EUROPEAN CHEMICALS AGENCY

Helsinki, 12 April 2019

Addressee: [redacted]

Decision number: TPE-D-2114466078-42-01/F
Substance name: Reaction product of Fatty acids, C18 alkyl with amines, polyethylenepoly-tetraethylenepentamine fraction
EC number: 701-046-0
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 19/09/2018
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 tests for Sub-chronic toxicity study (90-day), oral route (OECD TG 408) and Pre-natal developmental toxicity study OECD TG 414) using the analogue substance Fatty acids, C18-unsatd, dimers, polymers with tall-oil fatty acids and triethylenetetramine (EC No 500-191-5) are rejected, you are requested to perform:

1. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats using the registered substance.**
2. **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 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 an adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **19 April 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 Ofelia Bercaru, 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.

0. Grouping of substances and read-across approach

Article 13(1) of the REACH Regulation requires information on intrinsic properties of substances on human toxicity to be generated whenever possible by means other than vertebrate animal tests, including from information from structurally related substances (grouping or read-across), "*provided that the conditions set out in Annex XI are met*".

According to Annex XI, Section 1.5 there needs to be structural similarity among the substances within a group or category and furthermore, it is required that the relevant properties of a substance within the group can be predicted from the data for reference substance(s) by interpolation, and the data should be adequate for the purpose of classification and labelling and/or risk assessment.

Description of the grouping and read-across approach proposed by you

You have proposed to adapt the standard information requirements for a sub-chronic toxicity study (90-days; Annex IX, Section 8.6.2.) and a pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) by applying a read-across approach in accordance with Annex XI, Section 1.5. by performing the tests with a source substance Fatty acids, C18-unsatd., dimers, oligomeric reaction products with tail-oil fatty acids and triethylenetriamine (EC No. 500-191-5).

You have provided a read-across justification document [redacted] In this document you have addressed chemical and structural considerations, toxicokinetics and toxicological properties of the substances. You have also provided a data matrix on physico-chemical and (eco)toxicological properties of the substances.

In the read-across justification document you list the substances below as members of the polyamidoamine group:

[#8 Dimer trimer FA TETA PAA]	Fatty acids, C18-unsatd., dimers, oligomeric reaction products with tail-oil fatty acids and triethylenetriamine, CAS No. 68082-29-1 (EC No. 500-191-5), hereinafter the "source substance";
[#9 Dimer trimer FA TETA PAA]	Reaction products of fatty acid dimers and trimers, C18 (unsaturated) alkyl and fatty acids, C18 (unsaturated) alkyl with amines, polyethylenepoly-, triethylenetetramine fraction, CAS No. 68154-62-1 (EC No. 701-120-2);
[#11 MonoFA TEPA PAA]	Reaction product of Fatty acids, C18 alkyl with amines, polyethylenepoly-tetraethylenepentamine fraction, CAS No. 103758-98-1 (EC No. 701-046-0) hereinafter the "target substance"; and

[#12 DimerFA PEPA PAA] Fatty acids, C18-unsatd., dimers, reaction products with polethylenepolyamines, CAS No. 68410-23-1 (EC No. 614-452-7)

In summary, you use the following arguments to support the prediction of properties of the target substance(s) from data of the source substance:

- Similar structures: the substances are mixture of monoamide, diamide, residual amine and imidazoline (mono-, di- and tri-condensate) chemical structures, and have thus common functional groups based on amide, amine and imidazoline moieties;
- Comparable chemical characteristics due to starting reaction materials, manufacturing process and the composition of the reaction products;
- Similar physico-chemical properties, toxicokinetic behaviour and toxicological profile.

ECHA has analysed the provided information and documentation of the registration dossier in light of the requirements of Annex XI, 1.5.

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

Based on the information provided, ECHA understands that the proposed read-across hypothesis is based on similar chemical and structural characteristics, similar physico-chemical properties, toxicokinetic behaviour, and toxicological properties of the polyamidoamine substances.

Structural and chemical (dis)similarity

ECHA observes that based on the data on starting materials and manufacturing process you have addressed structural and chemical similarities of the group members as follows:

"The polyamidoamine substances are a mixture of constituents which include monoamide, diamide, residual amine and imidazoline (mono-, di and tri-condensate) chemical structures. The substances therefore have common functional groups based on amide, amine and imidazoline moieties and are sufficiently similar in terms of chemical structure to support a read-across approach", and

"Considering the starting reaction materials, the manufacturing process and the composition of the reaction products, the polyamidoamine substances are considered comparable in terms of chemical characteristics".

Regarding the free, unreacted amine, ECHA notes that based on the information provided in the read-across justification document, the concentrations of the unreacted amines are in the range of [redacted]% in all substances: *"As a result, part of the starting amine material does not react and is still present in the final reaction mixture. The unreacted amine is considered to be a constituent of the polyamidoamine substance (no attempt to remove the unreacted amine e.g. by distillation, preparative chromatography etc, is made). The concentration of free, unreacted amine in the polyamidoamine substances is in the range [redacted]% (wt)"*. Further, the source substance [#8 Dimer trimer FA TETA PAA] and [#9 Dimer trimer FA TETA PAA] contain the same unreacted amine, [redacted] However, the other group members contain different amine species: the target

substance [#11 MonoFA TEPA PAA] contains unreacted [redacted] and [#12 DimerFA PEPA PAA] contains unreacted [redacted].

ECHA observes there is a variation in chain length among the different starting amines as well as differences in the amount of linear, cyclic and branched structures. Further, ECHA considers that the concentration range of the free amines ([redacted]%) provided is broad and does not allow without further details to establish similarity in the concentration(s) of free amines between the substances. ECHA underlines that you have not included any consideration on how the differences among the amines may impact the toxicity of the polyamidoamine substances.

Based on the information provided in the read-across justification document [redacted] is the fatty acid starting material for all substances. In addition, [redacted] is the starting material for [#8 Dimer trimer FA TETA PAA] and [#11 MonoFA TEPA PAA] (the target substance), and [redacted] for [#12 DimerFA PEPA PAA]. ECHA underlines that you have not included any comparison on the starting material fatty acids, nor addressed how the differences among those fatty acids may affect the toxicity of the final products.

ECHA observes that in the read-across justification document you have provided very general information on the starting materials and on the final composition of the substances.

ECHA considers that you have not addressed sufficiently the structural and compositional differences of the starting materials and the final composition of the substances and did not explain why those differences would not lead to differences in the toxicity profile of the substances. ECHA therefore considers that you have not demonstrated that the substances are "*comparable in terms of chemical characteristics*".

ECHA therefore considers that there is not a sufficient basis for predicting the properties of the target substance from the data obtained with the source substance.

In your comments to the draft decision and the updated read-across justification, you have provided sufficient details on the composition of the fatty acid starting materials to clarify the concerns raised above. However, with regard to the unreacted amines in the substances you propose to use the available toxicity data on TETA and TEPA to address potential differences in repeated dose/developmental toxicity caused by the different amines. This may be an adequate approach to alleviate the concern raised by ECHA. However, additivity of effects needs to be considered and the information on the individual amines are currently not in the updated dossier. Thus, no conclusion on the feasibility of the proposed approach can be made at this point in time.

Physico-chemical properties

In your read-across hypothesis you state that the polyamidoamine substances are *sufficiently similar in terms of basic physicochemical properties to support a read-across approach.*" ECHA notes that the physico-chemical properties of the target and source substances are in similar range.

Toxicokinetics

In your read-across hypothesis you state that: "*according to Lipinski's Rule of Five (OECD QSAR Toolbox prediction using a representative structure), the polamidoamine substances*

will not be bioavailable and oral absorption and systemic distribution are not predicted. The long chain fatty acid derivative of the substances has a high molecular weight, limiting oral and dermal absorption and is of low water solubility. [...] Similarly, due to the large molecular weight of the substances, dermal uptake is unlikely. The vapour pressure for the polyamidoamine substances is calculated to be low; exposures to vapours by the inhalation route are not expected."

ECHA notes that the substances contain also free, unreacted amines and "Low molecular weight" constituents ([redacted] Da), which due to low molecular weight may have potential to absorb via oral route.

ECHA further notes that in the OECD TG 422 study conducted with the proposed source substance effects on e.g. liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT), heart weight and lymph nodes were observed, which indicate that systemic absorption occurs. You state in the endpoint study summary that "*It was therefore considered that the changes in AST and ALT plasma values were related to treatment with TOFA_DimerFA_TETA_PAA and may be indicative of liver damage*".

ECHA therefore considers that some constituents of the polyamidoamine substances have potential to absorb after administration via oral route and be bioavailable.

In your comments to the draft decision, you express your views that testing the source substance for sub-chronic and developmental toxicity would be sufficiently conservative and would provide sufficient information to better understand the absorption potential following oral administration. In addition, you state that TETA has lower molecular weight compared to TEPA and would therefore be a conservative estimate of toxicity. ECHA does not agree with this assumption because according to the assumption TEPA and TETA have the same toxicological profile. Currently, there is no information in the dossier to support such a claim. In addition, the assumption that higher molecular weight results in lower bioavailability is an oversimplification of the numerous factors which determine bioavailability of a substance. ECHA wants to highlight that the gastrointestinal tract have active absorption mechanisms for certain types of substances; this includes fatty acids. Given the lipophilic nature of the substances inclusion into micelles and subsequent absorption via the lymphatic system cannot be excluded for some constituents of the substances.

Toxicological data

In your read-across hypothesis you state that the polyamidoamine substances are of low acute toxicity, are skin and eye irritant, skin sensitizers, and are not genotoxic. Based on this data, lack of oral absorption and comparable chemical and structural characteristics of the substances, you conclude that read-across approach is acceptable.

ECHA notes that information on these properties alone is not sufficient to establish the toxicological profiles of the substances and support the prediction of repeated dose and pre-natal developmental toxicity of the target substance. ECHA further notes that as no higher tier studies are available for the target substance the presented information does not allow comparison of toxicological profiles of the substances.

In your comments to the draft decision, you propose to address this deficiency by conducting an "OECD TG 408 14-day preliminary study" on the source and target

substances to strengthen the support for the read-across approach. ECHA understands that this is intended to provide a basis for a comparison of the toxicological profiles of the source and target substances. However, ECHA does not agree that the "OECD TG 408 14-day preliminary study" is the best way to achieve this comparison. Firstly, there is an OECD TG 422 study available on the source substance; thus there is no need to conduct a new dose-range finding study before conducting the OECD TG 408 study. Secondly, your read-across proposal covers repeated-dose toxicity, developmental toxicity and toxicity to reproduction. ECHA understands that the 14-day preliminary study would be conducted on the basis of the recommendations of the OECD TG 408. ECHA stresses that this test guideline focuses on repeated-dose toxicity, therefore, the proposed study would not address the aspects of developmental toxicity and toxicity to reproduction. Finally, ECHA considers that the proposed duration (14-days) is likely too short for a meaningful comparison (given the type of the effects observed in the OECD TG 422 on the source substance). Therefore, ECHA considers that an OECD TG 422 study with the target substance would provide the information needed for a side-by-side comparison of the toxicity profiles of the source and target substances.

0.1 Conclusion on the read-across approach

ECHA concludes that the data currently provided does not provide sufficient evidence to conclude that the structural differences, such as the free, unreacted amine and different fatty acid adducts, within the polyamidoamine substances would not impact the toxicity of the substances. Further, comparison of toxicological profiles of the substances regarding repeated dose and pre-natal developmental toxicity cannot currently be done due to lack of relevant supporting information on the target substance. ECHA concludes that there is not an adequate basis for predicting the properties of the registered substance from the data obtained with the source substance. Thus, the criteria of Annex XI, 1.5. are not met, and the read-across approach, as presented by you, cannot be considered plausible to meet the information requirements.

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)

Pursuant to Article 40(3)(b) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test under modified conditions.

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. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a sub-chronic toxicity study (90 day) in rats by the oral route according to OECD TG 408 with the source substance (EC No. 500-191-5).

ECHA requested your considerations for alternative methods to fulfil the information requirement for Sub-chronic toxicity (90-day): oral. ECHA notes that you provided your considerations and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

ECHA has evaluated your proposal to perform the test with the source substance (EC No. 500-191-5) and, as explained above in Appendix 1, Section 0 of this decision, your read-across adaptation of the information requirement is rejected.

Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA agrees 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. More specifically, even though the information indicates that human exposure to the registered substance by the inhalation route is likely, the exposure concentrations reported in the chemical safety report for the inhalation route is low (maximum [redacted] mg/m^3). 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.

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, you are requested to carry out the modified study with the registered substance subject to the present decision: Sub-chronic toxicity study (90-day) in rats, oral route (test method: OECD TG 408)
while your originally proposed test for Sub-chronic toxicity study (90-day) in rats, oral route (test method: OECD TG 408) with the source substance (EC No 500-191-5) is rejected according to Article 40(3)(d) of the REACH Regulation.

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

Pursuant to Article 40(3)(b) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test under modified conditions.

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.

You have submitted a testing proposal for a pre-natal developmental toxicity study according to OECD TG 414 with the source substance (EC No 500-191-5).

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (pre-natal developmental toxicity). ECHA notes that you provided your considerations and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

ECHA has evaluated your proposal to perform the test with the source substance (EC No 500-191-5) and, as explained above in Appendix 1, Section 0 of this decision, your read-across adaptation is rejected.

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.

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 liquid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, you are requested to carry out the modified study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a first species (rats or rabbits), oral route (test method: OECD TG 414) while your originally proposed test for Pre-natal developmental toxicity study in a first species (rats or rabbits) (test method: EU OECD TG 414) with the source substance (EC No 500-191-5) 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.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 23 May 2014.

ECHA held a third party consultation for the testing proposals from 16 March 2015 until 30 April 2015. ECHA did not receive information from third parties.

This decision does not take into account any updates after **19 September 2018**, 30 calendar days after the end of the commenting period.

You updated your registration on 19 September 2018. ECHA took the information in the updated registration into account and did not amend the draft decision. The updated information is reflected in the Reasons (Appendix 1).

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.