Decision number: TPE-D-2114343507-49-01/F Helsinki, 5 September 2016

DECISION ON TESTING PROPOSAL(S) SET OUT IN A REGISTRATION PURSUANT TO ARTICLE 40(3) OF REGULATION (EC) NO 1907/2006

For Naphthenic acids, EC No 215-662-8 (CAS No 1338-24-5), registration number: [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 40(1) of the REACH Regulation, ECHA has examined the following testing proposals submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(d) thereof for Naphthenic acids, EC No 215-662-8 (CAS No 1338-24-5), submitted by [redacted] (Registrant).

- 90-day oral toxicity study (OECD 408) in rats, oral route or 90-day oral toxicity study (OECD 408) in rats, oral route as an extended study with a satellite group, depending on the outcome of the pre-natal developmental toxicity study.
- Developmental toxicity / teratogenicity study (OECD 414) in rats, oral route.
- Long-term toxicity to fish study (OECD 210)
- Long-term toxicity to aquatic invertebrates study (OECD 211)

This decision is based on the registration as submitted with submission number [redacted], for the tonnage band of 100 to 1000 tonnes per year.

This decision does not take into account any updates after **16 September 2015**, i.e. 30 calendar days after the end of the commenting period.

This decision does not imply that the information provided by the Registrant in his 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.

ECHA received the registration dossier containing the above-mentioned testing proposals for long-term toxicity to fish and long-term toxicity to aquatic invertebrates, for further examination pursuant to Article 40(1) on 19 November 2010. The registration was subsequently updated on 10 December 2013 containing all of the above-mentioned testing proposals.

ECHA held a third party consultation for the testing proposal for long-term toxicity to fish study from 01 July 2011 until 15 August 2011. ECHA did not receive information from third parties. Subsequently, ECHA held a third party consultation for the testing proposals for 90-day oral toxicity study and Developmental toxicity / teratogenicity study from 04 April 2014 until 19 May 2014. ECHA did not receive information from third parties.

On 9 July 2015 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision.

On 13 August 2015 ECHA received comments from the Registrant on the draft decision.

The ECHA Secretariat considered the Registrant's comments.
The information is reflected in the Statement of Reasons (Section III) whereas no amendments to the Information Required (Section II) were made.

On 21 July 2016 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals for amendment of the draft decision within 30 days of the receipt of the notification.

As no proposal for amendment was submitted, ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

II. Testing required

A. Tests required pursuant to Article 40(3)

The Registrant shall carry out the following proposed tests pursuant to Article 40(3)(a) and 13(4) of the REACH Regulation using the indicated test methods and the registered substance subject to the present decision:

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31/OECD 414) in rats or rabbits, oral route;

2. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211);

3. Fish, early-life stage (FELS) toxicity test (Annex IX, Section 9.1.6.1.; test method: Fish, early-life stage toxicity test, OECD 210).

Furthermore, the Registrant shall carry out the following test with modified conditions pursuant to Article 40(3)(b) and 13(4) of the REACH Regulation using the indicated test methods and the registered substance subject to the present decision:

4. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26/OECD 408) in rats.

Note for consideration by the Registrant:

The Registrant 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 of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring to and conforming with the appropriate rules in the respective Annex, and an adequate and reliable documentation.

Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the Enforcement Authorities of the Member States.

B. Deadline for submitting the required information

Pursuant to Articles 40(4) and 22(2) of the REACH Regulation, the Registrant shall submit to ECHA by **12 September 2018** an update of the registration dossier containing the information required by this decision, including, where relevant, an update of the Chemical Safety Report. The timeline has been set to allow for sequential testing as appropriate.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposals submitted by the Registrant for the registered substance.

A. Tests required pursuant to Article 40(3)

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

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 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.

The Registrant has submitted a testing proposal for a pre-natal developmental toxicity study in rats according to EU B.31/OECD 414 to be performed with the registered substance subject to the present decision with the following justification: *"As there were significant reductions in number of offspring, number live born and offspring body weights at 300 and 900 mg/kg in the OECD TG 422 study, the prenatal developmental toxicity study is proposed as the first step. Embryotoxicity and teratogenicity will be assessed versus maternal toxicity. The results of this study will allow the registrant to make a conclusive classification proposal as well as the derivation and evaluation of DNELs."*

ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

The Registrant proposed testing in rats. He proposed testing by the oral route. According to the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used.

c) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is requested to carry out the proposed study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414).

2. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

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.

"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. 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.

The Registrant has submitted a testing proposal for testing the registered substance for long-term toxicity testing on aquatic invertebrates (*Daphnia magna* reproduction test, EU C.20/OECD 211) with the following justification: "*The chronic Daphnia NOEC of naphthenic acids is 2.4 mg/l. This value is calculated from the experimental LLC50 value of 24 mg/l (see IUCLID chapter 6.1.3) and an acute-to-chronic ratio of 10. This value is of a tentative nature only, due to lacking experimental information*".

ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 9.1.5 of the REACH regulation.

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 2.0, November 2014), Chapter R7b (Section R.7.8.5 including Figure R.7.8-4), if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially more sensitive, long-term studies may be required on both. There were no indications in the dossier from the short-term toxicity studies on aquatic species that fish would be substantially more sensitive than aquatic invertebrates. In such case, according to the integrated testing strategy, the *Daphnia* study is to be conducted first. If based on the results of the long-term *Daphnia* study and the application of a relevant assessment factor, no risks are observed (PEC/PNEC<1), no long-term fish testing may need to be conducted as explained below in the next section.

c) Outcome

Therefore, pursuant to Article 40(3)(a)of the REACH Regulation, the Registrant is required to carry out the proposed study using the registered substance subject to the present decision: Long-term toxicity testing on aquatic invertebrates (Annex IX, 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211).

3. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.)

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.

"Long-term toxicity testing on fish" is a standard information requirement as laid down in Annex IX, Section 9.1.6. of the REACH Regulation. The information on this endpoint is not available for the registered substance.
The Registrant has submitted a testing proposal for testing the registered substance for long-term toxicity testing on fish (Fish, early-life stage toxicity test, OECD 210) with the following justification: "*The chronic fish NOEC of naphthenic acids is 0.9 mg/l. This value is calculated from the experimental LLC50 value of 9 mg/l (see IUCLID chapter 6.1.1) and an acute-to-chronic ratio of 10. This value is only tentative, due to lacking experimental information.*"

ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 9.1.6 of the REACH regulation.

As discussed in section A.2. above, according to the integrated testing strategy in ECHA *Guidance on information requirements and chemical safety assessment* (version 2.0, November 2014), the Daphnia study requested under Section A.2. is to be conducted first.

Once results of the proposed test on long-term toxicity to aquatic invertebrates required in section A.2. are available, the Registrant shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation. If the revised chemical safety assessment indicates the need to investigate further the effects on aquatic organisms, there is an information gap and it is necessary to provide information for this endpoint. Therefore the Registrant shall carry out the test for a long-term toxicity test on fish in order to fulfil the standard information requirement of Annex IX, 9.1.6.

If the Registrant comes to the conclusion, based on the revised chemical safety assessment, that no further investigation of effects on aquatic organisms is required, he shall update his technical dossier accordingly by clearly stating the reasons for adapting the standard information requirement of Annex IX, 9.1.6.

c) Outcome

Therefore, pursuant to Article 40(3)(a)of the REACH Regulation, the Registrant is required to carry out the proposed study using the registered substance subject to the present decision: Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.; test method: Fish, early-life stage toxicity test, OECD 210).

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

a) Examination of the testing proposal

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.

The Registrant has submitted a testing proposal for a sub-chronic toxicity study (90 day) by the oral route (EU B.26/OECD 408) with the following justification: "*The 90-day toxicity in rats and prenatal developmental toxicity in rats are standard information requirements in Annex IX of the REACH legislation.*" ECHA agrees that the oral route is the most appropriate route of administration for testing.
The Registrant proposed testing in rats. According to the test method EU B.26/OECD 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

The Registrant proposed a step-wise approach by performing first the pre-natal developmental toxicity study addressed in section A.1. of the present decision and the sub-chronic toxicity study as a second step. Depending on the outcome of the pre-natal developmental toxicity study, the Registrant proposed to perform the sub-chronic toxicity study either as a standard study or as an extended study with a satellite group:

"*A 90-day toxicity study in rats will be conducted as a follow-up study, taking into account the results of the OECD 414 study as follows:*

- *In the presence of embryotoxicity and teratogenicity, the appropriate classification for reproductive toxicity will be given. In that case, the 90-day study will be conducted as a standard study, without additional effort for reproductive toxicity.*

- *In case of absence of findings in the OECD 414 study, or if embryotoxicity without teratogenicity is observed, a satellite group will be added to the 90-day study to study potential reproductive toxicity effects and exclude further trigger for testing. This study allows a prolonged dosing period in males and females. Adverse effects on the reproductive system, if any, can therefore be better detected after this dosing period than in the prenatal developmental toxicity study (OECD TG 414) or the combined repeated dose/reproductive and developmental toxicity screening study (OECD TG 422) study. In the absence of relevant effects on reproductive organs and function, there would be no further testing need."*

The Registrant also described the observations to be made in this satellite group. In their justification, the Registrant states that the proposed satellite group will be used to "*study potential reproductive toxicity effects and exclude further trigger for testing*". In their comments, the Registrant clarifies that they intend to provide further evidence on the absence of effects on the reproductive organs and tissues, aiming to further support the conclusion on reproductive effects.

ECHA however considers that the proposed extension to the study with a satellite group as presented by the Registrant is not necessary in order to "*study potential reproductive toxicity effects and exclude further trigger for testing*", for the following reasons.

There were significant reductions in number of offspring, number live born and offspring body weights found at 300 and 900 mg/kg in the combined 28-day repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422).

The Registrant considered these findings as secondary to maternal toxicity, demonstrated for example by two mortalities in high dose group females, slightly reduced body weight gain and reduced food consumption in high dose group females and increased liver weights in mid and high dose group females. However, ECHA does not consider the described maternal toxicity as a valid explanation for the findings made in the offspring at least at the mid dose of 300 mg/kg body weight, where the most prominent effect was increased liver weight.

ECHA notes that the significant reductions in number of offspring, number live born and offspring body weights already reveal a concern in relation to reproductive toxicity as laid out in Annex IX, section 8.7.3 of the REACH regulation, and that no further trigger for reproductive toxicity testing is deemed necessary.

In their comments, the Registrant confirmed their opinion that the effects seen in the combined 28-day repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422) are solely related to developmental toxicity and that the observed concern will be adequately concluded through the proposed pre-natal developmental toxicity study.

ECHA however notes that reduced litter size and reduced body weight of offspring independent from litter size are also two of the triggers to conduct an extended one-generation reproductive toxicity study at REACH Annex IX level, according to the Guidance on information requirements and chemical safety assessment, chapter R7.a: endpoint specific guidance, version 4.0 from July 2015, R.7.6.2.3.2, pp370 and 371. The observed concern can therefore not be adequately concluded through the proposed pre-natal developmental toxicity study. Please see also the "note for consideration by the Registrant" below.

With regard to the proposed extension of a standard sub-chronic toxicity study (90 day) ECHA considers that in general an OECD 408 test would not fulfil the information requirements of Annex IX, section 8.7.3., unless there was adequate data to classify for reproductive toxicity at 1B. However, ECHA notes that the OECD 408 guideline contains a number of provisions allowing for additional investigations (e.g. specific investigations of target organ toxicity, recovery groups) that could assist an investigation of reproductive toxicity and provide additional useful information.

In general, when ECHA requests a registrant to perform a study according to a test guideline, ECHA expects that the Registrant will closely examine the provisions of the guideline, and accordingly perform investigations within the scope of the guideline. Therefore ECHA can accept extensions of the 90-day sub-chronic toxicity study, as far as the additional parameters to be investigated are within the scope of the Guideline.

ECHA can however not accept the Registrant's justification for using additional animals in a satellite group to "study potential reproductive toxicity effects and exclude further trigger for testing". For this reason, ECHA decided to modify the testing proposal as presented by the Registrant and requests the proposed study to be performed in a standard design, without an additional satellite group, irrespective of the outcome of the pre-natal developmental toxicity study.

c) Outcome

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, the Registrant is requested to carry out the following study with the registered substance subject to the present decision: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD 408).

Note for consideration by the Registrant

As laid down in Annex IX, 8.7.3. of the REACH regulation, an extended one-generation reproductive toxicity study is a standard information requirement for substances manufactured or imported in quantities of 100 tonnes more, if the available repeated dose toxicity studies (e.g. 28-day or 90-day studies, OECD 421 or 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. As outlined above, the findings made in the 28-day repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422) reveal a concern in relation with reproductive toxicity. ECHA therefore reminds the Registrant to address this concern adequately in the Registration dossier, by submitting a testing proposal for an extended one-generation reproductive toxicity study (EOGRTS, EU B.56, OECD 443) to ECHA or providing a justification for adaptation which complies with the specific rules outlined in Annex IX and/or the general rules contained in Annex XI of the REACH Regulation.

IV. Adequate identification of the composition of the tested material

The process of examination of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the new studies meet real information needs. Within this context, the Registrant's dossier was sufficient to confirm the identity of the substance to the extent necessary for examination of the testing proposal.

In relation to the proposed tests, the sample of substance used for the new studies must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is within the specifications of the substance composition that are given by the joint registrants. It is the responsibility of all joint registrants of the same substance to agree to the tests proposed (as applicable to their tonnage level) and to document the necessary information on their substance composition.

In addition, it is important to ensure that the particular sample of substance tested in the new studies 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 by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new studies must be suitable to assess these grades.

Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the studies to be assessed.

V. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

Authorised by[1] Claudio Carlon, Head of Unit, Evaluation E2

[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.