EUROPEAN CHEMICALS AGENCY

Helsinki, 22 March 2018

Addressee: [redacted]

Decision number: CCH-D-2114394004-54-01/F
Substance name: Ethanesulfonic acid, 2-(methylamino)-, N-coco acyl derivs., sodium salts
EC number: 263-174-9
CAS number: 61791-42-2
Registration number: [redacted]
Submission number: [redacted]
Submission date: 22/05/2013
Registered tonnage band: 100-1000

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD [421/422]) in rats, oral route with the registered substance;**

2. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats with the registered substance;**

3. **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 with the registered substance;**

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 to the REACH Regulation. 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 adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **29 September 2020**. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of 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 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

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".

In the registration, you have adapted the standard information requirements for

- Screening study for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.),
- Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.); and
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species.

by applying a read-across adaptation following REACH Annex XI, Section 1.5.

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 in both a generic and and property-specific context.

Support of the grouping and read-across approach

You have provided a read-across justification as a separate attachment in IUCLID Section 13. In summary you provide the following arguments to support the read-across approach:

'Common functional groups: Both, the target substance and the read-across substance are structurally similar fatty acid chlorides bound with sodium N-methyl taurinate. The only difference between both substances is seen in the origin of the fatty acid, which represents a C12-18-(even numbered, C18 unsaturated)-alkyl chain in the target molecule and a C18-(unsaturated)-alkyl chain in the source molecule. The molecular structure of both materials is characterized by the hydrophobic aliphatic alkyl chain with N-methyl taurine as hydrophilic head group, giving the whole molecule amphiphilic properties.'

'Similar physico-chemical properties: For the purpose of read-across of toxicological data, the most relevant physico-chemical parameters are physical state (appearance), vapour pressure, octanol/water partition coefficient and water solubility. Both substances are solid and exhibit a low vapour pressure (< 1 Pa at 20 °C). The log Pow of the target substance is < 3. The critical micelle concentration/water solubility is judged to be moderate to high. Physico-chemical properties follow a regular pattern with respect to differences in the alkyl chain lengths.'

'Similar metabolic pathways: The amide linkage of Sodium methyl cocoyl taurate will initially be hydrolyzed to generate sodium N-methyl taurine and fatty acids by fatty acid amide hydrolase, the principal catabolic enzyme for fatty acid amides having both, esterase and amidase activity (EPA, 2009). The resulting anionic sulfonate may be either directly excreted in the urine or converted to a dianionic salt with glucuronic acid that is excreted. The remaining fatty acids are metabolized in a second step via the ß-oxidation pathway.'

'Common levels and mode of human health related effects: The toxicological properties show that the target and source substance have similar toxicokinetic behaviour and that the constant pattern consists in a lack of potency change of toxicological properties. Thus, the analogue substance shows a low acute toxicity, no skin irritation and sensitisation properties, and reveals no systemic toxicity after sub-acute repeated oral exposure or genotoxic effects. Furthermore, the analogue substance does not exhibit toxicity to reproduction. Irritating effects on the eye were observed for target and source substance.'

'It should be noted that the read-across hypothesis relies not only on empirical considerations and common mechanistic (functional and metabolic) similarity and principles across N-acyl-N-methyl taurates, but takes also into account the read across principles of already established categories based on an incremental and constant change in alkyl chain lengths'.

In addition you have provided a data matrix which allow comparison of the physicochemical and toxicological properties of the source and target substances.

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

According to ECHA's understanding you suggests that predictions of the properties of the target substance is possible because:

1. The source and target substances are structurally similar;
2. *"the substances have similar physico-chemical and toxicological properties"*;
3. *Both substances are expected to be metabolised in a similar manner.*

With regard to the proposed predictions ECHA has the following observations:

(i) Structural (dis)similarities and their impact on the prediction

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.

Common functional groups: You argue that *'both, the target substance and the read-across substance are structurally similar fatty acid chlorides bound with sodium N-methyl taurinate. The only difference between both substances is seen in the origin of the fatty acid, which represents a C12-18-(even numbered, C18 unsaturated)-alkyl chain in the target molecule and a C18-(unsaturated)-alkyl chain in the source molecule.'*

ECHA notes that the registered (target) substance subject to this decision and proposed source substance display significant structural differences stemming from the fact that different fatty acids are used to produce the substances. More specifically, the carbon chain lengths of the fatty acids in the registered (target) substance are [redacted]. In contrast, the carbon chain lengths of the fatty acids in the source substance are [redacted] In

addition, to the chain length there is also a difference in the number of unsaturated fatty acids between the source and target substances. More precisely, the source substance contains [redacted] whereas the target substance contains no [redacted]. You have not provided any information on how these structural differences may impact the toxicity of the substances and thus affect the possibility to predict the properties of the registered substance from the data of the source substance.

(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 structurally similar and are likely to have similar properties. An important aspect in this regard is, firstly, to analyse the data matrix in order to compare the properties of source and target substances and, secondly, to establish whether indeed they are similar or follow a regular pattern.

Similar physico-chemical properties: You argue that the source and target substance have similar physico-chemical properties. You propose that the similar physico-chemical properties of the target and source substances support the read-across between the substances.

ECHA observes that the physico-chemical properties of target and source substances are in the same/similar range. ECHA considers that the fact that physico-chemical parameters are in the same range may support a prediction of similar toxicokinetic and toxicity profiles. However, substances may have similar physicochemical properties, but different toxicological properties. 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.

Similar metabolic pathways: You argue that '*the toxicological properties show that the target and source substance have similar toxicokinetic behaviour*' and refer to a ruling from the US Environmental Protection Agency (EPA, 2009)[2]. In addition, you state that '*this metabolic behavior also demonstrated for sodium N-oleoyl-N-methyltaurine in Pseudomonas Alcaligenes*'.

ECHA observes that there is insufficient toxicokinetic information available on the source or target substances.

ECHA also observes that the US EPA ruling reads: "*The registrant proposed a metabolic pathway based on analogy to accepted metabolic pathways for amide hydrolysis and fatty acid beta-oxidation. It has been proposed that the initial step involves hydrolysis of the amide linkage to generate oleic acid and sodium N-methyl taurine. The enzyme fatty acid amide hydrolase (FAAH) may be involved in hydrolysis, and is also a primary terminator of lipic oleoamides as well as for the N-acyl taurines*". While ECHA notes this statement on a proposed analogy to other pathways you have not substantiated the basis of the claim with

[2] https://www.gpo.gov/fdsys/pkg/FR-2009-07-29/html/E9-17960.htm

any supporting evidence in respect of your read across approach. In addition, the EPA ruling concerns the source substance and not the registered (target) substance.

Further, ECHA notes you do not explain how the fact that an aerobic bacteria can utilize sodium N-oleoyl-N-methyltaurine as a carbon source support the read-across supports your read across. Firstly, ECHA highlights that the vast majority of the bacteria in the gastrointestinal tract are anaerobic. Secondly, whether or not a substance is metabolised in bacteria is not predictive of its metabolic fate *in vivo*. In addition, ECHA observes that it has been reported that FAAH is an integral membrane enzyme that hydrolyzes the endocannabinoid anandamide and related amidated signalling lipids[3].

In accordance with Section 1.5 of Annex XI of REACH, the evidence to support your read-across approach with the target and source substances, *e.g.* toxicokinetic (metabolism/hydrolysis) information and/or modelling shall be provided. This information should cover e.g. the rate of hydrolysis, identification of the metabolites. In addition, ECHA notes that you have not considered the impacts which the parent compounds and non-common hydrolysis products may have on the predicted toxicological properties.

Common levels and mode of human health related effects: You argue that the toxicological properties show that the target and source substances have similar toxicokinetics.

ECHA notes that there are no data with regard to systemic toxicity following repeated administration on the registered (target substance) which would allow a side-by-side comparison of the same toxicological properties with the source substance. Furthermore, ECHA considers that acute toxicity, skin irritation/sensitisation, *in vitro* genotoxicity and sub-acute toxicity data alone are not sufficient to establish the toxicological profile of a substance and support the prediction with respect to the sub-chronic (90-day) and pre-natal developmental toxicity properties of the target substance.

In your comments on the draft decision you acknowledged that there is not sufficient information available to support the read-across adaptation.

Conclusion on the read-across approach

Pursuant to Article 41(1) of the REACH Regulation, ECHA concludes that the adaptation of the standard information requirements for the endpoints Screening study for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.), Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.), and Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in the technical dossier based on the proposed read-across approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. Therefore, ECHA rejects those adaptations in the technical dossier that are based on Annex XI, 1.5.

[3] Mallet, C *et al.* (2016) FAAH inhibitors in the limelight, but regrettably. *Int J Clin Pharmacol Ther.*; 54:498–501.

Consideration on uses of the substance in relation to the tests requested in the decision

In your comments on the draft decision you explained that 'this substance is used almost exclusively as a cosmetic ingredient' and that the adaptations made in the registration dosser 'were intended to replace the need for vertebrate testing.
ECHA notes that the substance, in addition to the use in cosmetic products, also is used in biocidal products, paper and board dye finishing and impregnation products and washing and cleaning products. Furthermore, ECHA notes that the substance has industrial use in the manufacture of "Cosmetics products" and "Moist wipe products" and that both of these processes have use descriptors which indicate potential for exposure to workers (*e.g.* PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact); or PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities). Moreover, you have indicated that the substance has a consumer use in moist wipe products. This use is described under product category 35 – washing and cleaning products. Furthermore, it is indicated that this use has an environmental release category ERC 11b - ERC11b: Widespread use of articles with high or intended release (indoor).

ECHA therefore concludes that, as you already indicated, there are not only cosmetic uses for the substance. Moreover, the dossier indicates that the substance is used for the manufacture of cosmetic products. Therefore, there is potential worker exposure to the substance. ECHA's factsheet on the interface between REACH and Cosmetics Regulations, which was developed jointly with the European Commission[4], provides that Registrants of substances that use the substance also for non-cosmetic uses (i.e. mixed-use substances) are permitted to perform animal testing, as a last resort, for all human health endpoints. Furthermore, and in any event, the same fact sheet permits animal testing to be performed on substances solely uses in cosmetics where testing is required to assess the risks from exposure to workers and the registrant has not shown that there is no expsorue to workers.

The requested human health tests are therefore justified for the purposes of assessing hazards for workers and consumers. 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)).

1. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a

4 Please see https://echa.europa.eu/documents/10162/13628/reach_cosmetics_factsheet_en.pdf

developmental toxicant. No such evidence is presented in the dossier. Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have not provided any study record of a screening for reproductive/developmental toxicity in the dossier that would meet the information requirement of Annex VIII, Section 8.7.1.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a Reproduction/Developmental Toxicity Screening Test (OECD TG 421) with the analogue substance(s) sodium 2-[methyl(oleoyl)amino]ethanesulfonate (EC no 205-285-7)].
However, as explained above, your adaptation of the information requirement is rejected.

As also explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test methods OECD TG 421/422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with rats.

ECHA considers 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.7.6.2.2.1. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

In your comments on the draft decision, you proposed to adapt the requirement for the OECD TG 421/422 study by performing only the OECD TG 408 (adapted) and OECD TG 414 studies.

ECHA notes that the following reproductive toxicity endpoints are not addressed by the required OECD TG 414 and OECD TG 408: mating behaviour, fertility and peri-natal effects. It is also noted that these endpoints are addressed by the screening reproductive/developmental toxicity test (OECD TG 421/422) required as the standard information requirement according to Annex VIII. Hence, it is strongly recommended that the registrant considers conducting both and an OECD TG 421/422 and an OECD TG 414 study.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Reproductive/developmental toxicity screening test (test method: OECD TG 421) *or* Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

Notes for your considerations

For the selection of the appropriate test, please consult ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Sections R.7.5 and 7.6 (version 6.0, July 2017).

The registrant should also carefully consider the order of testing especially the requested screening (OECD TG 421/422) and the developmental toxicity studies (OECD TG 414) to ensure unnecessary animal testing is avoided, paying particular attention to the end point specific guidance (https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf) p 461/2.

2. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a Sub-acute toxicity study (28-day; OECD TG 407) conducted with the source substance sodium 2-[methyl(oleoyl) amino]ethanesulfonate (EC No 205-285-7). In addition, you have provided a waiving statement which indicates that a Sub-chronic toxicity study (90-days; OECD TG 408) is proposed to be conducted with the analogue substance sodium 2-[methyl(oleoyl)amino]ethanesulfonate (EC No. 205-285-7). However, as explained above, your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA Guidance on information requirements and chemical safety assessment (version 6.0, July 2017) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration.
Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

According to the test method EU B.26./OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

In your comments on the draft decision you agreed to conduct the requested study.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD TG 408) in rats.

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a waiving statement which indicates that a Pre-natal developmental toxicity study (OECD TG 414) is proposed to be conducted with the analogue substance sodium 2-[methyl(oleoyl)amino]ethanesulfonate (EC No. 205-285-7). However, as explained above your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

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 assumption ECHA considers testing should be performed with rats or rabbits as a first species.

ECHA considers 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.7.6.2.2.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

In your comments on the draft decision you agreed to conduct the requested study.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a first species (rat or rabbit) by the oral route.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 17/05/2017.

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 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 compliance check decision does not prevent ECHA from initiating further compliance checks on the present 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 your Member State.

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.