~~Confidential~~

Helsinki, 26 October 2023

Addressee(s)
Registrant of JS_1445870-18-7 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
06 October 2022

Registered substance subject to this decision ("the Substance")
Substance name: Hexanoic acid, 3,5,5-trimethyl-, 2,2,6,6-tetramethyl-1-[2-[(3,5,5-trimethyl-1-oxohexyl)oxy]ethyl]-4-piperidinyl ester
EC/List number: 941-267-1

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

DECISION ON TESTING PROPOSAL(S)

Under Article 40 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by ***4 May 2026***.

Requested information must be generated using the Substance unless otherwise specified.

Information required from all the Registrants subject to Annex IX of REACH

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.; test method: OECD TG 408) by oral route, in rats. The study must include the following to investigate the kidney function after administration of the Substance:
    - urinalysis (for specifications see OECD TG 408, paragraph 37); and
    - histopathological examination of the kidneys (for specifications see OECD TG 408, paragraphs 45 and 47); and
    - an additional immunohistochemical staining for alpha-2µ globulin in male rats.

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rat or rabbit).

3. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: EU C.47./OECD TG 210)

4. Long-term toxicity testing on terrestrial invertebrates (triggered by Annex IX, Section 9.4.1., Column 2; test method: EU C.33/OECD TG 222)

The reasons for the decision(s) are explained in Appendix 1.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you in accordance with Articles 10(a) and 12(1) of REACH. The addressee(s) of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

To comply with your information requirements, you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also **update the chemical safety report**, where relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general requirements for testing and reporting new tests under REACH, see Appendix 4.

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

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Mike Rasenberg, Director of Hazard Assessment

Appendix 1: Reasons for the decision
Appendix 2: Procedure
Appendix 3: Addressees of the decision and their individual information requirements
Appendix 4: Conducting and reporting new tests under REACH

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons for the decision

Contents

Reasons related to the information under Annex IX of REACH

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

1 A sub-chronic toxicity study (90 day) is an information requirement under Annex IX, Section 8.6.2.

1.1. Information provided to fulfil the information requirement

2 You have submitted a testing proposal for a Sub-chronic toxicity study (90 day) according to OECD TG 408 with the Substance.

3 ECHA requested your considerations for alternative methods to fulfil the information requirement for Repeated dose toxicity. You provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

4 ECHA agrees that a 90-day study is necessary.

1.2. Specification of the study design

5 You proposed testing in the rat. ECHA agrees with your proposal because the rat is the preferred species according to the OECD TG 408. Therefore, the study must be conducted in the rat.

6 You proposed testing by the oral route. ECHA agrees with your proposal because this route of administration is appropriate to investigate systemic toxicity; Guidance on IRs and CSA, Section R.7.5.4.3.2.

7 In addition, adverse effects were observed in the kidneys of male and female rats in a dose range finding study, and in the kidneys of male rats in a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) with the Substance. This indicates that the kidney is a target organ of the Substance.

8 Alpha-2µ-globulin-mediated nephropathy may occur in male rats. Since this mode of action is not considered relevant to humans, the involvement of alpha-2µ-globulin in the kidney effects is a key parameter for establishing the relevance of the kidney effects for human risk assessment.

9 Therefore, the study must include the following to investigate the kidney function after administration of the Substance:

- urinalysis (for specifications see OECD TG 408, paragraph 37); and
- histopathological examination of the kidneys (for specifications see OECD TG 408, paragraphs 45 and 47); and
- an additional immunohistochemical staining for alpha-2µ globulin in all male rats of the control group and the high dose group, and to further extend the examination to all other dose groups as described in OECD 408, paragraph 47.

10 In the comments to the draft decision, you agree to conduct the requested sub-chronic toxicity study (90-day) in accordance with OECD TG 408 and to include the urinalysis according to OECD TG 408, paragraph 37.

11 ECHA further took account of your proposed alternative testing strategy for the histological analysis, including:

- a histopathological examination of hematoxylin and eosin (H&E) stained kidney slices of all animals in all dose groups;
- a chromotrope-Aniline-Blue (CAB)-staining of kidney slices of all male animals in all dose groups, and;
- confirmation of the association of hyaline droplets with alpha-2µ globulin by exemplary immunohistochemical staining for alpha-2µ globulin in two arbitrarily selected male specimens of control and high dose groups, each.

12 ECHA agrees that a full histopathological examination of the kidneys, for example by a standard H&E staining, is required to be performed in male and female rats, according to OECD TG 408, paragraph 47.

13 Since alpha-2µ globulin-mediated nephropathy occurs only in male rats, ECHA further agrees with your comments indicating that immunohistochemical staining for alpha-2µ globulin on kidney slices of female rats is not scientifically justified.

14 However, the CAB-staining proposed in your comments is not specific for alpha-2µ globulin. Therefore, ECHA does not consider this staining method appropriate to visualize alpha-2µ-globulin. Furthermore, conducting the immunohistochemical staining for alpha-2µ globulin in two male rats of the control group and the high dose group will not provide reliable results to conclude that the underlying mechanism of the observed kidney effects in the male rats is solely alpha-2µ globulin-mediated. Therefore, the immunohistochemical staining for alpha-2µ globulin must be conducted in all male rats of the control group and the high dose group, and further extended to all other dose groups as described in OECD 408, paragraph 47.

1.3. Outcome

15 Under Article 40(3)(b) your testing proposal is accepted under modified conditions, and you are requested to conduct the test with the Substance, as specified above.

2. Pre-natal developmental toxicity study

16 A pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is an information requirement under Annex IX, Section 8.7.2.

2.1. Information provided to fulfil the information requirement

17 You have submitted a testing proposal for a PNDT study according to the OECD TG 414 by the oral route with the Substance.

18 ECHA requested your considerations for alternative methods to fulfil the information requirement for Developmental toxicity. You provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

19 ECHA agrees that a PNDT study in a first species is necessary.

2.2. Specification of the study design

20 You proposed testing in the rat as a first species. You may select between the rat or the rabbit because both are preferred species under the OECD TG 414 (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

21 You proposed testing by the oral route. ECHA agrees with your proposal because this route of administration is the most appropriate to investigate reproductive toxicity (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

2.3. Outcome

22 Your testing proposal is accepted under Article 40(3)(a) and you are requested to conduct the test, as specified above.

23 In the comments to the draft decision, you agree to perform the requested study.

3. Long-term toxicity testing on fish

24 Long-term toxicity testing on fish is an information requirement under Annex IX to REACH (Section 9.1.6.).

3.1. Information provided to fulfil the information requirement

25 You have submitted a testing proposal for a Fish, Early-Life Stage Toxicity Test (test method: OECD TG 210).

26 Your registration dossier does not include any information on long-term toxicity on fish.

27 ECHA requested your considerations for alternative methods to fulfil the information requirement for long-term toxicity on fish. You provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

28 ECHA agrees that an appropriate study on long-term toxicity on fish is needed.

3.2. Test selection and study specifications

29 The proposed Fish, Early-Life Stage Toxicity Test (test method: OECD TG 210) is appropriate to cover the information requirement for long-term toxicity on fish (Guidance on IRs and CSA, Section R.7.8.4.1.).

30 The Substance is difficult to test due to the low water solubility (<0.4 ug/L) and adsorptive properties (log Kow >6.5). OECD TG 210 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 210. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solutions.

3.3. Outcome

31 Your testing proposal is accepted under Article 40(3)(a) and you are requested to conduct the test, as specified above.

32 In the comments to the draft decision, you agree to perform the requested study.

4. Long-term toxicity testing on terrestrial invertebrates

33 Short-term toxicity to invertebrates is an information requirement under Annex IX to REACH (Section 9.4.1). Long-term toxicity testing must be considered (Annex IX, Section 9.4., column 2) if the substance has a high potential to adsorb to soil or is very persistent.

4.1. Information provided to fulfil the information requirement

34 You have submitted a testing proposal for an Earthworm Reproduction Test (EU C.33/OECD TG 222).

35 Your registration dossier does not include any information on long-term toxicity to terrestrial invertebrates.

36 ECHA has assessed your testing proposal and notes the following:

37 Under Annex IX, Section 9.4., column 2, for substances that have a high potential to adsorb to soil or that are very persistent, long-term toxicity testing must be considered instead of short-term. Guidance on IRs and CSA, Section R.7.11.5.3. clarifies that a substance is considered to be very persistent in soil if it has a half-life >180 days. In the absence of specific soil data, high persistence is assumed unless the substance is readily biodegradable.

38 Based on the information from your registration dossier the Substance has a high potential to adsorb to soil and is potentially very persistent:

- the Substance is considered to have high adsorption potential to soil as you report a logKow value of > 6.5 based on OECD TG 117;
- the Substance is considered to be highly persistent in soil as it is considered as not readily biodegradable based on an OECD 301 B study (<10% degradation after 28d).

39 On this basis information on long-term toxicity on terrestrial invertebrates must be provided.

40 ECHA agrees that an appropriate long-term toxicity study on terrestrial invertebrates is needed.

4.2. Test selection and study specifications

41 The proposed Earthworm Reproduction Test (EU C.33/OECD TG 222) is appropriate to cover the information requirement for long-term toxicity on terrestrial invertebrates (Guidance on IRs and CSA, Section R.7.11.3.1).

4.3. Outcome

42 Your testing proposal is accepted under Article 40(3)(a) and you are requested to conduct the test with the Substance, as specified above.

43 In the comments to the draft decision, you agree to perform the requested study.

References

The following documents may have been cited in the decision.

Guidance on information requirements and chemical safety assessment (Guidance on IRs & CSA)

Chapter R.4 Evaluation of available information; ECHA (2011).
Chapter R.6 QSARs, read-across and grouping; ECHA (2008).
Appendix to Chapter R.6 for nanoforms; ECHA (2019).
Chapter R.7a Endpoint specific guidance, Sections R.7.1 – R.7.7; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Chapter R.7b Endpoint specific guidance, Sections R.7.8 – R.7.9; ECHA (2017).
Appendix to Chapter R.7b for nanomaterials; ECHA (2017).
Chapter R.7c Endpoint specific guidance, Sections R.7.10 – R.7.13; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Appendix R.7.13-2 Environmental risk assessment for metals and metal compounds; ECHA (2008).
Chapter R.11 PBT/vPvB assessment; ECHA (2017).
Chapter R.16 Environmental exposure assessment; ECHA (2016).

Guidance on data-sharing; ECHA (2017).
Guidance for monomers and polymers; ECHA (2012).
Guidance on intermediates; ECHA (2010).

All guidance documents are available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

RAAF, 2017 Read-across assessment framework (RAAF); ECHA (2017)
RAAF UVCB, 2017 Read-across assessment framework (RAAF) – considerations on multi- constituent substances and UVCBs); ECHA (2017).

The RAAF and related documents are available online:
https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

***OECD Guidance documents* (OECD GDs)**

OECD GD 23 Guidance document on aquatic toxicity testing of difficult substances and mixtures; No. 23 in the OECD series on testing and assessment, OECD (2019).
OECD GD 29 Guidance document on transformation/dissolution of metals and metal compounds in aqueous media; No. 29 in the OECD series on testing and assessment, OECD (2002).
OECD GD 150 Revised guidance document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption; No. 150 in the OECD series on testing and assessment, OECD (2018).
OECD GD 151 Guidance document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test; No. 151 in the OECD series on testing and assessment, OECD (2013).

Appendix 2: Procedure

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 5 January 2023.

ECHA held a third-party consultation for the testing proposal(s) from 31 January 2023 until 17 March 2023. ECHA did not receive information from third parties.

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

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 12 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

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(s).

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 3: Addressee(s) of this decision and their corresponding information requirements

In accordance with Articles 10(a) and 12(1) of REACH, the information requirements for individual registrations are defined as follows:

- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;

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.

Appendix 4: Conducting and reporting new tests for REACH purposes

1. Requirements when conducting and reporting new tests for REACH purposes

1.1. 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[2].

(4) Under the introductory part of Annexes VII/VIII/IX/X to REACH, where a test method offers flexibility in the study design, for example in relation to the choice of dose levels or concentrations, the chosen study design must ensure that the data generated are adequate for hazard identification and risk assessment.

1.2. Test material

(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 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[3].

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

2. General recommendations for conducting and reporting new tests

2.1. Environmental testing for substances containing multiple constituents

Your Substance contains multiple constituents and as indicated in Guidance on IRs & CSA, Section R.11.4.2.2, you are advised to consider the following approaches for persistency, bioaccumulation and aquatic toxicity testing:

- the "known constituents approach" (by assessing specific constituents), or
- the "fraction/block approach, (performed on the basis of fractions/blocks of constituents), or
- the "whole substance approach", or
- various combinations of the approaches described above

Selection of the appropriate approach must take into account the possibility to characterise the Substance (i.e., knowledge of its constituents and/or fractions and any differences in their properties) and the possibility to isolate or synthesize its relevant constituents and/or fractions.

References to Guidance on REACH and other supporting documents can be found in Appendix 1.