EUROPEAN CHEMICALS AGENCY

Helsinki, 23 September 2016

Addressee: [redacted]

Decision number: TPE-D-2114343730-56-01/F
Substance name: Carboxylic acids, C5-9, triesters with 2-ethyl-2-(hydroxymethyl)propane-1,3-diol
EC number: 941-924-2
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 17 March 2016
Registered tonnage band: 1000 tonnes or more per year

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA has taken the following decision.

You are requested to perform :

1. ***Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: Daphnia magna reproduction test, EU C.20./OECD TG 211)* using the registered substance,**

while your originally proposed test for *Long-term toxicity testing on aquatic invertebrates (Daphnia magna reproduction test, EU C.20./OECD TG 211)* using the analogue substance trimethylolpropane tripelargonate (CAS 126-57-8) is rejected.

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **30 June 2017**. You shall also update the chemical safety report, where relevant.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals.

Authorised[1] by Ofelia Bercaru, Head of Unit, Evaluation E3

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons

Grouping of substances and read-across approach

In the registration dossier, you intend to test an analogue substance and adapt the standard information requirement for a long-term toxicity on aquatic invertebrates (Annex IX, 9.1.5.) by means of grouping and read-across as laid down in REACH Annex XI, Section 1.5.

Annex XI, Section 1.5 requires a structural similarity among the substances within a group or category so that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation. Such prediction or properties need to be based on a similar or regular pattern of these properties as a result of the structural similarity.

The following analysis presents your justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and an endpoint-specific context. The analysis is based on the dossier update submitted on 17 March 2016.

A. Description of the grouping and read-across approach proposed by the Registrant

Your read-across approach is based on the claimed structural and toxicological similarity of trimethylolpropane tripelargonate (CAS number126-57-8) and the registered substance.

You state that "*source and target substances have similar toxicological properties due to their structural similarities and because they hydrolyze to common products and non-common products but predicted to have similar toxicological effects. This prediction is supported by toxicological data on the substances themselves and on the hydrolysis products of the substances, and subsequent metabolism of these substances.*"

You further elaborate that "*The target substance is a multi-constituent substance [.....] composed of several constituents (UV CB substance). All the constituents of the target substance are* [redacted] *differing only in the number of the repetitive moiety X (3, 4, 5, 6 and 7) in the side chains of the acid aliphatic chain and, consequently, in the chain length. The major chain length of the target substance (X = 7) is identical to the chain length of the source substance (mono-constituent, [....]). Therefore, the source and the target substances share structural similarities with common functional groups, esters, and side chains varying in their length. Moreover, the side chains are chemically simple structures which have no structural alerts for toxicity and which are closely related to substances of known low toxicity.*"

...and you conclude that "*Therefore, read-across from the existing TOXICITY STUDIES on the source substance is considered as an appropriate adaptation to the standard information requirements of Annexes of the REACH Regulation.*"

B. Information submitted by the Registrant to support the grouping approach and read-across hypothesis

No justification for the analogue approach was included in the testing proposal under IUCLID section 6.1.4. However, you have provided a general read-across justification document as an attachment under IUCLID section 13 entitled: "Analogue approach from the TMP Pelargonate to the TMP C5-9: Similarity based on structural or sub-structural assessment and functional groups", 14 pp. In this document you provide the following arguments to support the analogue approach from TMP Pelargonate to the TMP C5-9. Points below are ECHA's summary of your justification document related to your testing proposal and overall argumentation and conclusions:

1) Substance identity for target and source substance including the purity and impurities

The registered (target) substance is a UVCB substance (EC 941-924-2; IUPAC name: Carboxylic acids, C5-9, triesters with 2-ethyl-2-(hydroxymethyl)propane-1,3-diol). You explain in your justification that "*the constituents of the target are* [redacted]*, for all the constituents, with the* [redacted]". You elaborate that "*the side chains of the acid part of the esters differ only in the number of the repetitive moiety X (3, 4, 5, 6 and 7) for each of the constituents of the target substance and, consequently, in the chain length*". Molecular weights for the reported 11 constituents (from $C_{22}H_{40}O_6$ to $C_{32}H_{60}O_6$) vary from 400 to 540, respectively.

You describe the analogue (source) substance as "*a mono-constituent substance, again* [redacted] *having the same chain length most present in the multi-constituent substance* [redacted] *used as starting raw material of the target substance (EC No 204-793-6 e-/CAS No 126-57-8 /IUPAC name: 2-ethyl-2-[[(1-oxononyl)oxy]methyl] propan 1,3-diyl dinonan-1-oate.* Molecular weight reported for the source material is 554 (X=7, $C_{33}H_{62}O_6$).

You claim that the "*source and target substances are characterised by similar impurities*", namely the corresponding [redacted]. The impurities are not classified and are not considered as hazardous for the chemical safety assessment. You state that the amount of impurities in the source chemical (<3 % w/w) "*is not expected to influence the validity of the read-across*".

2) Structural similarity including functional groups and common breakdown products

You state that the "*basic structures of the target and source substances are the same*" and that the "*side chains of the source and target differ in the number of repetitive moiety (X) being 7 for the source and 3 to 7 for the corresponding constituents of the target*". Furthermore, "*One of the two main constituent fatty carbon chains of the substance is identical to the fatty carbon chain (*[redacted]*, from 15 to 50 % by weight calculated on the total fatty acids mixture used as starting material of the target substance) of the target substance*".

With regards to common breakdown products, you acknowledge that no data on hydrolysis of the target and source substance are available, because "*according to Column 2 of Annex VIII, the study is not necessary in case of substances highly insoluble in water*". However, you claim that "*no different pathways are expected from the two substances in consideration of their very similar chemical structure*. With regards to biotic degradation products, you used the EAWAG-BBD, Pathway Prediction Tool, and provided predictions of possible microbial degradation pathways relevant for the constituents of the target substance. However, you state that the "*tool predicts the biologically relevant degradation pathways based on the chemical structure of the addressed substance. As a consequence, the model cannot predict the pathways that will apply to a UVCB substance like TMP, C5-9*". You assume that, due to the recurring functionalities of the target substance, "*the pathways identified for one constituent will also be applicable to other constituents similar to the assessed constituent*".

3) Physicochemical properties

You claim that the "*structural differences in side chains do not significantly influence the physicochemical properties of both substances*". To support this statement, you provided a data matrix containing some measured physical chemical data for the source substance, such as viscosity, flash point and surface tension and properties predicted with EPISUITE for the main constituents of the target substance, like melting point, boiling point, vapour pressure, partitioning coefficient and water solubility. The calculated log Kow is very high (>6 for the source) and varying between 8.67 – 12.11 for the target substance's constituents. Overall the data matrix shows that predicted partition coefficient n-octanol/water (log Kow) is increasing with the molecular weight and none of the constituents are water soluble.

4) Comparison of data from human health endpoints including toxicity of target and source substances, toxicity of hydrolysis products and classification and labelling

You refer in your justification document to experimental data available for source substance which "*indicate that this substance has low oral and dermal acute toxicity (LD50>2000 mg/kg bw for both routes)*". Source substance is also "*not irritating to skin and eye, is not sensitising, and is negative in Ames test, in vitro chromosome aberration and in vitro mammalian gene mutation test, in vitro micronucleus in human lymphocytes*". However, you state that "*no toxicological studies are available for the target substance*" and instead you consider that the proposed read-across is supported based on "*the similar structures, similar local and systemic toxicity profiles*" between the source and target substances.

C. ECHA analysis of the grouping approach and read-across hypothesis in light of the requirements of Annex XI, 1.5 of the REACH Regulation.

(1) Substance characterisation of source and target substances

The characterisation of the source substance needs to be sufficiently detailed in order to assess what impact the composition and/or impurities may have on the proposed read-across. In the ECHA's practical guide 6 "How to report on Read-Across" it is recommended to follow the ECHA Guidance for identification and naming of substances under REACH and CLP (version 1.3, February 2014) also for the source substances. This ensures that the identity of the source substance and its impurity profile allows an assessment of the suitability of the substances for read-across purposes.

In the present case, the characterisation of the substance identified as source is sufficiently clear.

(2) Structural similarity and dissimilarity of the source and target substances and the scientific explanation on why and how the structural features allow predictions

ECHA acknowledges that the source substance is structurally similar to one of the possible constituents of the target UVCB substance (when moiety X = 7). In order to meet the provisions in Annex XI, Section 1.5. to predict human health and environmental effects from data from a reference substance, ECHA considers that structural similarity alone is not sufficient. It has to be justified why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. In particular, the structural similarities must be linked to a scientific explanation of how and why a prediction is possible and of how the structural dissimilarities impact the prediction.

For the registered UVCB target substance, it has not been explained scientifically why the additional constituents not present in the source substance still allow the source substance to be used as an analogue substance.

In the present case, you propose to use results that will be obtained in a long-term aquatic invertebrate study with one of the main constituents of the registered UVCB substance to predict its properties. However, ECHA notes that no further explanations are offered why and how this substance may be used to predict environmental properties for the registered (target) substance, especially as there are no measured ecotoxicological data available for the target substance.

From the composition of the registered substance provided in the registration dossier it is obvious that the overwhelming portion of the composition of the registered substance is not covered by the analogue approach chosen (i.e. to predict the properties of the registered substance using results obtained with trimethylolpropane tripelargonate). A moiety of X=7 may make up to [redacted]% (in terms of carbon chain distribution inside the trimester) of the total composition of the registered substance. You have not explained in which way the unaccounted percentage of the composition of the registered substance may influence its toxicity profile and, thereby, influence the reliability of predictions which do not take into account the presence of the full composition of the registered substance.

ECHA concludes that you have not addressed the obvious structural differences between the source and the target substances and you have not explained why those differences would not lead to differences in the mode of action and/or in the (eco)toxicity profile of target and source substances. The provided explanation is not considered as valid to establish the link between the structural similarity and the prediction. Consequently it is not possible to predict environmental effects based on the proposed approach.

(3) Information in the data matrix to support a similar or regular pattern as a result of structural similarity

Annex XI, Section 1.5 provides that "*substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances*". One prerequisite for a prediction based on read-across therefore is that the substances involved are structurally similar and are likely to have similar properties. One important aspect in this regard is the data matrix comparing properties of source and target substances.

The data matrix that you provided includes only a comparison of the physicochemical characteristics of the target and the source substances and provides no information on (eco)toxicity studies for the target substance. Therefore, the data matrix does not allow verification that source and target substances have a consistent (eco)toxicity profile which would support the claim of a similar pattern of toxicity for these properties.

In the present case, additional complications for the attempted prediction arise from the fact that the technical dossier contains aquatic toxicity data for the registered substance derived only by application of QSAR calculations on some of the main constituents of the registered substance. The same is the case for the prediction of the key physical-chemical properties that have also been estimated by use of the EPISUITE model. Also the possible action modes of the individual constituents and the consequences for the prediction have not been addressed.

ECHA concludes that the information in the data matrix does not confirm the statement that: "*...adequate, reliable and available scientific information indicates that the source and target substances and their subsequent degradation products have similar toxicity profiles*". The data matrix, therefore, does not allow verification of the claim of a similar pattern of toxicity. Consequently the information in the data matrix does not support the possibility to predict adverse effects within the proposed approach.

(4) Comparison of physical-chemical, environmental fate and bioavailability properties of source and target substances

Annex XI, Section 1.5. provides that "*substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances*". One prerequisite for a prediction based on read-across therefore is that the substances involved are structurally similar and are likely to have similar properties. One important aspect in this regard is the comparison of environmental fate (including biodegradation, bioaccumulation, etc.) properties of source and target substance.

You state that "*source and target substances have similar toxicological properties due to their structural similarities and because they hydrolyse to common products and non-common products but predicted to have similar toxicological effects*". However, ECHA notes that the justification document does not provide any data on hydrolysis for the target and source substances and there are also no quantitative degradation rates for the analogue (source) substance to compare with the registered one. Therefore, ECHA is not in a position to conclude that the source and target substances are similar with regard to hydrolysis products or rates. Concerning bioaccumulation, the technical dossier and justification document present modelled EPISUITE (Fragment constant approach) Log Kow estimates for the individual components of the registered substance (Log Kow between 8.7-12) and an unbounded estimate for the source substance (Log Kow> 6.2). No other information on the target substance is reported in the dossier.

In general, for many organic substances ecotoxicity, bioaccumulation and bioavailability can be predicted based on logKow. For most organic substances toxicity increases with increasing logKow. Such trends, however, often have a breakpoint at higher logKow values. You have not demonstrated if and how toxicity in this case is related to logKow for both source and target substance. Furthermore, it is not clear whether a breakpoint in a possible logKow – ecotoxicity trend has or has not been reached.

ECHA concludes that you did not establish that the source and the registered substances have the same physical-chemical and environmental fate properties which would lead to a similar pattern of bioavailability and ecotoxicity as a result of structural similarity. As a consequence it is not possible to predict properties within the proposed approach.

D. Conclusion on the read-across approach

ECHA considers that structural similarity alone is not sufficient for predicting (eco)toxicological properties. It has to be justified why and how such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. ECHA notes that in view of the issues listed above, it has not been demonstrated that the source and target substances have the same properties or follow a similar pattern with regard to studies on aquatic toxicity to invertebrates. Besides the reference to the structural similarity, there is no valid mechanistic explanation provided by you why predictions can be made using the results from the source substance. ECHA concludes that you have failed to meet the requirement of Annex XI, Section 1.5. that environmental effects for the registered substance may be predicted from data from the source substance indicated in your read-across approach. The proposed read-across is therefore rejected. Accordingly, it is necessary to perform testing on the registered substance.

ECHA notes further that in your comments according to Article 50(1) you already agreed to perform the study on the registered substance instead of the proposed analogue substance while the above described read-across justification was included in the dossier update referenced on the front page of this decision.

1. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require you to carry out other test in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a long-term toxicity testing on aquatic invertebrates (*Daphnia magna* reproduction test, EU C.20/OECD TG 211) to be performed with the analogue substance (Trimethylolpropane tripelargonate (CAS 126-57-8)). You have not provided any further justification for your testing proposal in section 6.1.4. of your technical IUCLID dossier but in section 6.1.3. you have provided the following justification: "*TMP Fatty acids, C5-9 is highly insoluble in water (see Section 4.8 of IUCLID for more details). Based on the properties of the substance, long-term toxicity testing is considered more relevant. A testing proposal on the analogue TMP tripelargonate (CAS: 126-57-8) was submitted for long-term toxicity to daphnia.*"

As explained above in the section 'Grouping of substances and read-across approach' of this decision, your proposed read-across approach does not meet Annex XI, 1.5 requirements and is, therefore, rejected.

ECHA considers that the proposed *Daphnia magna* reproduction study (test method EU C.20./OECD TG 211) is appropriate to fulfil the information requirement of Annex IX, Section 9.1.5 of the REACH Regulation.

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 2.0, November 2014), Chapter R7b (Section R.7.8.5 including Figure R.7.8-4), if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially more sensitive, long-term studies may be required on both. There were no indications in the dossier from the short-term toxicity studies on aquatic species that the fish would be substantially more sensitive than aquatic invertebrates.
In such case, according to the integrated testing strategy, the *Daphnia* study is to be conducted first. If based on the results of the long-term *Daphnia* study and the application of a relevant assessment factor no risks are observed (PEC/PNEC<1), no long-term fish testing may need to be conducted. However, if a risk is indicated, long-term fish testing may need to be conducted.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the following study with the registered substance subject to the present decision: Long-term toxicity testing on aquatic invertebrates (test method: *Daphnia magna* reproduction test, EU C.20/OECD TG 211).

Notes for your consideration

Once results of the proposed test on long-term toxicity to aquatic invertebrates are available, you shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation. If the revised chemical safety assessment indicates the need to investigate further the effects on aquatic organisms, you shall submit a testing proposal for a long-term toxicity test on fish in order to fulfil the standard information requirement of Annex IX, 9.1.6. If you come to the conclusion that no further investigation of effects on aquatic organisms is required, you shall update your technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex IX, 9.1.6.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposal for examination pursuant to Article 40(1) on 10 July 2015.

ECHA notified you of the draft decision on 20 January 2016 and invited you to provide comments. That draft decision was based on the registration dossier with submission number FC565640-53.

On 23 February 2016, ECHA received your comments agreeing to the draft decision.

You updated your registration with submission number WM608798-01 on 17 March 2016.

The ECHA Secretariat considered your comments and update. This has been reflected in the Appendix 1 (Reasons) whereas the information required was not amended.

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment.

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided by the Registrant in his registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the registration at a later stage.

2. Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the Enforcement Authorities of the Member States.

3. In carrying out the test(s) required by the present decision it is important to ensure that the particular sample of substance tested is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported. If the registration of the substance covers different grades, the sample used for the new test(s) must be suitable to assess these. Furthermore, there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.