EUROPEAN CHEMICALS AGENCY

Helsinki, 21 September 2016

Addressee: [redacted]

Decision number: TPE-D-2114344602-56-01/F
Substance name: Reaction mass of sodium hydrogen N-(1-oxooctadecyl)-L-glutamate and stearic acid
EC number: 939-201-1
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 18.12.2015
Registered tonnage band: 100-1000 tpa

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 the following test:

Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route using the registered substance;

while your originally proposed test for Pre-natal developmental toxicity study (EU B.31./OECD TG 414) oral route, using the analogue substance L-Glutamic acid, N-coco acyl derivs., disodium salts (CAS Nr 68187-30-4) 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 **28 September 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 Claudio Carlon, Head of Unit, Evaluation E2

[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

The decision of ECHA is based on the examination of the testing proposal(s) submitted by you.

0. Grouping of substances and read-across approach

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "*provided that the conditions set out in Annex XI are met*".

You have submitted a testing proposal for a pre-natal developmental toxicity study in rabbit according to EU B.31./OECD 414 to be performed with the analogue substance L-Glutamic acid, N-coco acyl derivs., disodium salts (CAS 68187-30-4) with the following justification: "*An OECD 414 study ith the homologuous substance L-Glutamic acid, N-coco acyl derivs., disodium salts (CAS 68187-30-4) is proposed in order to investigate the developmental toxicity in the rabbit. In accordance with ECHA position ECHA/PR/09/13 as of Sept 15, 2009, the OECD 414 proposal is a valid waiving argument to waive an OECD 421 or an OECD 422 screening study.*"

Annex XI, Section 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation. The following analysis presents your justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification.

0.1 Description of the proposed grouping and read-across approach

You explain in the general analogue approach hypothesis that "*the target substance and the sources substance belong to the same substance class of glutamate derivatives and differ only in the carbon chain distribution of the alkyl moiety*", and that, "*in general, same structural components can be considered as predictive for a great similarity of the toxicological profile.*"

Furthermore, you explain in the endpoint specific analogue approach hypothesis for reproductive toxicity endpoint that "*It is indicated in this document that the target and the source substance will hydrolyse immediately after oral intake and degrade into glutamic acid and coconut acid/stearic acid. Stearic and coconut acid are natural constituents present in food and not associated with a hazard regarding reproductive toxicity. Both fatty acids are approved direct food additives. Due to the structural similarity, the hydrolysis after oral intake and the same expected metabolic, it can be therefore concluded that the source substance can be used as read across substance with regard to prenatal developmental toxicity and the result can be used for the dossier of the target substance.*"

ECHA understands this as the hypothesis under which you make predictions for the properties listed above.

0.2 Support of the proposed grouping and read-across approach

You have provided a read-across justification as a separate attachment in IUCLID, Section 13 and as attachment to your comments on the draft decision. In summary you provide the following arguments to support the read-across approach:

The justification document comprises of i) OECD toolbox profiler prints of C8 Glutamate (CAS 167888-81-5) and C18 Glutamate (CAS not reported) and ii) bibliographic review of

two analogue substances, L-Glutamic acid, N-coco acyl derivs., monosodium salts (CAS 68187-32-6) **[1]** and L-Glutamic acid, N-coco acyl derivs., disodium salts (CAS 68187-30-4) **[2]**, structurally related to the registered substance. **[2]** is the proposed read-across source substance to be used for fulfilling the information requirement of Annex IX 7.8.2. Pre-natal developmental toxicity.

The bibliographic review is focusing on the below key points:

i. Common functional groups

ii. Common precursors and breakdown products via biological processes

iii. Structural similarity

iv. Similar metabolic pathways

v. Similar physic-chemical properties

vi. Similar (low) mammalian toxicity and ecotoxicity profiles

In the technical dossier the following toxicological studies conducted with **[1]** and/or **[2]**, respectively, have been provided: acute toxicity (OECD 401 and 402), sub-chronic toxicity (OECD 408), skin and eye irritation (OECD 404 and 405) and skin sensitisation (OECD 406). ECHA notes that no toxicological studies conducted with the registered substance have been provided.

In addition, OECD Toolbox profiler results for [redacted] (reported minor constituent of the analogue substance, [redacted] % (w/w)) and [redacted] (reported main constituent of the registered substance, [redacted] % (w/w)) have been provided as part of the read-across support documentation.

0.3 ECHA analysis of the proposed grouping and read-across approach in light of the requirements of Annex XI, 1.5.

(i) Substance characterisation of source and target substances

The substance characterisation of the source substance(s) need to be sufficiently detailed in order to assess whether the attempted prediction is not compromised by the composition and/or impurities. In the ECHA 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.

ECHA notes the following:

You have performed structural and compositional comparison of the target and source substances with regard to constituents and impurities.

Based on the information provided, ECHA understands that the proposed read-across hypothesis for the reproductive toxicity endpoint is based on structural similarities of glutamate substance class derivatives and similar expected metabolic behaviour leading to similar toxicological profiles through common breakdown products after oral administration.

(ii) Explanation on why and how the structural similarities allow predictions

In order to meet the provisions in Annex XI, Section 1.5. to predict human health effects from data for a reference substance within the group by interpolation to other substances in the group, 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.

You have identified the structural basis for the prediction, *i.e.* the constituents of target and source substances. In your read-across hypothesis you state that "*the target substance and the sources substance belong to the same substance class of glutamate derivatives and differ only in the carbon chain distribution of the alkyl moiety*", and that, "*in general, same structural components can be considered as predictive for a great similarity of the toxicological profile.*" ECHA understands that you claim that the structural differences will not affect the chemical reactivity of the substances and therefore it is expected that these substances will undergo similar metabolism in the body.

ECHA notes that the proposed source substance and the target substance are multi constituent substances with different compositions and main constituents. Moreover, the source substance main constituent ([redacted]% (w/w)) is not present in the registered (target) substance while the target substance main constituent ([redacted] (w/w)) is not present in the source substance. Additionally, ECHA notes that you have identified also other non-common target and source substance constituents. Furthermore, ECHA considers that different constituents may differ in terms of chemical reactivity and in particular have a different metabolic rate in the body (see iv below).

ECHA concludes that you have not addressed the obvious structural differences (*i.e.* variation in the isomerisation and the type of alkyl- substitution) between the source substance and registered (target) substance and have not sufficiently explained why those differences would not lead to differences in the toxicity profile of source and target(s) substances. The provided explanation is not considered as valid to establish a scientific credible link between the structural similarity and the prediction.

(iii) Support of 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 structural similar and are likely to have similar properties. One important aspect in this regard is the analysis of the data matrix to compare the properties of source and target substances and to establish whether indeed they are similar or follow a regular pattern.

You have proposed that toxicity to reproduction of the target substance can be predicted from data to be generated on the source substance **[2]**. You claim that "*Due to the structural similarity, the hydrolysis after oral intake and the same expected metabolic, it can be therefore concluded that the source substance can be used as read across substance with regard to prenatal developmental toxicity and the result can be used for the dossier of the target substance.*"

You claim that "*The hydrolysis represents the first chemical step in the absorption, distribution, metabolism and excretion (ADME) pathways.*" Furthermore, you claim that "*It is indicated in this document that the target and the source substance will hydrolyse immediately after oral intake and degrade into glutamic acid and coconut acid/stearic acid.*"

To support this argument, you have provided OECD Toolbox profiler results containing predictions of the hydrolysis rates for [redacted] in pH 6.5 - 7.4.

ECHA understands that you claim that the data available for glutamate derivative substances is adequate to support the read-cross approach for mammalian toxicology in general and specifically for the reproductive toxicity endpoint. Furthermore, you have proposed that the source substance **[2]** has similar toxicity profile as the target substance and that the properties of the target substance can be predicted from data obtained with the source substance. However, ECHA notes that no toxicological information on the registered substance have been provided. ECHA therefore considers that the available infromation does not support a claim of similar toxicity, with regard to toxicity to reproduction, because it does not allow comparision of the toxic profile or hazard between source **[2]** and the target substances.

ECHA concludes that the presented evidence in the data matrix does not support a similar or regular pattern of toxicity for the property under consideration as a result of structural similarity. Therefore it cannot be verified that the proposed group/analogue substance(s) can be used to predict properties of the registered substance.

(iv) Toxicokinetics

One important aspect in establishing that substances have similar effects or follow a regular pattern is the comparison of absorption, distribution, metabolism and elimination of source and target substances. This allows assessing the qualitative and quantitative internal systemic exposure of the test organism when exposed to source and target, respectively.

ECHA notes the following:

a) you have not provided any toxicokinetic information or other data supporting theoretical considerations on ADME properties or the assumed immediate hydrolysis after oral administration.
b) as explained in point (ii) you have clearly identified the compositional differences between the source and target substances. However, ECHA notes that you have not provided sufficient supporting information as to why these compositional differences do not influence the metabolic rate and behaviour of the substances.

ECHA concludes that you did not sufficiently address important aspects such as the metabolic rate and behaviour of the source and target substances and the resulting possible difference in the metabolite profile. Therefore, it is not possible to verify whether the proposed source substance and the target substance are likely to have similar toxicity profiles as a result of similar metabolic profiles. In the absence of such information there is not an adequate basis for predicting the properties of the registered substance from the data obtained with the source substance.

0.4 Conclusion on the read-across approach

The proposed adaptation of the standard information requirements for a Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species in the technical dossier is based on the proposed read-across approach examined above. ECHA does not consider the read-across justification to be a reliable basis to predict the properties of the registered substance for the reasons set out above. Thus, the adaptation does not comply with the general rules of adaptation as set out in Annex XI, 1.5. Therefore, ECHA rejects the adaptation in the technical dossier that is based on Annex XI, 1.5.

ECHA therefore concludes that the criteria of Annex XI, 1.5. are not met, and the read-across approach, as presented by you, cannot be considered plausible to meet the information requirements.

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

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

A pre-natal developmental toxicity study for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. 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.

ECHA has evaluated your proposal to perform the test with the analogue substance *L*-Glutamic acid, N-coco acyl derivs., disodium salts (CAS 68187-30-4). The proposed adaptation of the standard information requirements for a Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species in the technical dossier is based on the proposed read-across approach examined above.
ECHA does not consider the read-across justification to be a reliable basis to predict the properties of the registered substance for the reasons set out in section 0 above. Thus, the adaptation does not comply with the general rules of adaptation as set out in Annex XI, 1.5.

Therefore, ECHA rejects the testing proposal to meet the information requirement for Pre-natal developmental toxicity study (EU B.31./OECD TG 414) oral route, using the analogue substance.

Accordingly, ECHA considers that in order to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation the study should be performed with the registered substance.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with rats or rabbits as a first species.

You proposed testing by the oral route. According to the test method EU B.31./OECD TG 414, the test substance is usually administered orally. On the basis of this default consideration, ECHA considers testing should be performed by the oral route.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the modified study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a first species (rat or rabbit), oral route (test method: EU B.31/OECD TG 414) while your originally proposed test for Pre-natal developmental toxicity study (EU B.31./OECD TG 414) oral route, using the analogue substance L-Glutamic acid, N-coco acyl derivs., disodium salts (CAS Nr 68187-30-4) is rejected according to Article 40(3)(d) of the REACH Regulation.

Notes for your consideration

For the selection of the appropriate species you are advised to consult ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.6.2.3.2 (July 2015).

Appendix 2: Procedural history

ECHA received your registration containing the testing proposal(s) for examination pursuant to Article 40(1) on 22 March 2013.

ECHA held a third party consultation for the testing proposals from 25 June 2015 until 10 August 2015. ECHA did not receive information from third parties.

This decision does not take into account any updates after 23 December 2015, 30 calendar days after the end of the commenting period.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

ECHA notified you of the draft decision and invited you to provide comments.
ECHA took into account your comments and did not amend the request.
You updated your registration on 18 December 2015. ECHA took the information in the updated registration into account, and amended the draft decision. The updated information is reflected in the Reasons (Appendix 1).

On 21 July 2016, ECHA notified the competent authorities of the Member States of its draft decision and invited them to propose amendment to the draft decision under Article 51 of the REACH Regulation.
As no amendment was proposed, ECHA took the decision pursuant 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. 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.