EUROPEAN CHEMICALS AGENCY

Helsinki, 12 April 2019

Addressee: [redacted]

Decision number: TPE-D-2114466083-51-01/F
Substance name: Reaction products of fatty acid dimers and trimers, C18 (unsaturated) alkyl and fatty acids, C18 (unsaturated) alkyl with amines, polyethylenepoly-, triethylenetetramine fraction
EC number: 701-120-2
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.

Your testing proposal is accepted and you are requested to carry out:

1. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats using the analogue substance Fatty acids, C18-unsatd., dimers, polymers with tall-oil fatty acids and triethylenetetramine CAS no 68082-29-1 (EC no 500-191-5).**
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 analogue substance Fatty acids, C18-unsatd., dimers, polymers with tall-oil fatty acids and triethylenetetramine CAS no 68082-29-1 (EC no 500-191-5).**

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 and scientific information submitted by third parties.

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

a) Examination of the testing proposal

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

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 analogue substance Fatty acids, C18-unsatd, dimers, polymers with tall-oil fatty acids and triethylenetetramine (CAS No 68082-29-1, 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 analogue substance Fatty acids, C18-unsatd, dimers, polymers with tall-oil fatty acids and triethylenetetramine (CAS No 68082-29-1, EC No 500-191-5).

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, polymers with tall-oil fatty acids and triethylenetetramine CAS No 68082-29-1 (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.

ECHA notes that since the original submission of the dossiers identifiers of two substances have been changed and one has ceased manufacture. However, the read-across justification document (30th April 2013) has not been updated and therefore it contains old EC and CAS numbers. In the read-across justification document on page 1 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) hereinafter the "target substance";
[#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) ; 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.

You have provided a Combined repeated dose toxicity with reproduction/ developmental toxicity screening test (OECD 422) conducted the source substance.

ECHA has analysed the provided information and documentation of the registration dossier in light of the requirement 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

"Taking into account 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 and target substances contain the same unreacted amine, [redacted]

You have further provided data of starting materials for each substance in the read-across justification document. [redacted] is a starting material for both the target and source substance. In addition, the source substance contains [redacted] whereas the target substance contains [redacted].

ECHA considers that despite the lack of detailed data on the concentration of the starting materials and the differences in the starting fatty acids ([redacted]), the final composition of the target and source substances can be expected to be sufficiently similar due the same starting fatty acid [redacted] and the free, unreacted amine ([redacted] present in both substances. Substances can therefore be considered "*comparable in terms of chemical characteristics* " and there is a sufficient basis for predicting the properties of the target substance from the data obtained with the source substance.

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.

Additionally your clam that exposure to vapours by the inhalation route is not expected is in contradiction with information included in the Chemical Safety Reported (CSR) attached to your dossier. In the CSR you described workers' and professionals' spray applications, which are associated with conditions where the predominant exposure would be to liquid aerosols, regardless of the vapour pressure of the substance. Therefore the claimed absence of exposure through the inhalation route is not demonstrated.

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 in general 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. However, due to similar physico-chemical and toxicokinetic properties and reasons explained above in "Structural and chemical (dis)similarity" in this particular case ECHA considers that there is 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 data submitted by you, ECHA concludes that you have provided adequate and reliable information to demonstrate that the read-across approach is plausible for the endpoints in consideration.

ECHA therefore concludes that the criteria of Annex XI, 1.5. are met, and the read-across approach, as presented by you, can be considered plausible to meet the information requirements.

You proposed testing by the oral route. 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/kg bw/day).

Hence, the test shall be performed by the oral route using the test method OECD TG 408.

Therefore, ECHA considers that the proposed study performed by the oral route with the source substance (EC No 500-191-5) is appropriate to fulfil the information requirement of Annex IX, Section 8.6.2. of the REACH Regulation.

You proposed testing in rats. 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.

b) Consideration of the information received during third party consultation

ECHA has received third party information concerning the testing proposal during the third party consultation.

The third party has referred to the high molecular weight of the substance and lack of adverse effects observed in the OECD TG 422 study, and proposes the conduct of a bioavailability study to obtain data on toxicokinetic of the substance and consequently on the need to conduct further studies:

The molecular weight range of the polymer constituents between ca. [redacted] *g/mol combined with the absence of adverse findings after acute exposure and in an oral OECD TG 422 screening test with the read-across chemical (at concentrations up to 1000 mg/kg bw/d orally) are compatible with the hypothesis that the substance may not be significantly absorbed from the gastro-intestinal tract. Consequently, systemic exposure may be low. We therefore suggest the conduct of in vitro bioavailability studies which can provide data on toxicokinetics and help to make an informed decision on the need of the proposed sub-chronic toxicity study.*

ECHA notes that it is your responsibility to consider and justify in the registration dossier any adaptation of the information requirements in accordance with Annex IX, Section 8.6.2., column 2, fourth indent. This adaptation specifies that a sub-chronic toxicity study (90-day) does not need to be conducted if "*the substance is unreactive, insoluble and not inhalable and there is no evidence of absorption and no evidence of toxicity in a 28-day study, particularly if such a pattern is coupled with limited human exposure*". ECHA notes that all criteria need to be met.

ECHA notes that as stated above, the substances contain also low molecular weight constituents which may have potential to absorb via oral route, and that in the OECD TG 422 study conducted with the proposed source substance some adverse effects were observed. ECHA therefore considers that some constituents of the polyamidoamine substances have potential to absorb after administration via oral route and be bioavailable. ECHA further observes that according to information provided in the dossier the registered substance has a water solubility of 40 mg/L.

In your comments to the draft decision, you agreed to perform the requested study.

Therefore the criteria listed in Column 2 of Annex IX, section 8.6.2., fourth indent are not currently met and the information requirement for the sub-chronic toxicity study (90-day) cannot be adapted on this basis.

c) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed study with the source substance (EC No. 500-191-5): Sub-chronic toxicity study (90-day) in rats, oral route (test method: OECD TG 408).

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

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

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 in rats 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). As explained in Section 1 of this Appendix, your adaptation of the information requirement is accepted.

ECHA considers that the proposed study performed the source substance (EC No. 500-191-5) is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

You proposed testing with the rat as a first species. 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 did not specify the route for testing. 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 with a very low vapour pressure, ECHA concludes that testing should be performed by the oral route.

In your comments to the draft decision, you agreed to perform the requested study.

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

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 October 2014 until 1 December 2014 using the following identifiers: CAS no 68154-62-1, EC no 614-339-2. ECHA received information from third parties (see Appendix 1). On 29 May 2017 the substance identification was changed in REACH-IT: new EC no 701-120-2, CAS no -. ECHA held a third party consultation using the new identifiers from 28 February 2018 until 16 April 2018. 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.

In your comments you agreed to the draft decision. ECHA took your comments into account 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.

4. If the required tests are conducted with an analogue substance in the context of a read-across approach, the identity of the test material used to perform the test should be specified in line with the ECHA's Practical Guide on "How to use alternatives to animal testing to fulfil your information requirements" (chapter 4.4). This is required to show that the test material is representative of the analogue substance identified in the read-across approach and used to predict the properties of the registered substance.