIED (SPIN DATABASE, 2014).

EPDA is present in varying concentrations in the preparations. Therefore, the number of preparations has to be considered together with information on the tonnes of EPDA in the preparations. Figure 3.2 shows the tonnage of EPDA applied in the Nordic countries (SPIN database, 2014). In spite of the increasing number of preparations containing EPDA for Sweden, Finland and Norway, the tonnage seems to decline during the years from 2006 to 2012. The decline is most pronounced for Finland. Also the registered tonnage for Denmark has been decreasing in the period from 2006 to 2012. The total tonnage of EPDA in products in the Nordic countries is 53 tonnes in 2012.
In the figure, the reported tonnages for 2011 for Denmark (752 tonnes) and Norway (263 tonnes) have not been included as they are considered as errors since they differed markedly from the tonnage reported for previous years (SPIN database, 2014). According to information from the Danish product registry, the reported tonnages for 2011 and 2012 were errors and the corrected volume of EPDA registered for Denmark in 2012 (10 tonnes) was submitted and included in the figure (Data received August 2014).

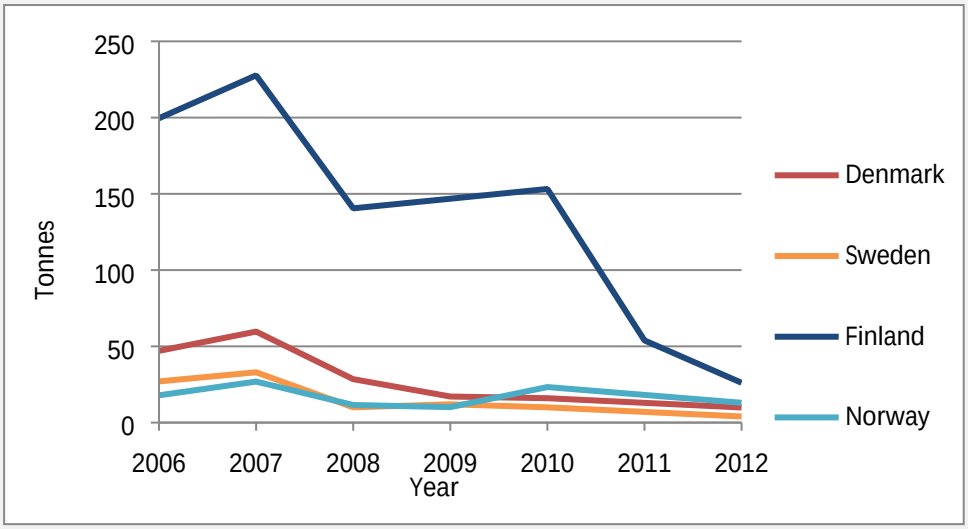


FIGURE 2
TONNES OF 2,3-EPOXYPROPYLNEODECANOATE (CAS: 26761-45-5) APPLIED IN PREPARATIONS ON THE NORDIC COUNTRIES (SPIN DATABASE, 2014, Reported in Danish EPA, 2015).

The same product categories for products containing EPDA in Denmark have been reported to the Nordic SPIN database from 2006 to 2012 (SPIN database, 2014).

The numbers of products in the categories are shown in Table 12 for 2012. Products registered in the other Nordic countries are within the same categories as in Denmark: Paints, lacquers and varnishes, surface treatment, adhesives, binding agents and construction materials. Furthermore, the product categories: Viscosity adjustors (Finland), laboratory chemicals (Norway) and process regulators (Sweden) have been reported. From the data it can be seen that in Sweden, Finland and Norway there is a general increase in the number of preparations with the highest increase within the product category “Paint, lacquers and varnishes”. This increase is also covering preparations with no content of EPDA.

TABLE 12
TYPES OF PRODUCTS CONTAINING 2,3-EPOXYPROPYLNEODECANOATE (CAS: 26761-45-5) AND CORRESPONDING NUMBER OF PRODUCTS WITHIN EACH CATEGORY IN DENMARK (SPIN DATABASE, 2014)

PRODUCT CATEGORY	Number of products (2012)
Paints, lacquers and varnishes	179
Surface treatment	18
Adhesives, binding agents	14
Construction materials	7
Fillers*	7
Solvents*	4
Total	229

*According to information from SPIN, fillers and solvents are not contributing to the tonnes of EPDA (SPIN database, 2014).

Types of products which contain EPDA and which were reported to the Danish Product Registry (August, 2014) represent a wider group of products categories. The product categories and typical concentration of EPDA within the products are presented in Table 13. The number of products containing EPDA is 194 products reported by 42 companies.

The data indicate that EPDA is present in a wide range of products within coatings, paints and construction materials. In addition to this, EPDA is reported in surfactants and in car care products. However, these products may be related to the application of coatings and paints.

TABLE 13
TYPES OF PRODUCTS CONTAINING 2,3-EPOXYPROPYLNEODECANOATE (CAS: 26761-45-5) AND TYPICAL CONCENTRATION (%) REPORTED FOR THESE PRODUCT TYPES ACCORDING TO INFORMATION RECEIVED FROM THE DANISH PRODUCT REGISTRY (AUGUST, 2014)

Product category	Typical concentration (%)
Solvents and thinners	<100
Binders	< 25
Floor coverings	<25
Paint and varnish	<25
Surfactants and products	<15
Coatings non-metallics	<15
Fillers	<15
Dyes	<5
Hardeners	<5
Paint- and lacquer additives	<5

Product category	Typical concentration (%)
Toners	<5
Car care product	<1
Gloss altering agents	<1
Glazes and enamels etc.	<1
Metal coatings	<1
Raw materials	<1
Inks	<1

Trends in use

In the Nordic countries, the types of preparations in which EPDA is applied has been the same since 2006 and forward. Before 2006, EPDA was registered in same categories including process regulator and viscosity regulator (Spin database, 2014). A decline in the tonnage of EPDA in products placed on the Nordic market was observed in the period from 2006 to 2012.
In the answers to the questionnaire part of this survey and which were received from companies that confirmed that they use EPDA in their products, two companies indicated an increase in the use of EPDA during the last 10 years, another four companies
indicated a decline and one company responded that the use is unchanged. ” (end of quotation)

7.12.2. Human health

7.12.2.1. Worker

Inhalation and dermal exposure is expected during industrial and professional uses of EPDA such as during formulation, roller application or brushing, industrial and non-industrial spraying, and hand-mixing with intimate contact and only personal protective equipment available. For details in uses see section 7.5.2.

7.12.2.2. Consumer

According to the registration dossier, there is no consumer use of EPDA. However, available material safety data sheets and the responses to the questionnaire of the survey of EPDA by the Danish EPA (Danish EPA, 2015) (see section 7.12.) from relevant European organizations (CEPE (European Council of the Paint, Printing Ink and Artists) and FEICA (The European Adhesive and Sealant Industry), as well as the Danish Coatings and Adhesives Association) also indicate that EPDA is applied in products for consumers such as coating products. This is further supported by information from the SPIN database (see section 7.12.) indicating that one or several uses very probably leads to consumer exposure.

7.12.3. Environment

Not evaluated

7.12.4. Combined exposure assessment

Not evaluated.

7.12.5. Conclusion on exposure

The available evidence on human exposure to EPDA points to frequent and/or long-term human exposure. EPDA is used at very high tonnage, in widespread use, and the wide range of end uses of EPDA, as well as the many uses in products demonstrate that despite consumer use is not included in the registration dossier, some of the products are also available for consumers. Reports on skin sensitisation in workers also corroborate the potential for exposure.

7.13. Risk characterisation

Not evaluated

7.14. References

Aalto-Korte et.al., 2015. Contact allergy to reactive diluents and related aliphatic epoxy resins, Contact Dermatitis, 2015, 72, 387-397.

Danish EPA (2015). Survey of 2,3-epoxypropyl-neodecanoate, A report under the LOUS review project, Danish Environmental protection Agency Environmental project No. 1713, 2015 https://www2.mst.dk/Udgiv/publications/2015/05/978-87-93352-26-1.pdf

Dahlquist,I. and S. Frigert (1979). Contact allergy to Cardura E, an epoxy reactive diluent of the ester type. Contact Dermatitis (5) 1979, 121-122.

ECHA. Guidance on the Application of the CLP Criteria. Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures. Version 4.1. June 2015

Geier et.al., 2004. An attempt to improve diagnostics of contact allergy due to epoxy resin systems. First results of the multicentre study EPOX 2002, Contact Dermatitis, 2004, 51, 263-272.

Jolanki. et. al., 1987. Contact allergy to an epoxy reactive diluent: 1,4-butanediol diglycidyl ether, Contact Dermatitis, 1987, 16, 87-92.

Lovell CR, Rycroft RJG, Matood J. 1984. Isolated Cardura E10 sensitivity in an expoxy resin chemical process. Contact Dermatitis 1984; 11: 190-191

Magnusson B. and Kligman A.M. (1969). The identification of contact allergens by animal assay. The guinea pig maximisation test. J. Invest. Dermatol., 52, 268.

SPIN the Nordic product registers (SPIN: http://spin2000.net/)

Marchetti, F., M. Aardema, C. Beevers, J. van Benthem, R. Godschalk, C.L. Yauk, B. Young, A. Williams and G.R. Douglas (2018), “Identifying germ cell mutagens using OECD test guideline 488 (transgenic rodent somatic and germ cell mutation assay) and integration with somatic cell testing”, Mutat. Res., 832-833: 7-18. Corrigendum: Mutat. Res., 2019, 844: 70-71.

Marchetti, F., M. Aardema, C. Beevers, J. van Benthem, G.R. Douglas, R. Godschalk, C.L. Yauk, B. Young and A. Williams (2018), “Simulation of mouse and rat spermatogenesis to inform genotoxicity testing using OECD test guideline 488”, Mutat. Res., 832-833: 19-28. Corrigendum: Mutat. Res., 2019, 844: 69.

O'Brien, J.M., Beal, M.A., Gingerich, J.D., Soper, L., Douglas, G.R., Yauk, C.L., Marchetti, F. Transgenic Rodent Assay for Quantifying Male Germ Cell Mutant Frequency. J. Vis. Exp. (90), e51576, doi:10.3791/51576 (2014)

O. E. C. D. (2003g). Bacterial reverse mutation assay. Institute for Health and Consumer Protection, Joint Research Centre.

The Danish (Q)SAR database (http://qsar.food.dtu.dk/).

Unpublished report, (1977a) Skin sensitisation study in Guinea pigs

Unpublished report, (1977b) Skin sensitisation study in Guinea pigs

Unpublished report (1979a). TOXICITY STUDIES WITH RESINS: IN VITRO MUTATION STUDIES WITH CARDURA E1O.

Unpublished report (1979b). TOXICITY STUDIES WITH RESINS: IN VITRO MUTATION STUDIES WITH CARDURA E1O AND AN IMPROVED FORM.

Unpublished report (1981). TOXICITY STUDIES WITH RESIN INTERMEDIATES: IN VITRO TRANSFORMATION STUDIES WITH CARDURA E1O.

Unpublished report, (1998a) Skin sensitisation study in Guinea pigs

Unpublished report (1998b). Cardura E10S: Bacterial Mutagenicity Assay (Ames) in Salmonella Typhimurium.

Unpublished summary, (2003), Guinea pig maximisation test.

Unpublished report (2012). 'Induction of lacZ-mutations in the liver, kidney, bone marrow and spermatozoa of treated Muta™Mice'.

Unpublished report (1981). STUDIES ON THE EFFECT OF CARDURA E10 ON THE INTEGRITY OF RAT LIVER - DNA IN VIVO.