EUROPEAN CHEMICALS AGENCY

Helsinki, 24 May 2019

Addressee: [redacted]

Decision number: TPE-D-2114471263-52-01/F
Substance name: Reaction mass of sodium hydrogen N-(1-oxooctadecyl)-L-glutamate and stearic acid
List number: 939-201-1
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 18/12/2015
Registered tonnage band: 100-1000

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation ((EC) No 1907/2006) (the REACH Regulation), ECHA examined your testing proposal(s) and decided as follows.

While your originally proposed test for OECD TG 414 using the analogue substance L-Glutamic acid, N-coco acyl derivs., disodium salts (CAS 68187-30-4) is rejected, you are requested to perform:

1. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rats or rabbits), oral route using the registered substance.**

You have to submit the requested information in an updated registration dossier by **30 November 2021**. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons for this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and 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, has to 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 **Wim De Coen**, Head of Unit, Hazard Assessment

[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 proposals submitted by you.

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.

a) Consideration on the uses of the substance

In accordance with your registration dossier the substance is used exclusively in cosmetic products. However, stages of manufacturing of chemical and formulation of cosmetic products are taking place in the EU and there is no indication that they are carried out under stricly controlled conditions. As potential worker exposure may exist, testing for prenatal developmental toxicity is necessary to assess the risks from exposure to workers and therefore in order to fulfil the relevant REACH requirements. This is in accordance with ECHA's factsheet[2] on the interface between REACH and Cosmetics Regulations, which was developed jointly with the European Commission. It provides that registrants of substances that are exclusively used in cosmetics may not perform animal testing to meet the information requirements of the REACH human health endpoints unless such tests are needed to assess the risks from exposure to workers.

Such testing would not trigger the testing and marketing bans under the Cosmetics Regulation as the testing is to be performed for the purposes of meeting the requirements of the REACH Regulation; see Commission Communication of 11 March 2013 on the animal testing and marketing ban and on the state of play in relation to alternative methods in the field of cosmetics (COM(2013)135))[3].

You submitted comments to the draft decision "*disagreeing with ECHA's interpretation that the requested animal testing would not trigger the testing and marketing bans under the Cosmetics Regulation.*" You furthermore consider that you are "*not in a position to perform the requested prenatal development study on animals taking into account the marketing ban under the Cosmetics Regulation*".

Firstly, ECHA notes that contrary to your opinion ECHA does not attempt to provide binding interpretation of Cosmetics Regulation on testing and marketing bans. ECHA only refers, as noted above, to the Communication on that subject, of the competent body in the field of cosmetics i.e. European Commission.

[2] https://echa.europa.eu/documents/10162/13628/reach_cosmetics_factsheet_en.pdf
[3] http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52013DC0135&from=EN

Secondly, it seems that you misinterpret the Board of Appeal decision in Case A-013-2016 which considered that ECHA should provide interpretation of the relationship between the REACH Regulation and the Cosmetics Regulation and explain how such interpretation applies in the particular case. ECHA has provided such analysis above.

Thirdly, you consider that the marketing ban under the Cosmetics Regulation would apply if ECHA requires animal testing. However, you seem to overlook the important considerations:

(i) Testing is required for the purposes of the REACH Regulation. There is a possibility of worker exposure to the substance at the stages of manufacture and formulation as you have not applied strictly controlled conditions. Therefore, there is a necessity to assess developmental hazard of the substance to ensure that the risks to workers can be adequately controlled.

(ii) Testing is not requested for the purposes of the Cosmetics Regulation. There is an important qualification in Article 18 of the Cosmetics Regulation, that you seem to overlook, that animal testing is prohibited as far as it is undertaken *'in order to meet the requirements of this [Cosmetics] Regulation'*. The importance of this qualification is confirmed by the European Commission, the body responsible in the field of cosmetics, in its Communication referred to above (COM(2013)135). In particular: *'The Commission considers that the marketing ban is triggered by the reliance on the animal data for the safety assessment under the Cosmetics Directive/Regulation, not by the testing as such'*.

(iii) The matter has already been considered by the competent body i.e. European Commission in the communication mentioned above. You do not refer to it in your comments or explain why you seem to have contrary position to the one expressed by the competent body in the field of cosmetics.

To conclude, the animal testing is required for the purposes of REACH Regulation and in accordance with its provisions.

b) Consideration of the testing proposed

You have submitted a testing proposal for a pre-natal developmental toxicity study according to OECD TG 414 by the oral route and to be performed on the analogue substance L-Glutamic acid, N-coco acyl derivs., disodium salts (EC 269-085-1, CAS 68187-30-4; hereafter referred to as "source substance") as a test material. You further intend to use the results to adapt the standard information requirement for your registered substance (hereafter referred to as "target substance") by using read-across and grouping approach following Annex XI, Section 1.5. of the REACH Regulation.

ECHA has evaluated below your proposal.

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*".

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.

Description of the proposed grouping and read-across approach

You provided the following hypothesis:

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.*" Therefore, you claim that "*due to the structural similarities and consistent trend in physico-chemical, toxicological and toxicokinetic behaviour, the read-across to the selected source substances are considered an appropriate adaptation to the standard information requirements of Annex IX of the REACH Regulation for the target substance.*"

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.

Support of the proposed grouping and read-across approach

You have provided a read-across justification as a separate attachment in IUCLID. The justification document comprises of i) OECD toolbox profiler prints of C8 Glutamate (CAS 167888-81-5, reported minor constituent of the analogue substance, [redacted]) and C18 Glutamate (CAS not reported, reported main constituent of the registered substance, [redacted]) and ii) bibliographic review of two analogue substances, L-Glutamic acid, N-coco acyl derivs., monosodium salts (CAS 68187-32-6), and L-Glutamic acid, N-coco acyl derivs., disodium salts (CAS 68187-30-4), structurally related to the registered substance.

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 the source substance and/or the other analogue substance indicated above, 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.

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

(i) 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.

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.*" You acknowledged the structural differences but you claim that they will not affect the chemical reactivity of the substances and therefore you expect that these substances will undergo similar metabolism in the body.

ECHA notes that the proposed source and the target substances are multi constituent substances with different compositions and main constituents. Moreover, the source substance main constituent (C12 Glutamate, [redacted]) is not present in the target substance while the target substance main constituent (C18 Glutamate, [redacted]) 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 iii below).

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

(ii) 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.

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 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 comparison of the toxic profile or hazard between source and the target substance.

You commented the draft decision agreeing to "*deliver additional and distinct information on the target substance to make the read across justification even more robust.*" More specifically, you intend to provide the following *in vitro* information in order to "*support the similar or regular pattern of toxicological properties as a result of structural similarity*:

- *in vitro skin irritation (OECD 439)*
- *in vitro eye irritation (OECD 437 + 492)*
- *skin sensitization (in vitro sensitization test battery: OECD 442 C, E, D)*
- *in vitro gene mutation study in bacteria (Ames, OECD 471)*
- *in vitro micronucleus test (OECD 487)*
- *in vitro Mouse-Lymphoma-Test (OECD 490)"*

In addition, you note "*the results from the Pre-natal development study with the source substance (CAS 68187-30-4) will be available by November 2018.*"

ECHA acknowledges your agreement to deliver the listed *in vitro* studies, as requested in the simultaneously processed compliance check decision (CCH-D-2114471262-54-01/F). However, those *in vitro* studies will not provide relevant information to support read-across for developmental toxicity.

With respect to the pre-natal developmental study with the source substance to which you refer to, ECHA notes that the results, on its own, will only deliver information regarding the relevant properties of the source substance and not of the target substance. Currently, as noted in the initial draft decision, there is no other relevant and toxicological study that would allow any comparison of the toxic profile or hazard between source and the target substance.

ECHA concludes that the presented evidence does not support a similar or regular pattern of toxicity for the property under consideration as a result of structural similarity, as it provides only information about the toxicological properties of the source substance and nothing about the target substance. Consequently, currently there is not an adequate basis for predicting the relevant property of the target substance from the data to be performed with the source substance.

(iii) 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.

You claim that "*the hydrolysis represents the first chemical step in the absorption, distribution, metabolism and excretion (ADME) pathways*" and 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 in pH 6.5 - 7.4, and metabolism half-life (in fish) for C8 Glutamate and C18 Glutamate, respectively.

ECHA notes the following:

(a) you have not supported your theoretical considerations on ADME properties and the assumed immediate hydrolysis after oral administration by any experimental data or toxicokinetic information.

First, the provided OECD Toolbox profiler results for hydrolysis half-life are not applicable for predicting the hydrolysis after oral uptake. More specifically, the model is not applicable for predicting parent compound degradation and hydrolysis rate to glutamic acid and coconut acid/stearic acid as the predictions concern dissociation of the sodium ion(s) instead of the amide bond hydrolysis. Therefore, ECHA finds the provided QSAR predictions of hydrolysis rates not supporting your assumption of *immediate hydrolysis after oral intake*.

Second, a model for metabolic half-life (in fish) is not applicable for predicting rate of the hydrolysis in mammalian toxicity study after oral uptake because the prediction is based on values for fish biotransformation during a bioaccumulation experiment and not related to mammalian toxicity test.

(b) as explained in point (i) you have clearly identified the compositional differences between the source and target substances. However, you have not demonstrated why these compositional differences do not influence the metabolic rate and behaviour of the substances.

In addition, ECHA notes a publicly available bibliographical reference[4] that seems to contradict your claims, as it describes only slight hydrolysis of long-chain aliphatic amides by rabbit liver extract at pH 7.4 after five hours. Moreover, according to the publication, the enzymatic hydrolysis slows down with increasing chain length, which implies slower metabolic degradation rate for the target substance than for the source substance after oral intake.

In your comments to the draft decision you noted several points: "*The comparable hydrolysis is already reported in the Bray et al paper cited by ECHA. Furthermore, the breakdown products will be discussed in more detail with literature data. The registrant wishes to point out that both substances (target and source substance) are amino acid alkyl amides (glutamates). A likely metabolic pathway was presented - and agreed between the parties during the Oral Hearing at the Board of Appeal - and the resulting metabolites are part of the daily diet and consumed by humans on a gram scale. The metabolites are without any concern. This is underlined by the fact that these glutamates are used in cosmetic products and by cosmetic companies which need to perform a safety assessment*

[4] The Fate of Certain Organic Acids and Amides in the Rabbit; FURTHER OBSERVATIONS ON THE HYDROLYSIS OF AMIDES BY TISSUE EXTRACTS, Bray et al., 1950 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1275209/

of the products and had no concern to use the substance purely on theoretical considerations and expert knowledge. If there was any concern with regards to the cosmetic use of this substances, the SCCS – within its mandate given by the EU Commission – would anyway have already asked for additional data for a re-evaluation, which has not been the case."

Additionally, *you expressed an* intention to provide *in vitro* hydrolysis studies with the target and the source substances "*to strengthen the argumentation that the source and the target substance have a similar toxicokinetic behaviour.*"

Firstly, ECHA notes that the publication by Bray et al contradicts your assumption rather than supports it, as it provides, "*amides with less than 3 or more than 11 carbon atoms were only hydrolysed to a small extent.*" Therefore, your initial claim of immediate hydrolysis after oral intake seems questionable. ECHA thus concludes that systemic exposure to the parent substances cannot be excluded based on the current information. There is therefore a need to understand the toxicological property of the target substance (or both the target substance and the source, in case of intended read-across).

Secondly, ECHA acknowledges your intention to provide *in vitro* hydrolysis studies in support of your read-across arguments with respect to developmental toxicity. However, as such data is not currently provided (even though this shortcoming has already been discussed during the appeal process to which you refer to) there is no scientific information which would prove your assumption, while there is data (as discussed above) that contradicts it.

ECHA notes also that you did not provide detailed information on the Scientific Committee on Consumer Safety (SCCS) opinion. ECHA is therefore not able to take this information into account. ECHA notes in addition that REACH information requirements remiain to be fulfilled regardless of existence or non-existence of a relevant SCCS opinion especially as worker exposure is also concerned (as explained above).

ECHA concludes that you did not sufficiently address important aspects such as the transformation rate (i.e. hydrolysis) and behaviour of the source and target substances and the resulting possible difference in the metabolite profile and its consequences on the prediction possibility. Therefore, currently it is not possible to conclude that 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.

Conclusion on the read-across approach

Based on the above considerations, ECHA concludes that you have not provided adequate and reliable information to demonstrate that developmental property of the registered substance can be predicted based on the test performed with the source substance.

ECHA therefore concludes that the criteria of Annex XI, Section 1.5. are not met, and consequently the testing proposed on the source substance is not appropriate to fulfil the information requirement of the substance subject to the present decision.

Therefore, ECHA considers that a study performed with the registered substance is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

According to the test method 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 the rat or rabbit as a first species.

You proposed testing by the oral route.

ECHA agrees that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

c) Conclusion on the testing proposed

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the additional study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a first species (rats or rabbits), oral route (test method: OECD TG 414) while your originally proposed test with the analogous substance L-Glutamic acid, N-coco acyl derivs., disodium salts (CAS No. 68187-30-4; EC No. 269-085-1) 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* (version 6.0, July 2017), Chapter R.7a, Section R.7.6.2.3.2.

Deadline to submit the requested information in this decision

The deadline to submit the requested information in this decision is set to allow for sequential testing together with the information requests made under the compliance check decision which was simultanously notified to you.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with 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 **22 August 2018**, 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(s).

ECHA notified the draft decision to the competent authorities of the Member States for proposals 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 in your 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 requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of the Member States.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests 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 by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed