~~Confidential~~

Helsinki, 20 April 2022

Addressees
Registrant(s) of JS_Isononanoic Acid_3302-10-1 as listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject to this decision
22 April 2021

Registered substance subject to this decision ("the Substance")
Substance name: 3,5,5-trimethylhexanoic acid
EC number: 221-975-0

Decision number: Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/D)

DECISION TAKEN UNDER ARTICLE 42(1) OF THE REACH REGULATION

By decision of 21 September 2016 ("the original decision") ECHA requested you to submit information by 28 March 2019 in an update of your registration dossier.

Based on Article 42(1) of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA examined the information you submitted with the registration dossier specified in the header above, and concludes that

Your registration still does not comply with the following information requirement(s):

A. Information required from all the Registrants subject to Annex X of REACH

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rabbit), oral route with the registered substance

You are therefore still required to provide this information requested in the original decision.

Reasons for the request(s) are explained in the following appendix:

- Appendix A entitled "Reasons to request information required under Annex X of REACH".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

The respective Member State competent authority (MSCA) and National enforcement authority (NEA) will be informed of this decision. They have the duty under Articles 125 and 126 of Regulation No 1907/2006 to ensure that the requests in the original decision are enforced and complied with and, to that end, inter alia, to carry out checks and impose effective, proportionate and dissuasive penalties[1].

Authorised[2] under the authority of Mike Rasenberg, Director of Hazard Assessment

[1] See paragraph 143 of the judgment of the European Court of Justice of 21 January 2021 in Case C-471/18 P Germany v Esso Raffinage.

[2] 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 A: Reasons to request information required under Annex X of REACH

1. Pre-natal developmental toxicity study in a second species

You were requested to submit information derived with the Substance for the Pre-natal developmental toxicity endpoint.

In the updated registration dossier subject to follow-up evaluation, you have provided the results of a pre-natal developmental toxicity study according to OECD test guideline (TG) 414 (2019), via oral route (gavage), in rabbits, performed with the Substance.

We have assessed the provided information and identified the following issue(s):

To be considered compliant and enable concluding whether the Substance has dangerous properties, a study has to meet the requirements of OECD TG 414.

With regard to dose selection, OECD TG 414 states that *"Unless limited by the physical/chemical nature or biological properties of the test chemical, the highest dose should be chosen with the aim to induce some developmental and/or maternal toxicity (clinical signs or a decrease in body weight) but not death or severe suffering. At least one intermediate dose level should produce minimal observable toxic effects. The lowest dose level should not produce any evidence of either maternal or developmental toxicity. A descending sequence of dose levels should be selected with a view to demonstrating any dosage-related response and no-observed-adverse-effect level (NOAEL) or doses near the limit of detection that would allow the determination of a benchmark dose."*

In addition, the study has to be adequate for the purpose of classification and labelling as stated in Annex I Section 1.0.1. of REACH, *"the objectives of the human health hazard assessment shall be to determine the classification of a substance in accordance with Regulation (EC) No 1272/2008".*

The doses used in the key rabbit study were 0, 25, 80 and 250 mg/kg bw/day. As no adverse maternal or developmental effects were observed, the NOEL was set to 250 mg/kg bw/day.

You indicated that the doses were selected based on a dose range finding study (DRF) which is shortly summarised, with tabular data included, in the updated dossier subject to this follow-up evaluation.

In the rabbit DRF study, pregnant females were treated from gestation day (GD) 6 to 29 with doses of 0, 100 and 250 mg/kg bw/day. There was no effect on clinical condition, food consumption or macropathology. You report that effects were limited to an initial loss in body weight (GD6-7/8) and low overall weight gain (GD6-29) at 100 and 250 mg/kg/day; the maternal body weight loss when adjusted for the gravid uterine weight was also slightly greater at 250 mg/kg/day than in controls.

A high dose of 250 mg/kg/day was therefore selected by you based on the preliminary studies with a low dose of 25 mg/kg/day and an intermediate dose of 80 mg/kg/day to achieve approximate 3-fold dose intervals.

ECHA notes that in the DRF study, there was a very slight initial loss in body weight on GD 6-8 at 250 mg/kg bw/day (0.07 kg). The body weight loss in control rabbits at the same time interval was 0.02 kg. Even though the overall weight gain in the treated rabbits on GD 6-29

was lower than controls, there were no differences in the terminal body weights on GD 29 (3.86 kg at 250 mg/kg bw/day vs. 3.92 kg in controls) or adjusted body weights (3.40 kg at 250 mg/kg bw/day vs. 3.42 kg in controls). There was no effect on clinical condition, food consumption or macropathology.

In the OECD TG 414 key study conducted with rabbits, you reported that no test item related changes were observed in any of the parameters investigated (maternal toxicity or developmental toxicity) in any of the doses tested.

Taken together the results of the DRF study and the key OECD TG 414 study in rabbits, ECHA thus considers that the highest dose used in your pre-natal developmental toxicity study was not chosen in accordance with the aforementioned provisions set out in the EU Test Method B.31 and OECD TG 414.

Consequently, ECHA is of the opinion that the doses used in the study are not justified.

ECHA therefore concludes that the pre-natal developmental toxicity study in rabbits provided by you is not adequate to fulfil the information requirement due to the too low dose range selection in which it also deviated from the test guideline.

ECHA notes that currently, due to too low dose level selection, the study does not allow to conclude whether the Substance has dangerous properties and therefore no conclusion on classification and labelling for developmental toxicity in accordance with the CLP Regulation can be made, as adverse effects on the tested parameters at higher doses cannot be excluded. Thereby the study is inconclusive for hazard assessment.

In your comments to the draft decision, you reiterated that the provided pre-natal developmental toxicity study in rabbits is adequate to fulfil the information requirement and that the study is conclusive for hazard assessment.

You explain that corn oil has been selected as a vehicle because it represents a worst-case scenario in terms of absorption or bioavailability, and ascertains comparability with the existing rat data. You emphasise the need of maximum comparability especially because the available OECD TG 414 rat study shows developmental toxicity at maternally toxic dose level of 200 mg/kg bw/day. However, no toxicity was observed in the rabbit study up to and including 250 mg/kg bw/day, the highest possible dose limited by the corn oil volume of 0.5 ml/kg bw. You admit that other vehicles may have allowed dosing with higher doses but would have prevented the direct comparison with the other reproductive toxicity studies.

Further, you question the scientific benefit of a new developmental toxicity study in rabbits. You argue that there is already a large database in rats and the substance demonstrates a steep dose-response relationship with lethality/morbidity at the highest dose and no or minor toxic effects at the next lower dose level in OECD TGs 414 and 443 rat studies. You assume that an additional developmental toxicity study in rabbits using higher doses, which would induce distinct maternal toxicity, will follow the same pattern, i.e. effects in offspring will probably only occur at doses which cause maternal toxicity and increasing the dose will increase the risk of occurring mortality.

However, ECHA maintains the opinion that the OECD TG 414 study in rabbits has not been conducted using sufficient high dose level and is therefore inconclusive for hazard assessment.

First, with a view to the comments on the extensive rat database, it is noted that pre-natal developmental toxicity studies in two species is an information requirement under Annex X to

REACH (Section 8.7.2.). As also outlined in ECHA's Guidance R.7a (section 7.6.4.2.2), information on two different animal species is needed for a comprehensive assessment of pre-natal developmental toxicity.

Secondly, you do not provide substance-specific evidence that could support your argument that similar results would follow at higher doses in rabbits as those already observed in the rat. Furthermore, you do not substantiate why corn oil allows the highest absorption or bioavailability (and toxicity) in the rabbit compared to other vehicles for the Substance. Lack of developmental toxicity at maternally non-toxic dose levels in rats does not mean that developmental toxicity cannot occur at maternally non-toxic dose levels in rabbits. In addition, developmental toxicity must be always considered for classification and labelling, even when occurring only at maternally toxic dose levels, as outlined in the CLP Regulation.

Thirdly, you note that the rat seems to be more susceptible to toxic effects than the rabbit and that liver toxicity may be considered as a rodent specific effect. However, due to the significant inter-species differences between rat and rabbit, information gathered for the rat cannot be used to inform on dose level selection or predict the reliability of results for the rabbit and vice versa. There is no need to have comparable dose levels or toxicity in rats and rabbits for classification and labelling purposes for developmental toxicity or sexual function and fertility. The main purpose of the reproductive toxicity studies conducted for REACH Regulation is to investigate intrinsic hazardous properties of the Substance.

Therefore, a new study in rabbits with sufficiently high dose levels is needed to address the prenatal developmental toxicity property in the rabbit. The highest dose must aim to be as high as possible without causing deaths or severe suffering.

ECHA conclusion

The original decision requested you to provide a study according to the OECD TG 414.

Taken together the results of the DRF study and the main OECD TG 414 study with rabbits, ECHA considers that the dose levels in the main OECD TG 414 study were not selected according to the principles of EU Test Method B.31, OECD TG 414, i.e. with "*the aim to induce some developmental and/or maternal toxicity (clinical signs or a decrease in body weight) but not death or severe suffering*".

Therefore the provided study is not valid.

As detailed above, ECHA therefore considers that the information requirement addressed by the original decision has not been met and you still have to provide results of the prenatal developmental study in rabbits, oral route using the registered substance, and according to the test guideline EU Test Method B.31/OECD TG 414, as requested in the original decision.

Appendix B: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[3].

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

1. Selection of the Test material(s)

   The Test Material used to generate the new data must be selected taking into account the following:
   - the variation in compositions reported by all members of the joint submission,
   - the boundary composition(s) of the Substance,
   - the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

2. Information on the Test Material needed in the updated dossier
   - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   - The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[4].

[3] https://echa.europa.eu/practical-guides
[4] https://echa.europa.eu/manuals

Appendix C: Procedure

The Substance is listed in the Community rolling action plan (CoRAP) for the start of substance evaluation in 2022/2023.

In accordance with Article 42(1) of the REACH Regulation, the Agency examined the information submitted by you in consequence of decision of 21 September 2016 ("the original decision"). Agency considered that this information did not meet one or more of the requests contained in that decision. Therefore, a new decision-making process was initiated under Article 41 of the REACH Regulation.

This decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and did not amend the request.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix D: List of references - ECHA Guidance[5] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[6]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[7]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[8]

[5] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[6] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[7] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[8] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

Appendix E: Addressees of this decision and the corresponding information requirements applicable to them

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.