EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000002435-77-05/F Helsinki, 10 April 2014

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

For Heptanal, CAS No 111-71-7 (EC No 203-898-4), 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)(e) thereof for Heptanal, CAS No 111-71-7 (EC No 203-898-4), by [redacted] (Registrant).

- Long-term toxicity to aquatic invertebrates, OECD guideline 211 (*Daphnia magna* reproduction test);
- Short-term toxicity to invertebrates, OECD guideline 207 (Earthworm, acute toxicity tests);
- Effects on soil micro-organisms, OECD guideline 216 (Soil micro-organisms: nitrogen transformation test);
- Short-term toxicity to plants, OECD guideline 208 (Terrestrial plants test: seedling emergence and seedling growth test);
- Sub-chronic toxicity study (90-day), in rats, oral route, OECD guideline 408, with a read-across substance, heptanoic acid (CAS 111-14-8); and
- Pre-natal developmental toxicity study, in rabbits, OECD guideline 414, with a read-across substance, heptanoic acid (CAS 111-14-8).

This decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band of 1000 tonnes or more per year. This decision does not take into account any updates after 31 October 2013, the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) of the REACH Regulation.

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 to initiate a compliance check on the present dossier at a later stage.

On 2 November 2010, pursuant to Article 40(1) of the REACH Regulation, ECHA initiated the examination of the testing proposals set out by the Registrant in the registration dossier for the substance mentioned above.

ECHA held a third party consultation for the testing proposals from 15 July 2011 until 29 August 2011. ECHA did receive information from third parties (see section III below).

On 17 August 2012 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 17 September 2012 the Registrant provided comments on the draft decision. ECHA considered the Registrant's comments received. On basis of the comments, Section II was amended. The Statement of reasons (Section III) was changed accordingly.

On 31 October 2013 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 to amend the draft decision within 30 days of the receipt of the notification.

Subsequently, Competent Authorities of the Member States submitted proposals for amendment to the draft decision.

On 5 December 2013 ECHA notified the Registrant of proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on those proposals for amendment within 30 days of the receipt of the notification.

The ECHA Secretariat reviewed the proposals for amendment received and amended the draft decision.

On 16 December 2013 ECHA referred the draft decision to the Member State Committee.

By 7 January 2014, in accordance to Article 51(5), the Registrant provided comments on the proposal(s) for amendment. The Member State Committee took the comments of the Registrant on the proposal(s) for amendment into account.

After discussion in the Member State Committee meeting on 3-7 February 2014, a unanimous agreement of the Member State Committee on the draft decision was reached on 5 February 2014. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Testing required

Concerning environmental endpoints, the Registrant shall carry out the following proposed tests pursuant to Article 40(3)(a) of the REACH Regulation using the indicated test methods and the registered substance Heptanal, CAS No 111-71-7 (EC No 203-898-4):

1. Long-term toxicity testing to aquatic invertebrates (Annex IX, 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211);
2. Short-term toxicity to terrestrial invertebrates (Annex IX, 9.4.1.; test method: Toxicity for earthworms, EU C.8/OECD 207); and
3. Effects on soil micro-organisms (Annex IX, 9.4.2.; test method: Soil microorganisms: nitrogen transformation test, EU C.21/OECD 216).

In addition, the Registrant shall carry out the following modified test pursuant to Article 40(3)(b) of the REACH Regulation using the indicated test method and the registered substance Heptanal, CAS No 111-71-7 (EC No 203-898-4):

4. Short-term toxicity to plants (Annex IX, 9.4.3.; test method: Terrestrial Plant Test: Seedling emergence and seedling growth test, OECD 208 with at least 3 species tested, two dicotyledonous and one monocotyledonous species).

Concerning human health endpoints, the Registrant shall carry out the following additional test pursuant to Article 40(3)(c) of the REACH Regulation using the indicated test method and the registered substance Heptanal, CAS No 111-71-7 (EC No 203-898-4):

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

while the originally proposed test for sub-chronic toxicity (90-day) proposed to be carried out using the analogue substance heptanoic acid (CAS No 111-14-8) is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

In addition, the Registrant shall carry out the following test pursuant to Article 40(3)(a) of the REACH Regulation using the indicated test method:

6. Pre-natal developmental toxicity study, oral route (Annex IX, 8.7.2.; test method: EU B.31/OECD 414) either
   a. in rabbits, using the read-across substance Heptanoic acid (CAS No 111-14-8), if the results of a toxicokinetic study indicate that the metabolism of Heptanal (CAS No 111-71-7, EC No 203-898-4) to Heptanoic acid can be considered fast and extensive enough to conclude that the effects observed after Heptanal exposure are predominantly caused by Heptanoic acid, as explained in detail in section III.B. of this draft decision;
   or
   b. in rats or rabbits, using the registered substance Heptanal (CAS No 111-71-7, EC No 203-898-4).

The Registrant shall determine the appropriate order of the studies taking into account the possible outcome and considering the possibilities for adaptations of the standard information requirements according to column 1 or 2 provisions of the relevant Annexes of the REACH Regulation.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **10 April 2016** an update of the registration dossier containing the information required by this decision.

Once results of the proposed test on long-term toxicity to aquatic invertebrates 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, the Registrant shall consider submitting a testing proposal for a long-term toxicity test on fish in order to fulfil the standard information requirement of Annex IX, 9.1.6.

Data from a second pre-natal developmental toxicity study on another species is a standard information requirement according to Annex X, 8.7.2. of the REACH Regulation, subject to the Annex IX, 8.7.2. column 2 requirements. If the Registrant considers that testing is necessary to fulfil this information requirement taking into account the outcome of the pre-natal developmental toxicity study on a first species and all other relevant and available data, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species.

At any time, the Registrant shall take into account that there may be an obligation to make every effort to agree on sharing of information and costs with other Registrants.

III. Statement of reasons

The statement of reasons considers separately the information required to fulfil the environmental endpoints concerned by the present decision (section A) from the human health endpoints (section B).

A. Environmental endpoints

The decision of ECHA is based on the examination of the testing proposals submitted by the Registrant for the registered substance and scientific information submitted by third parties.

1. Long-term toxicity testing to aquatic invertebrates

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.

According to column 1 of Section 9.1.5. of Annex IX of the REACH Regulation, long-term toxicity testing on invertebrates is required to fulfil the standard information requirements. 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 provided the following justification for conducting the proposed test: "According to claimed uses of heptanal, aquatic compartment exposure is likely. At the moment no data is available for characterizing heptanal long term effects on organisms inhabiting aquatic compartment. Even if the risk assessment demonstrates that there is no risk for those organisms using the PNEC derived with short term data, a test is proposed for covering this question and will permit to refine the PNEC value."

There were no indications in the dossier from the short-term toxicity studies on aquatic species that the fish would be substantially more sensitive than Daphnia.

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 1.1., August 2008), Chapter R7b, Figure R.7.8-4 page 53, 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. 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 an applied assessment factor of 50 no risks are indicated, no long-term fish testing may need to be conducted.

In his comments, the Registrant expressed consent to perform this experimental study.

b) Outcome

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

2. Short-term toxicity to terrestrial invertebrates

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 short-term toxicity study on terrestrial invertebrates is a standard information requirement as laid down in Annex IX, section 9.4.1., column 1 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 generate the data for this endpoint.

The Registrant provided the following justification for conducting the proposed test:

"According to claimed uses of heptanal terrestrial exposure is likely. At the moment no data is available for characterizing heptanal effects on organisms inhabiting terrestrial compartment. Even if the risk assessment demonstrated that there little risk for those organisms using the PNEC derived through equilibrium partitioning method, tests are proposed for covering this question.
Indeed, the RCR for Grassland at the level of the manufacturing site is higher than 1. However, the 0.02 release factor to wastewater is a worst case that is ten times higher than the actual release factor to wastewater of the manufacturing site. The releases to soil in general, including to grassland, are directly related to the amount of substance entering the STP. Thus we can assume that the Grassland PEC will be in fact ten times lower and thus the PEC/PNEC ration will be below 1. However we propose tests to refine the PNEC soil."

ECHA considers the proposed test to be suitable and justified for filling the information gap.

In his comments, the Registrant expressed consent to perform this experimental study.

b) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: Short-term toxicity to terrestrial invertebrates (Annex IX, 9.4.1.; test method: Toxicity for earthworms, EU C.8/OECD 207) using the registered substance.

3. Effects on soil micro-organisms

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.

Effects on soil micro-organisms is a standard information requirement as laid down in Annex IX, section 9.4.2 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 generate the data for this endpoint.

The Registrant provided the following justification for conducting the proposed test:

"According to claimed uses of heptanal terrestrial exposure is likely. At the moment no data is available for characterizing heptanal effects on organisms inhabiting terrestrial compartment. Even if the risk assessment demonstrated that there little risk for those organisms using the PNEC derived through equilibrium partitioning method, tests are proposed for covering this question.

Indeed, the RCR for Grassland at the level of the manufacturing site is higher than 1. However, the 0.02 release factor to wastewater is a worst case that is ten times higher than the actual release factor to wastewater of the manufacturing site. The releases to soil in general, including to grassland, are directly related to the amount of substance entering the STP. Thus we can assume that the Grassland PEC will be in fact ten times lower and thus the PEC/PNEC ration will be below 1. However we propose tests to refine the PNEC soil."

ECHA considers the proposed test to be suitable and justified for filling the information gap.

In his comments, the Registrant expressed consent to perform this experimental study.

b) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: Effects on soil micro-organisms (Annex IX, 9.4.2.; test method: Soil microorganisms: nitrogen transformation test, EU C.21/OECD 216) using the registered substance.

4. Short-term toxicity to plants

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.

Short-term toxicity testing on terrestrial plants is a standard information requirement as laid down in Annex IX, section 9.4.3. 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 generate the data for this endpoint.

The Registrant provided the following justification for conducting the proposed test:

"According to claimed uses of heptanal terrestrial exposure is likely. At the moment no data is available for characterizing heptanal effects on organisms inhabiting terrestrial compartment. Even if the risk assessment demonstrated that there little risk for those organisms using the PNEC derived through equilibrium partitioning method, tests are proposed for covering this question.

Indeed, the RCR for Grassland at the level of the manufacturing site is higher than 1. However, the 0.02 release factor to wastewater is a worst case that is ten times higher than the actual release factor to wastewater of the manufacturing site. The releases to soil in general, including to grassland, are directly related to the amount of substance entering the STP. Thus we can assume that the Grassland PEC will be in fact ten times lower and thus the PEC/PNEC ration will be below 1. However we propose tests to refine the PNEC soil."

ECHA considers the proposed test to be suitable and justified for filling the information gap.

The OECD test guideline 208 reflects on the need to choose the number of species to be tested depending on relevant regulatory requirements and on the need for a reasonably broad selection of species to account for interspecies sensitivity distribution. For short-term toxicity testing (Annex IX, 9.4.3.) ECHA considers three species as the minimum necessary to achieve a reasonably broad selection. The short term toxicity testing shall be conducted with species from different families, as a minimum with two dicotyledonous and one monocotyledonous species, selected according to the criteria indicated in the OECD 208 guideline. The Registrant should consider if testing on additional species is needed to cover the information requirement.

In his comments, the Registrant expressed consent to perform this experimental study.

b) Outcome

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, the Registrant is required to carry out the proposed study: Short-term toxicity to plants with at least three species tested from different families, two dicotyledonous and one monocotyledonous species (Annex IX, 9.4.3.; test method: Terrestrial Plant Test: Seedling emergence and seedling growth test, OECD 208) using the registered substance.

B. Human health endpoints

The decision of ECHA is based on the examination of the testing proposals submitted by the Registrant for the registered substance proposed to be performed with the analogue substance heptanoic acid, on the submitted read-across justification and scientific information submitted by third parties. ECHA has considered first the scientific validity of the read-across hypothesis (preliminary considerations below), before assessing the testing proposed (sections 5 and 6).

Preliminary considerations concerning the proposed read-across hypothesis

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*". The first Recital and the first Article of the REACH Regulation establish the "promotion of alternative methods for assessment of hazards of substances" as an objective pursued by the Regulation. In accordance with that objective, ECHA considers whether a prediction of the relevant properties of the substance subject to this decision by using the results of the proposed tests is sufficiently plausible based on the information currently available.
More specifically, Section 1.5 of Annex XI to the REACH Regulation opens the possibility for substances to be assessed by the use of grouping approaches but explicitly requires that physico-chemical properties, human health and environmental effects or fate may be predicted from data for reference substances within the group by interpolation to other substances in the group.

In the dossier initially submitted, ECHA noted that the Registrant intended to cover the human health information requirements for a sub-chronic toxicity study (90-day) (standard information requirement of Annex IX, 8.6.2.) and for a first pre-natal developmental toxicity study (standard information requirement of Annex IX, 8.7.2.) by performing the test with a

read-across substance, heptanoic acid. The Registrant provided a justification based on the metabolism of aldehydes and their subsequent oxidation ("*aldehydes are rapidly oxidised to the corresponding carboxylic acids, and based on the known biochemical fate of straight chain aliphatic aldehydes and carboxylic acid, it is concluded that the aldehydes undergo functional group oxidation to the corresponding carboxylic acid that is subsequently completely oxidised to carbon dioxide and water in the fatty acid pathway and tricarboxylic acid cycle*"). However, in a draft decision sent to the Registrant, ECHA considered that the read-across hypothesis and documentation of the argument that data on heptanoic acid could be applied for heptanal in a read-across approach is inadequate. More specifically, the Registrant had not submitted any data to support the read-across hypothesis, i.e. the metabolism of heptanal to heptanoic acid, and the requirements of Annex XI, section 1.5., in conjunction with Article 13(1) and Annex IX, third introductory paragraph, of the REACH Regulation are not met.

In the comments to the draft decision, the Registrant provided a more detailed justification and a toxicokinetic study plan to support the read-across approach. The Registrant referred to

(i) The assessment of C7-C9 Aliphatic Aldehyde and Carboxylic Acids category that has been accepted by US EPA as a suitable category under HPV Challenge Program. The Registrant states that US EPA agrees with the Registrant that based on the rapid metabolism of an aldehyde to an acid, the studies on acids are appropriate for characterising the effects of corresponding aldehydes.

ECHA notes that although the US EPA assessment indicates low acute, repeated dose, reproductive and developmental toxicity of the category members, no repeated dose, reproductive and developmental toxicity studies have been conducted with heptanal. In addition, the category justification is based on the rapid metabolism of aldehydes to corresponding carboxylic acids but no experimental data has been provided to support such rapid metabolism or to investigate other possible metabolic pathways. Moreover, a suitable category under the US HPV Challenge Programme does not mean per se that endpoint specific data for the substance and endpoint in question or reliable predictions for such data is available. This however is necessary under REACH to ensure that reliable and robust information on intrinsic properties is made available.

(ii) The use of heptanal and heptanoic acid as flavouring agents and naturally occurring components in food, and hazard assessment performed by US FDA and WHO/FAO JECFA who consider these substances as "Generally Recognised As Safe" and "NO safety concerns at current levels of intake when used as a flavouring agent".

ECHA notes that indeed, both heptanal and heptanoic acid are widely used in fragrances and flavouring agents and are considered not to have any safety concerns by US FDA and WHO/FAO JECFA. The basis for these recommendations seems to be only acute toxicity studies, i.e. no repeated dose toxicity studies have been used for these evaluations.

(iii) Data matrix on physico-chemical and toxicological properties of heptanal and heptanoic acid.

ECHA notes that based on the summary data matrix provided by the Registrant, both substances have comparable physico-chemical values, have similar core structure (carbon chain length) but different functional groups. The substances have low acute

toxicity, and they are not genotoxic and not sensitising. It is noted that no data are available in the data matrix for the registered substance with regard to studies conducted with repeated administration.

(iv) A proposal to perform a toxicokinetic study in the rat to confirm whether heptanoic acid is the major metabolite of heptanal.

ECHA understands that the aim of the planned toxicokinetic study is to quantify the extent of metabolism of heptanal to heptanoic acid and confirm whether heptanoic acid is the major metabolite of heptanal. Depending on the outcome of the tests, the Registrant may then be in a position to be able to address some or all aspects of the information that is missing and to provide this information in their registration dossier. ECHA emphasises that all elements of the required information on metabolism stated in this decision above need to be addressed.

ECHA has analysed the more detailed justification and data in light of the requirements of Annex XI, 1.5 and notes that the Registrant has based his read-across justification on metabolism of heptanal to heptanoic acid, and on toxicological data on other structurally similar aldehydes and carboxylic acids.

According to the proposed toxicokinetic study, only the peripheral blood will be collected and thus the study provides no information on heptanal that absorbs already in the gut and is transported to the liver via portal vein. Therefore, the sub-chronic (90-day) toxicity and pre-natal developmental toxicity studies are discussed separately below.

- Sub-chronic toxicity study (90-day)

ECHA notes that in toxicokinetic study proposed by the Registrant, only the peripheral blood is sampled and thus the study does not provide information on the effects on the liver caused by heptanal absorbed in the gut and transported to the liver via portal vein. The absence of heptanal in the peripheral blood does not necessarily imply the absence of the exposure of the liver and effects caused by this exposure. Thus, even if the toxicokinetic test shows that heptanal is not present in the peripheral blood, the read-across hypothesis cannot be accepted for sub-chronic toxicity (90-day) endpoint as the proposed study does not provide conclusive information on the exposure of liver to heptanal via portal vein.

- Pre-natal developmental toxicity

ECHA considers the read-across hypothesis for pre-natal developmental toxicity study plausible if heptanal is not detected in the peripheral blood, or if the concentrations are negligible as the effects depend on the exposure of chemicals via peripheral blood.

In order for ECHA to eventually assess the read-across approach it has to be demonstrated that the metabolism of heptanal to heptanoic acid is rapid enough to prevent significant systemic exposure to heptanal and that metabolism to heptanoic acid is the predominant metabolic pathway. Such demonstration should include information on the extent and the speed of metabolism of heptanal, and on the presence/absence of other metabolites than heptanoic acid. It is at the Registrant's discretion to initiate any such investigations to acquire sufficient data to substantiate his read-across hypothesis.

ECHA notes that if heptanal is not detected in the peripheral blood, or the concentrations are negligible, the read-across approach may be justified for the pre-natal developmental toxicity study as the effects in this case depend on the exposure of chemicals via peripheral blood. In line with the objective of "*promotion of alternative methods for assessment of hazards of substances*", ECHA considers the read-across hypothesis plausible, although the dossier does not yet contain the results of the toxicokinetic study to demonstrate the metabolism of heptanal to heptanoic acid.

In the case where the planned toxicokinetic test would not confirm the grouping and read-across hypothesis relied upon by the Registrant, this outcome shall not alter the obligation of the Registrant to meet the standard information requirements. Should the read-across strategy be inadequate, it is the responsibility of the Registrant to ultimately submit reliable information or adaptations which is used in a way that does not underestimate hazards of the registered substance in relation to the relevant endpoints.

5. Sub-chronic toxicity study (90-day)

a) Examination of the testing proposal

Pursuant to Article 40(3)(c) of the REACH Regulation, ECHA may require the Registrant to carry out one or more additional tests in case of non-compliance of the testing proposal with Annexes IX, X or XI of the REACH Regulation. Pursuant to Article 40(3)(d) ECHA may reject a 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 generate the data for this endpoint.

The Registrant had proposed to carry out the sub-chronic study (90-day) by the oral route. In the light of the physico-chemical properties of the substance and the information provided on the uses and human exposure, ECHA considers that testing by the oral route is appropriate. According to the test method EU B.26/OECD 408 the rat is the preferred rodent species. ECHA considers this species as being appropriate.

The Registrant proposed testing with the read-across substance heptanoic acid. ECHA does not consider the read-across approach justified as explained above and testing shall be performed with the registered substance heptanal.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

<u>Third party information 1:</u>
A third party has proposed a weight-of evidence / read-across approach for ECHA to consider before further tests on animals are requested. As part of this approach, the third party provided results from repeated dose toxicity studies conducted with read-across substance 2,6-dimethylhept-5-en-1-al and dermal study conducted with the registered substance.

As the weight-of-evidence / read-across justifications provided by the third party are not robust enough to allow the conclusion that the requirements of Annex XI, 1.2. / 1.5. of the REACH Regulation are met ECHA concludes that this is not a sufficient basis to fulfil the information requirement.

ECHA acknowledges the information provided by the third party but notes that it is the responsibility of the Registrant to build a weight-of-evidence approach or to use read-across. Furthermore, the registrant has to justify that the criteria set out in Annex XI, 1.2. or 1.5. of the REACH Regulation, respectively, are met and that the information is a sufficient basis to fulfil the information requirement.

Third party information 2:
Another third party has proposed a weight-of evidence / read-across approach for ECHA to consider before further tests on animals are requested. As part of this approach, the third party provided results from repeated dose toxicity studies conducted with read-across substances octanoic acid (CAS No. 124-07-2) and 2-ethylhexanoic acid (CAS No. 149-57-5). The third party refers to the category justification provided in the attached review paper (US EPA Initial Risk-Based Prioritization of High Production Volume Chemicals for the C7-C9 Aliphatic Aldehydes and Carboxylic Acids Category (2009)).

ECHA acknowledges the information provided by the third party but notes that it is the responsibility of the Registrant to build a weight-of-evidence approach or to use read-across. Furthermore, the registrant has to justify that the criteria set out in Annex XI, 1.2. or 1.5. of the REACH Regulation, respectively, are met and that the information is a sufficient basis to fulfil the information requirement.

c) Outcome

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant is required to carry out the following study: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD 408) using the registered substance heptanal, while the proposed test on the read-across substance, heptanoic acid, is rejected in accordance with Article 40(3)(d).

6. Pre-natal developmental toxicity study

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.

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

There is information available on this endpoint only for a pre-natal developmental toxicity study in a first species for the analogue substance heptanoic acid in the technical dossier. There is no information available for a pre-natal developmental toxicity study in a second species. Consequently there is an information gap for Annex X, Section 8.7.2. and it is necessary to provide information for this endpoint.

The Registrant proposed testing in rabbits. He did not specify the route for testing. The test in the first species on the read-across substance was carried out by testing a rodent species and ECHA therefore considers that the test in a second species should be carried out in a non-rodent species. According to the test method EU B.31/OECD 414, the rat is the preferred rodent species and the rabbit is 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 rabbit, as defined under point c) below.

The Registrant proposed testing with a read-across substance heptanoic acid. ECHA considers the read-across approach justified as explained above and testing shall be performed with the read-across substance heptanoic acid or alternatively with the registered substance subject to the present decision, heptanal, as defined under point c) below.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

Third party information 1:
A third party has proposed a strategy for ECHA to consider before further tests on animals are requested. However, third parties were invited, as specified by Article 40(2) of the REACH Regulation to submit "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal". As the proposal for a strategy as such cannot be regarded information or studies, ECHA concludes that this is not a sufficient basis to fulfil the information requirement.

Third party information 2:
A third party has proposed a weight-of evidence / read-across approach for ECHA to consider before further tests on animals are requested. As part of this approach, the third party provided results from a pre-natal developmental toxicity limit study by read-across substance heptanoic acid, and pre-natal developmental toxicity studies conducted with read-across substances octanoic acid (CAS No. 124-07-2), nonanoic acid (CAS No. 112-05-0) and 2-ethylhexanoic acid (CAS No. 149-57-5). The third party refers to the category justification provided in the attached review paper (US EPA Initial Risk-Based Prioritization of High Production Volume Chemicals for the C7-C9 Aliphatic Aldehydes and Carboxylic Acids Category (2009)).

ECHA acknowledges the information provided by the third party but notes that it is the responsibility of the Registrant to build a weight-of-evidence approach or to use read-across. Furthermore, the registrant has to justify that the criteria set out in Annex XI, 1.2. or 1.5. of the REACH Regulation, respectively, are met and that the information is a sufficient basis to fulfil the information requirement.

c) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the following study: Pre-natal developmental toxicity study, oral route (test method: EU B.31/OECD 414) either in rabbits using the read-across substance, heptanoic acid or in rats or rabbits and using the registered substance subject to the present decision,

heptanal.
ECHA notes that based on a toxicokinetic study that the Registrant indicated to perform in its own discretion, the Registrant may be able to demonstrate that based on the toxicokinetic parameters determined, such as C_{max}, AUC (Area Under the Curve), the metabolism of heptanal to heptanoic acid can be considered fast and extensive enough to conclude that the effects observed after heptanal exposure are predominantly caused by the metabolite, heptanoic acid. In such case the required pre-natal developmental toxicity study shall be performed with heptanoic acid.

ECHA also notes that if further investigations, i.e. the proposed toxicokinetic study, of the Registrant, conducted in his own discretion, do not provide sufficient data to substantiate a read-across strategy, the Registrant is requested to conduct the pre-natal developmental toxicity study in rabbits with the registered substance.

7. Deadline to provide the requested information

In his comments, the Registrant requested six more months to provide the required environmental information, i.e. 30 months in total. ECHA notes that the Registrant did not claim any substance-specific technical difficulties in carrying out the proposed tests. The Registrant claimed that the originally-granted 24-month period was not adequate for sequential testing. However, this was not further detailed nor justified by the Registrant. Furthermore, the claims of the Registrant concerning laboratory load as a reason for a longer timeline is general in nature and not substantiated by relevant documentation even though requested by ECHA via separate communication. For these reasons, ECHA did not extend the timeline to 30 months. ECHA considers a 24-month period adequate for the testing required by the present decision.

IV. Adequate identification of the composition of the tested material

The process of evaluation 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 evaluation of the testing proposal. The Registrant must note, however, that this information, or the information submitted by other registrants of the same substance, has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

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. If the registration of the substance covers different grades, the sample used for the new studies must be suitable to assess these.

Finally, there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the studies to be assessed.

V. General requirements for the generation of information and Good Laboratory Practice

ECHA reminds registrants of the requirements of Article 13(4) of the REACH Regulation that ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP). National authorities monitoring GLP maintain lists of test facilities indicating the relevant areas of expertise of each facility.

According to Article 13(3) of the REACH Regulation, tests that are required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or the European Chemicals Agency as being appropriate. Thus, the Registrant shall refer to Commission Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 as adapted to technical progress or to other international test methods recognised as being appropriate and use the applicable test methods to generate the information on the endpoints indicated above.

VI. 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://echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

[redacted]
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Director of Evaluation