EUROPEAN CHEMICALS AGENCY

Helsinki, 11 April 2019

Addressee: [redacted]

Decision number: CCH-D-2114465759-29-01/F
Substance name: N-methyl-N-[C18-(unsaturated)alkanoyl]glycine
EC number: 701-177-3
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 14 December 2017
Registered tonnage band: Over 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. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats with the registered substance;**

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

3. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) in a second species (rat or rabbit), oral route with the registered substance;**

You are required to submit the requested information in an updated registration dossier by **19 April 2021** except for the information requested under point 1 for a Sub-chronic toxicity study (90-day) which shall be submitted in an updated registration dossier by **20 April 2020**. You shall also 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.

This decision does not address the information requirement of the Extended one-generation reproductive toxicity study according to Annex X, Section 8.7.3. of the REACH Regulation.

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, Hazard Assessment C4

[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

You have sought to adapt the information requirements for a sub-chronic (90-day) toxicity study (Annex IX, 8.6.2), a pre-natal developmental toxicity study in a first species (Annex IX, 8.7.2) and a pre-natal developmental toxicity study in a second species (Annex X, 8.7.2) by applying a read-across approach in accordance with Annex XI, Section 1.5. According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural aspects the chemical structures have in common and the differences between the structures of the source and registered substances[2]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Thus physicochemical properties influence the human health and environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[3]- (1) (Bio)transformation to common compound(s) and (2) Different compounds have the same type of effect(s).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

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[2] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.
[3] Please see ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

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

You seek to adapt the human health information requirements for a sub-chronic (90-day) toxicity study (Annex IX, 8.6.2), a pre-natal developmental toxicity study in a first species (Annex IX, 8.7.2) and a pre-natal developmental toxicity study in a second species (Annex X, 8.7.2) by applying a read-across approach according to Annex XI, Section 1.5.

You propose read-across between the structurally similar substance, sodium [dodecanoyl(methyl)amino]acetate (CAS No 137-16-6) as source substance and the substance subject to this decision, N-methyl-N-(C18-(unsaturated)alkanoyl)glycine (EC 701-177-3) as target substance.

Your dossier contains read-across documentation as a separate attachment in the registration. You use the following arguments to support the prediction of properties of the registered substance from data for reference substance(s) within the group by interpolation to other substances in the group: *"The target substance and the source substance belong to the same class of organic compounds: sarcosines and sarcosinates. Due to the similar structural features, with a sarcosine head which is identical in all sarcosines and a variable hydrocarbon tail, the chemistry and some physico-chemical properties are similar. Moreover, due to the identity or close similarity of chemical moieties present in the respective molecules, reactivity and hence toxicological profiles are expected to be similar. For endpoints relevant to human health, it is predicted that the structural similarity of the constituents in the target and source substance will lead to similar (lack of) effects in the organism. The impurities of the source substance that are not present in the target substance are structurally similar to biotransformation products predicted for the target and source substance (sarcosine moiety and fatty acid rest). The same is true for the constituents present in the target substance but not in the source substance. When considering the chemical moieties present (constituents of the source and target and impurities of source) in the source substance and target substance, always the same kind of "building blocks" are used: sarcosine (N-methylglycine) and fatty acids of different carbon-chain lengths. A similar fate and similar toxicological effects are therefore expected following exposure to the target substance and source substance."*

ECHA considers that this information is your read-across hypothesis, which provides the basis whereby you predict the properties of the registered substance from the source substance.

B. ECHA analysis of the grouping and read-across approach

ECHA considers that your read-across hypothesis is based upon the presence of similar structural features, i.e. a sarcosine head and a variable hydrocarbon tail, in the target and source substances, which you predict will lead to similar (lack of) effects in the organism. Furthermore, you consider that impurities present in the source substance but absent in the composition of the target substance are structurally similar to biotransformation products predicted for the constituents of the target and source substances. However, there is insufficient information to support this element of your read-across hypothesis in the registration dossier.

The target substance is defined as a Substance of Unknown or Variable Composition, Complex reaction products and Biological materials (UVCB Substance). By definition, the

composition of such substances is complex, the number of constituents is relatively large, the composition is, to a significant part, unknown, and/or the variability of composition is relatively large. In the read-across justification document included in the technical dossier you have reported on the composition of this substance, identifying the following three specific sarcosines with unsaturated hydrocarbon tails of different length as constituents and providing typical concentration ranges:

[redacted]

You further listed three groups of constituents identified based on their generic structures:

[redacted]

The source substance, on the other hand, is a mono-consituent substance with a well defined composition. This substance is mainly composed of the [redacted] Identified impurities are lauric acid and sodium laurate.

ECHA understands from this information that you intend to use the main constituent of the source substance, sodium [dodecanoyl(methyl)amino]acetate, as a surrogate for all the sarcosine constituents of the target substance.

In your read-across justification document you address the structural differences between the identified constituents of the target substance and the main constituent of the source substance indicating that "*the principal difference between the target substance and the source substance is the length of the carbon-chain of the fatty acid moiety*" and pointing at "*the absence of unsaturated C=C bonds in the alkyl chain (no alkene/allyl groups identified*)" in the source substance. You have assessed the impact of these structural differences using QSAR tools and reported on predicted similarity with regard to binding specific receptors (DART and rtER expert system), protein binding (OASIS) and general predictions of properties for repeated dose toxicity (HESS). You report that "*profilers related to the endpoints covered by read-across did not show any differences*" between these constituents. On that basis you conclude that "*the results of the comparative profiling using the OECD Toolbox support the read-across strategy*".
Whilst this information may constitute relevant information in support of the read-across approach, considering the complexity of the endpoints under consideration ECHA is of the opinion that these QSAR predictions cannot be seen, on their own, as evidence of similarity in the properties of these constituents. The data set included in the technical dossier does not include studies of comparable design and duration to establish that the target and the source substances have similar properties. Therefore ECHA considers that you have not established that the target and the source substances are likely to have similar properties for the endpoints under consideration.

ECHA further observes that you have dismissed any impact of the constituents of the target substance included in the generic group of [redacted] You consider that these constituents are [redacted], *not including any functional groups that are not present in the target*" and in the source substance. No further information on the structural features of these constituents is provided. Since [redacted] may represent up to [redacted] of the composition of the target substance, ECHA considers that

further details are required on the structures and the distribution of the constituents included in this group of [redacted] with regard to the identified structural differences, i.e. length of their hydrocarbon chain and saturation/unsaturation. In the absence of this information, ECHA is of the opinion that your claim that "*these constituents are therefore not expected to impact the profile of the two substances*" is not justified.

For the reasons presented above and on the basis of the information provided in your registration dossier, there is not sufficient support for your proposal that structural differences between the constituents of the target substance and the main constituent of the source substance do not impact the toxicological properties of the target substance. Accordingly your hypothesis based upon based upon the presence of similar structural features, i.e. a sarcosine head and a variable hydrocarbon tail, in the target and source substances, leading to similar (lack of) effects in the organism is not substantiated. For this reason, your hypothesis is not a reliable basis whereby the properties of the registered substance may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group.

In your comments, you have provided further detailed information on the constituents covered by the group of [redacted]. This information allows for a better characterisation of these constituents and reveals structural similarity with the main constituent of the registered substance and with the source substance. The only structural differences between these constituents appears to consist in the carbon chain length and the number and position of unsaturation on the carbon chain length. However, ECHA notes that the information provided in your comments only addresses the composition of the registered substance as produced by the lead registrant. Details on the composition of the substance from the co-registrant are still missing and therefore no definitive revised view on your conclusion that "*these constituents are therefore not expected to impact the profile of the two substances*" can be formed on the basis of the information provided in your comments.

You have indicated in your comments your intentions to investigate the "*hydrolysis behaviour in digestive fluid simulants of both the source and the target substance*". You consider that this will provide "*relevant information demonstrating their toxicological (metabolical) comparability and at the same time taking into account consideration the most relevant (oral) route of exposure*". You anticipate that "*the source substance and target substance exhibit a very similar metabolism in the human digestive and intestinal tract*" and suggest that this hydrolysis study would indicate that "*non-toxic compounds are formed during digestion*". You have substantiated your plans by providing an offer from a testing laboratory for these investigations and supported their reasoning by referring to extracts from monographs from MAK and from the US EPA Federal register.

ECHA has assessed the information provided in your comments. The hydrolysis study proposed has the potential to establish that the source and the target substance have a comparable or similar behaviour in the conditions of this test. You anticipate that non-toxic compounds will be formed from the hydrolysis of the constituents of the substances. As you indicated in your comments, no data supporting this assumption currently exist. No information on the rate and extent of the hydrolysis of the constituents is available. These are important parameters to take into account before concluding on the impact of exposure to these constituents on the toxicological properties of the substances. Since this information is not yet available and as indicated in the draft decision, ECHA considers that there is currently no information available from studies of comparable design and duration

to establish that the target and source substances are likely to have similar properties for the endpoints under consideration.

C. Conclusion on the grouping and read-across approach

For the reasons as set out above, ECHA considers that this grouping and read-across approach does not provide a reliable basis whereby the human health effects of the registered substance may be predicted from data for reference substance(s) within the group. Hence, this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation.

As described above, further elements are needed to establish a reliable prediction for toxicological or ecotoxicological properties, based on recognition of the structural aspects the chemical structures have in common and the differences between the structures of the source and registered substances. This could be achieved (if it is possible) by a well-founded hypothesis of (bio)transformation to a common compound(s), or that the registered and source substance(s) have the same type of effect(s), together with sufficient supporting information to allow a prediction of human health properties.

1. 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 more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X 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.

Even though you have set the purpose flag for these endpoint study records to "weight of evidence", ECHA understands from the information provided in the read-across justification document that you have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for a 90-day sub-chronic toxicity study (OECD TG 408) ([redacted] 1997) and a 2-year oral chronic toxicity study (no test guideline reported) ([redacted] 1994). Both studies have been conducted with the analogue substance sodium [dodecanoyl(methyl)amino]acetate (EC no 205-281-5)].

As explained above in Appendix 1, section "Grouping of substances and read-across approach" of this decision, your adaptation of the information requirement is rejected.

Furthermore, ECHA highlights the following limitations in the reporting of the 2-year study ([redacted] 1994) in the technical dossier which limit its reliability and adequacy as source study in a read-across approach:

- Whilst the test material was administered to the animals via their diet, at nominal concentrations of 0, 0.05%, 0.2% and 1%. No information on food consumption is reported in the robust study summary (RSS). In the absence of this information, no conclusion on the doses of test material actually ingested can be made. Consequently, ECHA considers that the NOAEL of 1000 mg/kg/d derived from this

study is not reliable and cannot be used for risk assessment.

- The test doses are indicated to have been selected based "*on a maximum possible exposure in humans*". According to the recommendations of the OECD TGs 408 and 452, dose levels intended to be used in toxicological studies for hazard identification purposes are to be based on the results of shorter term repeated dose or range finding studies and the highest test dose should be chosen to elicit evidence of toxicity. This principle is not met in this case as the test doses were based on exposure considerations.
- The scope of the investigations reported in the RSS for this study does not cover all the parameters intended to be investigated according to the OECD TGs 408 or 452. In particular, no information on detailed clinical investigations, clinical chemistry, organ weights and exhaustive histopathology are reported in the RSS for this study.

Therefore, ECHA considers that this source study ([redacted] 1994) does not fulfil the requirement of Annex XI, Section 1.5. of the REACH Regulation for an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3).

As your adaptation is rejected, 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 5.0, December 2016) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, even though the information indicates that human exposure to the registered substance by the inhalation route is likely, potential inhalation-specific effects are already addressed by providing a sub-acute toxicity study by the inhalation route conducted with the registered substance. Hence, the test shall be performed by the oral route using the test method OECD TG 408.
According to the test method 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 to the draft decision you indicated that "*the requested study is already available and used in a read-across approach*". You intend to improve the read-across justification by providing an improved chemical composition of the target substance and a hydrolysis study.

ECHA notes that whilst repeated dose toxicity studies conducted with the source substance sodium [dodecanoyl(methyl)amino]acetate (EC no 205-281-5) are available and mentioned above, the study requested in this decision with the registered substance is currently not available. Regarding your comments on the rejection of your read-across approach, please see ECHA's response under "B. ECHA analysis of the grouping and read-across approach" above.
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: OECD TG 408) in rats.

Notes for your considerations:

The Extended one-generation reproductive toxicity study (EOGRTS) according to Annex X, Section 8.7.3. is not part of this decision because the results of the Sub-chronic toxicity study (90-day) are considered crucial to inform on the study design of the EOGTRS. Therefore, the results of the Sub-chronic toxicity study (90-day) should be used, among other relevant information, to decide on the study design of the EOGRTS.

ECHA may therefore launch a separate compliance check at a later stage addressing the EOGRTS information requirement.

Alternatively, you may also consider submitting a testing proposal for an Extended one-generation reproductive toxicity study together with the results of the requested Sub-chronic toxicity study (90-day). The testing proposal should include a justification for its study design following ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017), taking into account the results of the Sub-chronic toxicity study (90-day).

2. 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 more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X 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 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 study record for a pre-natal developmental toxicity study in rats (OECD TG 414) with the analogue substance sodium [dodecanoyl(methyl)amino]acetate (EC no 205-281-5) [redacted], 2014). However, as explained above in Appendix 1, section "Grouping of substances and read-across approach" of this decision, your adaptation of the information requirement is rejected. Consequently there is an information gap and it is necessary to provide information for this endpoint.

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 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.7.6.2.3.2. Since the substance to be tested is a viscous liquid, ECHA concludes that testing should be performed by the oral route.

In your comments to the draft decision you indicated that "*the requested study is already available and used in a read-across approach*". You intend to improve the read-across

justification by providing an improved chemical composition of the target substance and a hydrolysis study.

ECHA notes that whilst developmental toxicity study conducted with the source substance sodium [dodecanoyl(methyl)amino]acetate (EC no 205-281-5) are available and mentioned above, the study requested in this decision with the registered substance is currently not available. Regarding your comments on the rejection of your read-across approach, please see ECHA's response under "B. ECHA analysis of the grouping and read-across approach" above.

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: OECD TG 414) in a first species (rat or rabbit) by the oral route.

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

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

Pre-natal developmental toxicity studies (test method OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

You have sought to adapt the information requirement for a pre-natal developmental toxicity study in a second species according to Annex XI, Section 1.5. of the REACH Regulation by providing a pre-natal developmental toxicity study in rabbits (OECD TG 414) with the analogue substance sodium [dodecanoyl(methyl)amino]acetate (EC no 205-281-5) ([redacted], 2017).

However, as explained above in Appendix 1, section "Grouping of substances and read-across approach" of this decision, your adaptation of the information requirement is rejected. Consequently there is an information gap and it is necessary to provide information for this endpoint.

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 rabbits or rats as a second species, depending on the species tested in the first pre-natal developmental toxicity study.

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.7.6.2.3.2. Since the substance to be tested is a viscous liquid, ECHA concludes that testing should be performed by the oral route.

In your comments to the draft decision you indicated that "*the requested study is already available and used in a read-across approach*". You intend to improve the read-across justification by providing an improved chemical composition of the target substance and a hydrolysis study.

ECHA notes that whilst developmental toxicity study conducted with the source substance sodium [dodecanoyl(methyl)amino]acetate (EC no 205-281-5) is available and mentioned above, the study requested in this decision with the registered substance is currently not available. Regarding your comments on the rejection of your read-across approach, please see ECHA's response under "B. ECHA analysis of the grouping and read-across approach" above.

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: OECD TG 414) in a second species (rabbit or rat) by the oral route.

Notes for your consideration

You are reminded that before performing a pre-natal developmental toxicity study in a second species you must consider the specific adaptation possibilities of Annex X, Section 8.7., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species with other available information enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement.

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 9 May 2018.

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 carrying out the tests 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 tests must be suitable to assess these.

   Furthermore, 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.