~~CONFIDENTIAL~~

European Chemicals Agency

Decision number: CCH-D-0000001694-70-06/F Helsinki, 24 October 2011

DECISION ON A COMPLIANCE CHECK OF A REGISTRATION PURSUANT TO ARTICLE 41(3) OF REGULATION (EC) NO 1907/2006

For 2,3-epoxypropyl neodecanoate, CAS No. 26761-45-5 (EC No. 247-979-2), Registration Number: [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration dossier for **2,3-epoxypropyl neodecanoate, CAS No. 26761-45-5 (EC No. 247-979-2)** submitted by [redacted] (Registrant), latest submission number [redacted], for above 1000 tonnes per year.

The present compliance check was initiated on 21 June 2010.

On 7 January 2011 ECHA notified the Registrant of its draft decision and invited him pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

On 4 February 2011 the Registrant provided to ECHA comments on the draft decision. On 1 March 2011 the Registrant updated the IUCLID dossier and the CSR with a new submission.

ECHA reviewed the further information received and amended the draft decision accordingly.

On 18 June 2011 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals to amend the draft decision within 30 days. Subsequently, Competent Authorities of the Member States submitted proposals for amendment to the draft decision.

On 20 July 2011 ECHA notified the Registrant of proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments within 30 days of the receipt of the notification.

ECHA reviewed the proposals for amendment and modified the draft decision accordingly.

On 1 August 2011, the modified draft decision was referred to the Member State Committee.

On 19 August 2011 the Registrant provided comments on the proposals for amendment.

The Member State Committee took the comments of the Registrant into account.

After discussion in the Member State Committee meeting on 20-23 September 2011, the draft decision was further modified by the Member State Committee and a unanimous agreement of the Member State Committee on the modified draft decision was reached on 23 September 2011.

This compliance check decision does not prevent ECHA to initiate further compliance checks on the present dossier at a later stage.

II. Information required

1. Pursuant to Articles 41(1)(a), 41(3) and 10(a)(ii) as well as Annex VI, Section 2 of the REACH Regulation the Registrant shall submit an update for the registered substance, which includes:
    - consistent identifiers in all fields that refer to substance identity (EC, CAS, IUPAC, SMILES, structural formula), (Annex VI, 2.1 and 2.2)
    - spectral data and description of the analytical methods to enable the substance composition to be quantified (Annex VI, 2.3.5 and 2.3.7)
    - substance composition, including information on the stereo chemistry of the substance (Annex VI, 2.2.2)

2. Pursuant to Articles 41(1)(a), 41(3), 10(a)(vii) and 12(1)(e) as well as Annexes VII-IX of the REACH Regulation, the Registrant shall submit the information using the test method as indicated below, and update the CSR accordingly:

    - Boiling point (Annex VII, 7.3., EU Method A.2.)
    - Vapour pressure (Annex VII, 7.5., EU Method A.4.)
    - Water solubility (Annex VII, 7.7., EU Method A.6.)
    - Self ignition temperature (Annex VII, 7.12., EU Method A.15.)
    - Viscosity (Annex IX, 1.17., OECD Method TG 114)
    - Surface tension (Annex VII, 7.3., EU Method A.5.)
    - Dissociation constant (Annex IX, 7.16., OECD Method TG 112)
    - Hydrolysis (Annex VIII, 9.2.2.1., EU Method C.7.)

- Growth Inhibition study aquatic plants (algae preferred) (Annex VII, 9.1.2., EU Method C.3.)

and if deemed necessary based on the outcome of the hydrolysis study to be performed first (see statement of reasons below III, 2.7, 2.8. and 2.9):

- Degradation (Annex IX, 9.2, further biotic degradation testing e.g. modified or enhanced biodegradability test; Annex IX, 9.2.1, simulation testing in appropriate media according to the methodologies as indicated in ECHA Guidance R.11 to fulfil the P assessment, and ECHA Guidance R.7.9
- Bioaccumulation (Annex IX, 9.3.2., EU Method C.13.)
- Adsorption/Desorption (Annex VIII, 9.3.1., EU Method C.18.).

3. Pursuant to Articles 41(1)(a), 41(3), 12(1)(e), 10(a)(vii) and 13(1) as well as Annexes VII-X and XI.1.1.2 of the REACH Regulation, the Registrant shall submit the information using the test method as indicated below, and update the CSR accordingly:
   - *In vitro* cytogenicity study in mammalian cells (Annex VIII, 8.4.2., EU Method EU B. 10.) or *in vitro* micronucleus study (Annex VIII, 8.4.2., OECD Method TG 487)
   - Mutagenicity, *in vivo* (Annex IX, 8.4.,OECD Guideline 488). The test shall be conducted in mice treated for 42 days, and tissues (liver, kidney, bone marrow and developing germ cells from the seminiferous tubules) will be harvested 3 days after the cessation of treatment. Mutation frequency shall be assessed in liver, kidney, bone marrow and developing germ cells from the seminiferous tubules.

Pursuant to Article 41(4) of the REACH Regulation, the Registrant shall submit the information in the form of an updated IUCLID dossier to ECHA by **24 October 2012**.

III. Statement of reasons

Based on the examination of the technical dossier, ECHA concludes that the information therein submitted by the Registrant for registration of the above mentioned substance in accordance with **Article 6** of the REACH Regulation, does not comply with the requirements of Articles **10, 12 and 13 and with Annexes VI to XI** thereof. Consequently, the Registrant is requested to submit the information required above that is needed to bring the registration into compliance with the relevant information requirements.

1. Missing information related to substance identity

Pursuant to Article 10(a)(ii) and Annex VI, Section 2 of the REACH Regulation, the technical dossier of the registration shall include information on the identity of the substance. Annex VI, Section 2 lists the information requirements that shall be sufficient to identify the registered substance.

The identity information included in section 1.1 of the IUCLID dossier is inconsistent and the identity of the substance to be registered cannot be verified. The CAS and EC entries reported in section 1.1 of the IUCLID dossier refer to a UVCB substance while the information included in the SMILES notation and structural formula fields refer to

well-defined constituents. As the information refers to different substances, the identity of the substance cannot be determined. The Registrant shall clarify this inconsistency.

The Registrant has not included a description of how the chromatographic data included in the dossier was used to quantify the substance composition. The Registrant provides only a Fourier transform infrared spectroscopy (FT-IR) spectrum, which alone is not sufficient to verify the substance identity. The gel permeation chromatogram (GPC) provided by the Registrant is not sufficient to verify the composition of the substance. Annex VI, 2.3. requires the Registrant to provide:

- Spectral data (ultra-violet, infra-red, nuclear magnetic resonance or mass spectrum)
- High-pressure liquid chromatogram, gas chromatogram
- Description of the analytical methods or appropriate bibliographic references for the identification of the substance, impurities and additives.

In addition, the Registrant provides no information on the stereochemistry, optical activity, and ratio of stereo-isomers of the main constituent of the substance as required by Annex VI, 2.2.2.

Accordingly, the Registrant is requested to provide the description of the type of the substance, the ratio of stereo-isomers and analytical identification of the registered substance, to enable the correct identification of the substance.

2. Missing information related to endpoints

Pursuant to Articles 10(a)(vii) and 12(1)(e) of the REACH Regulation, a registration for a substance produced in quantities of above 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII and VIII of the REACH Regulation and testing proposals for the provision of the information specified in Annexes IX and X.

2.1 Boiling point

The Registrant has provided

- a QSAR estimate using the MPBP EPISUITE, with a boiling point of 272 C and an assigned reliability of 4
- the result of an experimental study, indicating the boiling point as 484-491 C with an assigned reliability of 2. However, no information on the atmospheric pressure is provided.

The QSAR estimate has been assigned a Klimisch score of 4, and is therefore unassignable. The experimental study has some uncertainty as the boiling point from the experiment is higher than the self ignition temperature of the substance, and the atmospheric pressure is not indicated. This is therefore also unreliable. Consequently, the Registrant has provided no reliable data on the information requirement. The Registrant is requested to submit the information for this endpoint using the test method A.2 of Regulation (EC) No 440/2008.

2.2. Vapour pressure

The Registrant has provided the result of an experimental study, with an assigned reliability of 2, showing a vapour pressure of 15 Pa at 20 C.

There are not enough details to evaluate the validity of this study. Consequently, the information requirement is not fulfilled. The Registrant is accordingly requested to submit the information for this endpoint using the test method A.4 of Regulation (EC) No 440/2008.

2.3. Water solubility

The Registrant has provided:

- A QSAR study on the registered substance using EPISUITE water solubility fragments, with a water solubility of 68 mg/L and an assigned reliability of 4
- A QSAR study on the corresponding diol form of the substance, with a reported solubility of 156 mg/L and an assigned reliability of 4. The Registrant claims that the diol is the relevant form of the substance, as the registered substance undergoes rapid hydrolysis to the diol. The Registrant uses this value for the Chemical Safety Assessment.

Given the Registrant's assigned reliability of 4, the studies cannot be considered to fulfill the requirements of Annex XI 1.3. In addition, the assumption that the relevant form of the substance is the diol is not supported by the information provided by the Registrant on the endpoint hydrolysis (see section 2.6 of this document). The Registrant is accordingly requested to submit the information for this endpoint using the test method A.6 of Regulation (EC) No 440/2008.

2.4 Self-ignition temperature

The Registrant has provided the result of an experimental study with a reported self-ignition temperature of 397 °C and with an assigned reliability of 3 (not reliable). No further information on the study method or guideline is available in the dossier. The information provided does not fulfill the data requirements, and the Registrant is accordingly requested to submit the information for this endpoint using the test method A.15 of Regulation (EC) No 440/2008.

2.5. Viscosity

The Registrant has provided the result of an experimental study using OECD guideline 114. However, the Registrant has assigned a reliability of 3 (not reliable), and states "Viscosity data is not reliable, no study detail is available". The information provided does not fulfill the data requirements, and the Registrant is accordingly requested to submit the information for this endpoint using the test method OECD Method TG 114.

2.6. Surface tension

The Registrant has waived the test with the justification that the "In accordance with Column 2 of REACH, Annex VII the test (required in Section, 7.6) does not need to be conducted based on the findings of the Chemical Safety Assessment and surface activity is not a desired property of the material." However, Column 2 of Annex VII, Section 7.6. states that the test need only be conducted if 1) based on structure, surface activity is expected or can be predicted, or 2) surface activity is a desired property of the material.

The Registrant has not addressed whether surface activity is expected based on the structure of the substance. The substance contains a polar group on one end, and a hydrophobic alkyl chain on the other end of the molecule. Based on the structure of the substance, some surface activity may be expected, and therefore an experimental

study is needed to provide information on surface tension. The Registrant is accordingly requested to submit the information for this endpoint using the test method A.5 of Regulation (EC) No 440/2008.

2.7. Dissociation constant

The Registrant has waived the test with the justification that "In accordance with REACH Chapter R.7A Endpoint Specific Guidance, specifically R.7.1.17.1 Information Requirements on Dissociation Constant, if the substance cannot dissociate due to a lack of relevant functional groups, the dissociation constant is irrelevant. Vinyl Neodecanoate does not contain functional groups subject to dissociation, consequently a study is not justified."

However, this statement addresses the dissociation constant of a substance other than the registered substance, and provides no justification for why this waiver is applicable to the registered substance. Therefore, the justification for the data waiving does not fulfill the data requirements for the registered substance, and the Registrant is accordingly requested to submit the information for this endpoint using the test method OECD Method TG 112 and to update the CSR accordingly.

2.8. Hydrolysis

For this endpoint the Registrant has provided a QSAR prediction using HYDROWIN v1.67 of EPISUITE with estimated half-lives at 25 °C of these compounds at pH=7 and 8 of 17.26 and 1.73 years, respectively.

ECHA notes that the substance contains a molecular fragment that is not covered by HYDROWIN v1.67, namely the ester functionality. The Registrant has not demonstrated that the QSAR prediction falls within the applicability domain of the QSAR model, as required by Annex XI, 1.3. Consequently, the adaptation of the testing requirement is not acceptable, and the information requirement for this endpoint is not fulfilled. The Registrant is accordingly requested to submit the information for this endpoint using the test method EU Method C.7.

2.9 Growth Inhibition study aquatic plants

The Registrant has provided the result of an experimental study according to OECD Guideline 201 (Algae, Growth Inhibition Test). However, ECHA considers that the test is invalid for the following reasons. The study summary indicates that globules of test material were observed during the performance of the study potentially causing physical effects and suggesting that concentrations in the study exceeded the water solubility of the substance. Due to the lack of chemical analysis it is not clear what dissolved concentrations the algae were exposed to. Given that the test is invalid, the information requirements for this endpoint are not fulfilled. The Registrant is accordingly requested to submit the information for this endpoint using the test method EU Method C.3 and to update the CSR accordingly.

Given that the knowledge of water solubility is a prerequisite for the performance of the growth inhibition test, the Registrant is requested to undertake the water solubility test before conducting the growth inhibition study to aquatic plants test.

2.10. Degradation

The Registrant has investigated the potential for degradability of the substance and indicated in section 8 of the CSR under the PBT assessment that the substance does not fulfill the P criterium.

The substance was found to be not readily biodegradable. The Registrant performed an Inherent Biodegradability Test (OECD 302A) and modeled data (BIOWIN 2, 3, 6) are provided to confirm non - persistency. However, an OECD 302A is not suitable to confirm non-persistency. This test system is not comparable with other Inherent Biodegradability tests, due to its test design which allows for a strong adaptation. According to ECHA guidance R.7B, test methods such as modified or enhanced ready biodegradability tests can be used to confirm non-persistence without the need for further simulation testing. Regarding the QSAR prediction, the BIOWIN indicates that the substance does not biodegrade fast and ultimate biodegradation is estimated to be in the order of months. According to ECHA Guidance R11, QSAR estimates may be used to preliminary identify substances with a potential for persistency. ECHA concludes therefore that there is insufficient evidence to conclude that the substance is not persistent. Thus further degradation test(s) are required under Annex IX 9.2.

The Registrant is accordingly requested to submit the information for this endpoint using a modified or enhanced ready biodegradability test (according to ECHA guidance R.7B, 7.9.4). However, should further biodegradation testing found to be necessary and lack of evidence of non-persistency found, the Registrant needs to continue to further assess the persistency of the substance by performing simulation degradation testing in appropriate media, as indicated by the results of the chemical safety assessment (see also ECHA Guidance R.11).

The Registrant is also requested to update the CSA and the PBT assessment in the CSR, as necessary.

Prior to conducting the above recommended degradation tests, the Registrant is requested to undertake the hydrolysis test first. In accordance with ECHA Guidance R11, 'if significant and substantial abiotic degradation has been confirmed and the hydrolysis transformation products have been assessed and concluded not to be PBT/vPvB, no further testing of degradation is required'. The substance is in this case deemed not to be persistent.

2.11. Bioaccumulation

The Registrant has provided QSAR estimations performed by EPISUITE BCFBAF v3.00. In the absence of a clear indication on the potential of the registered substance to hydrolyze, the predictions are provided both for the parent compound epoxide (logKow=4.4) and for the expected hydrolysis product diol (logKow=2.3).

In the case of the hydrolysis product, very low BCF are predicted both considering the biotransformation or not. In the case of the parent compound, very low BCF are predicted, except when considering that there is no biotransformation. In this case the BCF prediction (Arnot-Gobas BCF & BAF Methods, assuming biotransformation rate of zero) indicates a potential for bioaccumulation (BCF=2469 L/Kg).

While the diol fragment falls in the domain of applicability of the BCFBAF model, the epoxide fragment is neither included in the training set nor in the validation set of the

model, as opposed to the Registrant's claim. Therefore, the prediction for the BCF value for the parent compound is uncertain. Consequently, the adaptation of the testing requirement fails to comply with the requirements of Annex XI, 1.3.

ECHA considers that, in the absence of definite data on the potential of the substance to hydrolyze, the Registrant fails to demonstrate that in any circumstances the substance does not have a potential for bioaccumulation. The Registrant is accordingly requested to submit the information for this endpoint using the test method C.13 of Regulation (EC) No 440/2008.

Given that hydrolysis is crucial to understanding the fate and behavior of the substance in the environment and it constitutes a basic knowledge prior to perform the test, the Registrant is requested to undertake the hydrolysis test before conducting the bioaccumulation test. Depending on the potential to hydrolyse of the parent compound, the Registrant shall consider whether the bioaccumulation test is necessary.

2.12. Adsorption/Desorption

The Registrant has provided QSAR estimations performed by EPISUITE KOCWIN v1.66 for the parent compound. The epoxide fragment is neither included in the training set nor in the validation set of the model, as opposed to the Registrant's claim. The Registrant has not demonstrated that the QSAR prediction falls within the applicability domain of the QSAR model, as required by Annex XI, 1.3. Consequently, the adaptation of the testing requirement is not acceptable, and the information requirement for this endpoint is not fulfilled. The Registrant is accordingly requested to submit the information for this endpoint using the test method C.18 of Regulation (EC) No 440/2008.

Given that hydrolysis is crucial to understanding the fate and behaviour of the substance in the environment and it constitutes a basic knowledge prior to perform the test, the Registrant is requested to undertake the hydrolysis test before conducting the adsorption/desorption test. On the basis of the stability of the parent compound, the Registrant shall consider whether the adsorption/desorption test is necessary.

3. Missing information related to genotoxicity studies

The Registrant has provided the results of six *in vitro* genotoxicity studies and one *in vivo* study. Three Ames tests showed positive results in genotoxicity. Three other *in vitro* studies (from 1970's) and the *in vivo* study are documented as negative. The Registrant has summarised that because of the *in vivo* study results, the substance does not meet the criteria for classification as mutagenic.

3.1. *In vitro* cytogenetics: Mammalian chromosome aberration assay

The Registrant has data on a non-guideline chromosome aberration assay (1979), testing 2,3-epoxypropyl neodecanoate for its ability to induce chromosome aberrations in rat liver epithelial cell line RL1. Low levels of chromosome aberrations were observed in treated cultures. However, these chromosome aberrations occurred at or near cytotoxic dose levels. Therefore, the Registrant has concluded that it is likely that the chromosome damage observed in rat liver RL1 cells was due to cytotoxic events, and not to genotoxic DNA damage.

Article 13(3) of the REACH Regulation provides that tests "shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or the Agency as being appropriate." The rat liver cell chromosome aberration assay does not meet the standard of current test guidelines. Article 13(3) further provides "Information on intrinsic properties of substances may be generated in accordance with other test methods provided that the conditions set out in Annex XI are met." The rat liver cell chromosome aberration assay lacks coverage of the endpoint with and without metabolic activation. ECHA considers that measurement of chromosome aberration with and without metabolic activation is a "key parameter{s} foreseen to be investigated in the corresponding test methods referred to in Article 13(3)" (Annex XI, 1.1.2.(2)), and that consequently, the rat liver cell chromosome aberration assay does not meet the requirements of Annex XI, 1.1.2.(2). It follows that the requirements of Article 13(3) are not met, and that this assay is not adequate to meet the information requirement of Annex VIII, 8.4.2. The yeast genetic assay (1979) also does not adequately cover the information requirement of Annex VIII, 8.4.2. The information requirement of Annex VIII, 8.4.2 is not fulfilled, and the Registrant is requested to submit the information for this endpoint by an *in vitro* cytogenicity study in mammalian cells (Annex VIII, 8.4.2., EU Method EU B. 10.) or *in vitro* micronucleus study (Annex VIII, 8.4.2., OECD Method TG 487).

3.2. *In vivo* mutagenicity

For *in vivo* genotoxicity the Registrant has data on a non-guideline test from 1981 (on a rat liver DNA assay), reporting that 2,3-epoxypropyl neodecanoate did not induce evidence of DNA damage detectable by alkaline elution at a dose level of approximately 4850 mg/kg of body weight. The Registrant concludes that 2,3 - epoxypropyl neodecanoate did not cause DNA damage and is not genotoxic *in vivo*.

The substance is clearly positive in the Ames assay, an Annex VII *in vitro* mutagenicity test. ECHA considers that the old non-guideline study, *in vivo* rat liver DNA strand break assay does not adequately address the concerns for gene mutation. The information requirement of Annex VIII, 8.4, column 2 is thus not fulfilled. The Registrant is accordingly requested to submit the results of an *in vivo* test using test method OECD 488, Transgenic rodent somatic and germ cell gene mutation assays. There is an indication of toxicity in more than one tissue, and so the transgenic rodent somatic and germ cell gene mutation assay is more appropriate for the determination of genotoxic potential. This assay also has the ability to determine if the substance is a germ cell mutagen, which cannot be undertaken with the assay for unscheduled DNA synthesis (EU Test method B.39). The test shall be conducted in mice treated for 42 days, and tissues (liver, kidney, bone marrow and developing germ cells from the seminiferous tubules) will be harvested 3 days after the cessation of treatment. Mutation frequency shall be assessed in liver, kidney, bone marrow and developing germ cells from the seminiferous tubules.

IV. General requirements for the generation of information and Good Laboratory Practice

ECHA always reminds registrants of the requirements of Article 13(4) of the REACH Regulation that reads:

> "Ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice provided for in

Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or the Agency and with the provisions of Directive 86/609/EEC, if applicable."

According to Article 13(3) of the REACH Regulation, tests that are required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or the European Chemicals Agency as being appropriate. Thus, the Registrant shall refer to Commission Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 as adapted to the technical progress and use the applicable test methods to generate the information on the endpoints indicated above.

National authorities monitoring good laboratory practice (GLP) maintain lists of test facilities indicating the relevant areas of expertise of each facility.

V. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on ECHA's internet page at http://echa.europa.eu/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

Done at Helsinki,

Jukka Malm
Director of Regulatory Affairs