EUROPEAN CHEMICALS AGENCY

Helsinki, 11 December 2018

Addressee: [redacted]

Decision number: CCH-D-2114453667-38-01/F
Substance name: Fatty acids, tall-oil, compds. with N-[3-(dimethylamino)propyl]tall-oil amides
EC number: 295-714-4
CAS number: 92128-22-8
Registration number: [redacted]
Submission number: [redacted]
Submission date: 10/01/2018
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. **Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: Alga, growth inhibition test, EU C.3./OECD TG 201) 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 ***18 March 2020***. You shall also update the chemical safety report, where relevant.

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 **Kevin Pollard**, Head of Unit, Evaluation, **E1**

[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.

(ECO)TOXICOLOGICAL INFORMATION

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.

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

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 of the REACH Regulation. Although not further specified your adaptation could be interpreted as an attempt to meet the provisions under Annex XI, Section 1.2, weight of evidence. Hence, ECHA has evaluated your adaptation with respect to this provision.

You have provided the following justification for the adaptation:

"In accordance with section 1 of REACH Annex XI, a subchronic repeated dose toxicity study (OECD TG 408) is not required. A subacute oral toxicity study (29 days; [redacted], 2010) with the test substance revealed only slight to moderate liver findings in males (reduced lipid content) and females (cytoplasmic changes of hepatocytes) at 800 mg/kg bw. The derived NOAEL was 200 mg/kg bw for both sexes. In a further study on developmental toxicity [redacted], 2010) with 14-day oral administration of the test substance no substance-related macroscopic findings were observed in dams at the limit dose of 1000 mg/kg bw. In this study the NOAEL for maternal toxicity was set at 100 mg/kg based on a reduced body weigh gain at 300 mg/kg bw and above. Taken together, the test substance showed a slight to moderate toxicity in the liver which is not sufficient to justify classification. It is not assumed that a longer treatment duration would substantially change the hazard assessment of the substance. For DNEL derivation of systemic effects after long-term exposure a time extrapolation factor of 6 was used to take into account the exposure duration subacute to chronic. Therefore, taking also into consideration the need to balance the value of information generation by animal testing with animal welfare a subchronic (90-day) repeated dose toxicity study with the substance has no priority."

To support your weight of evidence adaptation you have provided the following sources of information:

- Key study: "Short-term repeated dose toxicity study" in rat, oral route (OECD TG 407; GLP) with the registered substance, [redacted], 2010 (study report), rel. 1;
- Key study (in section 7.8.3 in IUCLID): "Developmental toxicity study" in rat, oral route (OECD TG 414; GLP) with the registered substance, [redacted], 2010 (study report), rel. 1.

An adaptation pursuant to Annex XI, Section 1.2. requires sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property with respect to the information requirement in question including an adequate and reliable documentation.

Your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance with respect to a sub-chronic toxicity study (OECD TG 408). Relevant elements are in particular exposure route, duration and levels, two genders, sensitivity and depth of investigations to detect specific organ toxicity.

You have provided a study record for a "short-term repeated dose toxicity study" (test method: OECD TG 407) in support of your adaptation. However, this study does not provide the information required by Annex IX, Section 8.6.2., because exposure duration is less than 90 days and the number of animals per dose group is significantly lower than in the 90 day sub-chronic toxicity study (OECD TG 408). Therefore, the sensitivity of a 28-day study to detect specific organ toxicity is much lower than that of a 90-day study.

You have also provided a study record for a "pre-natal developmental toxicity study" (test method: OECD TG 414) in support of your adaptation. However, this study does not provide equivalent information as of the sub-chronic toxicity study (OECD TG 408 study). More specifically this study exposes animals only for a duration of less than 90 days and it does not include, for example, a thorough histopathological and clinical/chemical investigation of the animals. Furthermore, the study according to OECD TG 414 provides information on the effects of prenatal exposure on the pregnant test animals and on the developing organism, while the study according to OECD TG 408 provides information on the possible health hazards likely to raise from repeated exposure over prolonged period of time covering post-weaning maturation and growth well into adulthood. Therefore, the sensitivity of the pre-natal developmental toxicity study (OECD TG 414) to detect specific organ toxicity is lower than in the 90 day sub-chronic toxicity study (OECD TG 408).

Hence, the sources of information you provided, together with your justification for the adaptation, do not allow to assume/conclude that the substance does not have a particular dangerous (hazardous) property with respect to the information requirement for Annex IX, Section 8.6.2.

Therefore, the general rules for adaptation laid down in Annex XI, Section 1.2. of the REACH Regulation are not met and 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 5.0, December 2016) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the substance is a liquid of very low vapour pressure and no uses with spray application are reported that could potentially lead to aerosols of inhalable size. 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 agreed to perform the test.

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 [IX/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. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

"Growth inhibition study aquatic plants" is a standard information requirement as laid down in Annex VII, Section 9.1.2. 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.

In the technical dossier you have provided a study record for a study on species *Desmodesmus subspicatus* performed according to EEC method for Determination of Ecotoxicity, Annex to Directive 92/69/EEC Part C, Method 3 "Algal inhibition test", equivalent to OECD test guideline 201 ([redacted] 2006a)[2].

ECHA has analysed it and considers the study not valid and not adequate to meet the information requirement of this endpoint, for the following reasons:

Firstly, the test concentrations could not be confirmed analytically and therefore it is not clear to what concentrations of the test substance algae were actually exposed. Specifically, a water accommodated fraction (WAF) was prepared for this test. After 72 hours of exposure, the following effect concentrations were derived, based on nominal

[2] [redacted] (2006a).

concentrations: E_rC50 of 0.53 mg/L, E_rC10 of 0.23 mg/L and $NOEC_r$ of 0.13 mg/L. However, the method of measuring test substance applied in this study, based on the measurement of the dissolved organic carbon (DOC), has a poor sensitivity (limit of detection of 5 mg/L) and did not allow that the test item could be detected analytically. As a result, the above noted effect concentrations were below the limit of detection of the analytical method applied.

Secondly, due to the physico-chemical properties of the registered substance, it has a very high adsorption potential (log Koc of 8.2 - 8.5 is reported in your registration dossier). Thus, losses of the test substance due to its adsorption to the test vessels may have occurred. Indeed, important losses of the substance were observed in another study provided in your dossier - in the short-term study on *Daphnia* ([redacted], 2009)[3]: only 6.5 -22.9% of the nominal values were measured in the test media after 24 hours of exposure.

OECD test guideline 201 ("Freshwater Alga and Cyanobacteria, Growth Inhibition Test") recommends that test concentrations should be analysed at the beginning and at the end of the test if concentrations are unlikely to remain within 80-120% of nominal. For volatile, unstable or strongly adsorbing test substances, the test guideline further recommends that additional analyses should be performed at 24 hour intervals during the exposure period in order to better define loss of the test substance. However, no such analysis were performed in the algae study you provided ([redacted] 2006a).

Thirdly, the adequate information on algae is necessary as it appears from the information in your dossier that algae could be the most sensitive species. This would have an impact on the calculation of predicted no-effect concentrations (PNEC) and may imply that a more severe classification and labelling of the substance would be warranted. Specifically,

- Based on the measurements reported in the short-term study on *Daphnia* ([redacted], 2009), the recovery percentage after 1 day could be as low as 6.5%. Assuming an exponential decay model and a similar recovery percentage in the algae study as well, the remaining concentration at the end of the test (i.e. after 3 days) can be estimated as being less than 0.03% of the nominal concentration and the corresponding time weighted average (TWA) concentration can be calculated as being approximatively 12% of the nominal concentration, i.e. for the 72h-EC50 of 0.53 mg/L based on nominal, the corresponding TWA 72h-EC50 can be estimated as 0.065 mg/L and for the 72h-NOEC of 0.13 mg/L based on nominal, the corresponding TWA 72h-NOEC can be estimated as 0.016 mg/L. Based on the reported EC50 for *Daphnia* of 0.111 mg/L (based on measured concentrations) and assuming the same exponential decay model and recovery rate for the fish study ([redacted] 2006b)4, it appears that algae is potentially more sensitive than *Daphnia* and fish.

- ECHA further notes that the registered substance is a complex mixture of different constituents, i.e. fatty acids, aminopropyldimethylamine fatty acid amides, and resin acids. Available data for aquatic toxicity of the different constituents or their analogues have been investigated by ECHA and suggest that algae is the most sensitive species for the most abundant and the most toxic constituents in the

[3] [redacted] (2009).
[4] [redacted] (2006b).

substance, i.e. aminopropyldimethylamine fatty acid amides.

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

Algae growth inhibition test (test method EU C.3. / OECD TG 201) is a validated standard international test laid down in the Test Methods Regulation (EC) No 440/2008 and therefore it meets the requirements of Article 13(3) of the REACH Regulation. According to ECHA ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017), it is the preferred test to cover the standard information requirement of Annex VII, Section 9.1.2. of the REACH Regulation.

As the substance is highly adsorptive and is expected to adsorb to the test vessels, the results needs to be based on measured concentrations. An adequate and sufficiently sensitive analytical method to allow detection of the test item shall be used. ECHA notes that for example, for the short-term toxicity study on *Daphnia* ([redacted], 2009) high-performance liquid chromatography-mass spectrometry (HPLC-MS) was used which allowed measurements of concentrations as low as 0.001 mg/L.

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

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: Algae growth inhibition test, EU C.3./OECD TG 201). The results shall be based on measured concentrations.

Notes for your consideration

If based on the results of the required study algae is observed to be the most sensitive species, then the PNECs will have to be revised accordingly. Also, more severe classification and labelling of the substance may be warranted. For environment, the registered substance is currently classified as Aquatic Acute 1 (H400: Very toxic to aquatic life) and Aquatic Chronic 1 (H410: Very toxic to aquatic life with long lasting effects). An M-factor of 1 is currently applied both for acute and chronic toxicity. ECHA notes that a higher M-factor may have to be applied depending on the results of the algae study.

Deadline to submit the requested information

In the draft decision communicated to you the time indicated to provide the requested information was 12 months from the date of adoption of the decision. In your comments on this draft decision, you requested an extension of the timeline to 24 months. You sought to justify this in your comments to the corresponding testing proposal draft decision by stating "We would like to please you to expand the timeline up to two years according to the following points: the available test institutes are limited in their capacities due to an increasing order volume, the time necessary to carry out the analytics and the test, time for evaluation of the test results and writing the report, update of the dossier to our experiences and under the actual situation in the test institutes the steps mentioned above take up to 2 years. Thus, a timeline of 2 years seems reasonable. In addition we would like

to please you to perform the requested studies of this draft decision in parallel to the one requested in TPE-D-2114412428-53-01/D as this would increase the comparability of the results and give a complete assessment of the substance."

Upon request from ECHA, you provided documentary evidence from your selected testing laboratory, with indicative timeline for a sub-chronic toxicity study (90-day), oral route in rats, indicating a requested deadline extension for the end of September, 2019 (if the method development starts at 01 October 2018). Note, you also indicated an indicative timeline for the corresponding testing proposal draft decision request, pre-natal developmental toxicity study, oral route in rabbit.

Considering the indicative timeline and the decision making process step, ECHA has modified the deadline of the compliance check and testing proposal decisions from the original 12 months to 15 months, from the date of the decision.

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 01 March 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 requests, but amended the deadline in the decision.

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 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.