~~Confidential~~

Helsinki, 18 January 2024

Addressee(s)
Registrant(s) of JS_945-883-1 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
14 December 2020

Registered substance subject to this decision ("the Substance")
Substance name: 3,5,5-Trimethylhexanoic acid, mixed esters with dipentaerythritol and heptanoic acid
EC/List number: 945-883-1

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by ***26 January 2026***.

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

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

1. Long-term toxicity testing on aquatic invertebrates (triggered by Annex VII, Section 9.1.1., Column 2; test method: EU C.20./OECD TG 211).

2. Growth inhibition study on aquatic plants (Annex VII, Section 9.1.2.; test method: EU C.3/OECD TG 201).

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

3. *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: EU B.17./OECD TG 476 or EU B.67./OECD TG 490).

4. Screening study for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) by oral route, in rats.

5. Long-term toxicity testing on fish (triggered by Annex VIII, Section 9.1.3., Column 2; test method: EU C.47./OECD TG 210).

The reasons for the request(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.

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 request(s)
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.

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Appendix 1: Reasons for the request(s)

Reasons related to the information under Annex VII of REACH

1. Long-term toxicity testing on aquatic invertebrates

1 Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII, Column 1, Section 9.1.1. However, under Column 2, long-term toxicity testing on aquatic invertebrates may be required by the Agency if the substance is poorly water soluble, i.e. solubility below 1 mg/L.

1.1. Triggering of the information requirement

2 In the provided OECD TG 105 (2018), the saturation concentration of the Substance in water was determined to be <1mg/L. In addition, you have provided QSAR predictions on different examples of possible structures for the constituents of the Substance which show that all those constituents are expected to be poorly water soluble (predicted water solubility <0.00001 mg/L).

3 Therefore, the Substance is poorly water soluble and information on long-term toxicity on aquatic invertebrates must be provided.

1.2. Information requirement not fulfilled

4 You have provided a short-term toxicity study on aquatic invertebrates but no information on long-term toxicity on aquatic invertebrates for the Substance.

5 Therefore, the information requirement is not fulfilled.

1.3. Study design

6 The Substance is difficult to test due to the low water solubility (<1 mg/L) and adsorptive properties (log Koc >5.63). OECD TG 211 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 211. 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 solution.

7 For multi-constituents/UVCBs, the analytical method must be adequate to monitor qualitative and quantitative changes in exposure to the dissolved fraction of the test material during the test (e.g. by comparing mass spectral full-scan GC or HPLC chromatogram peak areas or by using targeted measures of key constituents or groups of constituents).

8 If you decide to use the Water Accommodated Fraction (WAF) approach, in addition to the above, you must:

- provide a full description of the method used to prepare the WAF (including, among others, loading rates, details on the mixing procedure, method to separate any remaining non-dissolved test material including a justification for the separation technique);

- prepare WAFs separately for each dose level (i.e. loading rate) and in a consistent manner.

2. Growth inhibition study aquatic plants

9 Growth inhibition study on aquatic plants is an information requirement under Annex VII to REACH (Section 9.1.2.).

2.1. Information provided

10 You have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on experimental data from the following substance(s):

(i) Growth inhibition study on aquatic plants/algae (2000) with the source substance "Dipentaerythritol with fatty acids, C5 and C9iso" (EC 444-000-2).

11 You provide a read-across justification document in IUCLID Section 13.

12 ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted to be quantitatively equal to those of the source substance.

2.2. Assessment of the information provided

2.2.1. Inadequate or unreliable study on the source substance

13 Under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 201, and meet the specifications of OECD GD 23 if the substance is difficult to test. Therefore, the following specifications must be met:

Validity criteria

a) exponential growth in the control cultures is observed over the entire duration of the test;

b) the mean coefficient of variation for section-by-section specific growth rates (days 0-1, 1-2 and 2-3, for 72-hour tests) in the control cultures is ≤ 35%;

Technical specifications impacting the sensitivity/reliability of the test

c) for *Desmodesmus subspicatus* the initial cell density is 2-5 x10^3 cells/mL;

Characterisation of exposure

d) where a measured concentration at the end of the exposure period indicates that the substance is not detected, the concentration may be taken as the limit of detection for the method (Guidance on IRs & CSA Chapter R.7b, Appendix R.7.8—1).

14 In the study provided:

Validity criteria

a) exponential growth in the control cultures was not observed over the entire duration of the test. The raw data presented in Table 1 of the robust study summary (RSS) show that the control cultures did not growth exponentially

over the entire duration of the test. The cell density increases only very slowly after 24 hours;

b) the mean coefficient of variation for section-by-section specific growth in the control was above 35%. Coefficients of variation are not presented in the RSS, but can be recalculated from the raw data presented in Table 1 of the RSS. Based on those data, the mean coefficient of variation for section-by-section specific growth rates in the control cultures is calculated to be 131%, i.e. well above the threshold of 35% required by the current applicable version of the OECD 201 test guideline;

Technical specifications impacting the sensitivity/reliability of the test

c) the test was conducted on *Desmodesmus subspicatus* and the initial cell density appears to have exceed 5 $x10^3$ cells/mL in at least one control group. The information reported in the RSS for the initial cell density is contradictory. The initial cell density is said to be 10^4 cells/mL in section "Details on test conditions" in the RSS, whereas measured cell densities at t_0 are reported in Table 1 of the RSS as 6.65 $x10^3$, 5 $x10^3$ and 5 $x10^3$ cells/mL for control replicates R1, R2 and R3 respectively;

Characterisation of exposure

d) the test item could not be detected at the beginning of the exposure period. Its concentration was below the limit of quantification of 0.18 mg/L of the analytical method used, but the effect concentrations were reported based on nominal concentrations.

15 Based on the above,

- the validity criteria of OECD TG 201 are not met
- there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, the current applicable version of OECD 201 recommends an initial cell density of 2 - 5 $x10^3$ cells/mL for *Desmodesmus subspicatus*. It explains that the initial biomass in the test cultures should be sufficiently low to allow exponential growth throughout the incubation period without risk of nutrient depletion. The raw data presented in Table 1 of the RSS show that exponential growth in the control was not maintained over the entire duration of the test. A rapid increase of biomass was followed by a much lower increase after 24 hours. A possible explanation could be the too high initial cell density which may have caused a depletion of nutrients or of CO_2 in the test medium. This is also reflected by the very high mean coefficient of variation for section-by-section specific growth rates in the control cultures: it indicates that the specific growth rates in the controls differs dramatically throughout the duration of the test.

16 On this basis, the specifications of OECD TG 201 are not met.

17 Based on the above, the study submitted in your adaptation, as currently reported in your dossier, does not provide an adequate and reliable coverage of the key parameters of the corresponding OECD TG.

18 As explained above, you have not established that relevant properties of the Substance can be predicted from data on the source substance. On this basis, your read-across approach under Annex XI, Section 1.5. is rejected.

19 Therefore, the information requirement is not fulfilled.

2.3. Study design

20 OECD TG 201 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in "Study design" under request 1.

Reasons related to the information under Annex VIII of REACH

3. *In vitro* gene mutation study in mammalian cells

21 An *in vitro* gene mutation study in mammalian cells is an information requirement under Annex VIII, Section 8.4.3., in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

3.1. Triggering of the information requirement

22 Your dossier contains negative results for both an *in vitro* gene mutation study in bacteria and an adequate *in vitro* cytogenicity study.

23 Therefore, the information requirement is triggered.

3.2. Information provided

24 You have adapted this information requirement by using Annex XI, Section 1.3. (Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs). To support the adaptation, you have provided the following information:

(i) a prediction from Danish (Q)SAR database/models (2020).

3.3. Assessment of the information provided

3.3.1. (Q)SAR adaptation rejected

25 Under Annex XI, Section 1.3., the following conditions must be fulfilled whenever a (Q)SAR approach is used:

(1) the prediction needs to be derived from a scientifically valid model,

(2) the substance must fall within the applicability domain of the model,

(3) results need to be adequate for the purpose of risk assessment or classification and labelling, and

(4) adequate and reliable documentation of the method must be provided.

3.3.1.1. The prediction is not adequate due to low reliability

26 Under ECHA Guidance R.6.1.3.4. a prediction is adequate for the purpose of classification and labelling and/or risk assessment when the model is applicable to the chemical of interest with the necessary level of reliability. ECHA Guidance R.6.1.5.3. specifies that, among others, the following cumulative conditions must be met:

- the model predicts well substances that are similar to the substance of interest, and
- reliable input parameters are used, and
- the prediction is consistent with other information available (e.g. for related endpoint(s)).

27 Your registration dossier provides the following information:

- an endpoint study record containing of 13 attachments (9 QMRFs and 4 QPRFs) describing the predictions of selected structures i.e. constituents of the Substance.

28 The following information is also available for the selected structures used as input for the prediction:

- Three analogues for the in vivo Comet assay prediction
- five analogues for the in vitro HGPRT-locus prediction, and
- ten analogues for the in vitro TK-locus prediction.
- The similarity of each analogue to the selected structures.

29 The prediction(s) for the selected structures used as input are not reliable because you have not demonstrated that the model predicts well substances that are similar to the selected structures, i.e. constituents of the Substance given the low similarity (at or below 50%) between the analogues and the selected structures reported in the QPRFs.

30 Therefore, you have not demonstrated that the prediction for the Substance is adequate for the purpose of classification and labelling and/or risk assessment.

31 Based on the above, your QSAR adaptation under Annex XI, Section 1.3. is rejected.

32 Therefore, the information requirement is not fulfilled.

3.4. Study design

33 To fulfil the information requirement for the Substance, either the *in vitro* mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) or the thymidine kinase gene (OECD TG 490) are considered suitable.

4. Screening study for reproductive/developmental toxicity

34 A screening study for reproductive/developmental toxicity study (OECD TG 421 or OECD TG 422) is an information requirement under Annex VIII, Section 8.7.1.

4.1. Information provided

35 You have adapted this information requirement by using Annex VIII, Section 8.7.1., Column 2. To support the adaptation, you have provided the following information:

(i) Prenatal developmental toxicity study (2004) with Trimethylolpropane caprylate caprate (CAS 11138-60-6, currently identified as EC 812-652-0 Fatty acids, C8-10-(even numbered), diesters and triesters with trimethylolpropane).

36 As you submitted a study on an analogue substance, that study is assessed under Annex XI, Section 1.5.

37 In addition, you have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on experimental data from the following substances:

(ii) a sub-acute repeated dose toxicity study (28-days) (1999) with the source substance Dipentaerythritol hexaesters of nC5/iC9 acids, EC 444-000-2.

38 You provide a read-across justification document in IUCLID Section 13.

39 ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted to be quantitatively equal to those of the source substance.

4.2. Assessment of the information provided

4.2.1. Source studies not adequate for the information requirement

40 Under Annex XI, Section 1.5., the study to be read across must have an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in the case of a Column 2 adaptation, OECD TG 414. Therefore, the following specifications must be met:

a) the exposure duration is at least from implantation until one day prior to scheduled caesarean section;

b) the route of administration is oral if the substance is a solid or liquid. A justification is provided in case of deviations (Annex IX, Section 8.7.2.).

41 In study (i):

a) the exposure duration was 10 days;

b) the route of administration was dermal rather than oral despite the substance being a liquid and no justification for the deviation was provided.

42 The information provided does not give adequate and reliable coverage of the key parameters of by the OECD TG 414.

43 Therefore, the provided study is not reliable.

44 Under Annex XI, Section 1.5., the study to be read across must have an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case EU B.63/OECD TG 421 or EU B.64/OECD TG 422. Therefore, the following specifications must be met:

a) at least 10 male and 12-13 female animals are included for each dose and control group;

b) the exposure duration is at least four weeks for males, including a minimum of two weeks prior to mating, and approximately 63 days for females to cover premating, conception, pregnancy and at least 13 days of lactation;

c) parameters for sexual function and fertility such as those for mating and fertility/duration of gestation, parturition and lactation are reported;

d) oestrous cycles are monitored;

e) offspring parameters such as number and sex of pups/stillbirths and live births/gross abnormalities/pup body weight/litter weight/anogenital distance/nipple retention in male pups are reported.

45 In study (ii):

a) a) 5 males/females (i.e., less than 10 male animals/12-13 female animals) were included in each dose and control group;

b) the exposure duration was 28 days for females (i.e., less than 63 days for females);

c) data on parameters for sexual function and fertility such as those for mating and fertility/duration of gestation, parturition and lactation are missing, as in the study provided these parameters were not investigated;

d) data on oestrous cycles is missing;

e) data on number and sex of pups/stillbirths and live births/gross abnormalities/pup body weight/litter weight/anogenital distance/nipple retention in male pups is missing, as in the study provided these parameters are not investigated.

46 The information provided does not give adequate and reliable coverage of the key parameters of OECD TG 421/422.

47 Therefore, the provided study is not reliable.

48 Based on the above, your adaptation is rejected.

4.3. Study design

49 A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats.

50 As the Substance is a liquid, the study must be conducted with oral administration of the Substance (Annex VIII, Section 8.7.1., Column 1).

51 In addition, you consider under toxicokinetic assessment that dermal absorption potential is considered to be low due to the properties of the Substance. Therefore, there is no evidence of equivalent or higher systemic exposure via another relevant route of human exposure.

52 Therefore, the study must be conducted in rats with oral administration of the Substance.

5. Long-term toxicity testing on fish

53 Short-term toxicity testing on fish is an information requirement under Annex VIII, Column 1, Section 9.1.3. However, long-term toxicity testing on fish may be required by the Agency (Section 9.1.3., Column 2) if the substance is poorly water soluble, i.e. solubility below 1 mg/L.

5.1. Triggering of the information requirement

54 As already explained in request 1, the Substance is poorly water soluble and information on long-term toxicity on fish must be provided.

5.2. Information requirement not fulfilled

55 You have provided a short-term toxicity study on fish but no information on long-term toxicity on fish for the Substance.

56 Therefore, the information requirement is not fulfilled.

5.3. Study design

57 To fulfil the information requirement for the Substance, the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is the most appropriate (Guidance on IRs and CSA, Section R.7.8.2.).

58 OECD TG 210 specifies that, for difficult to test substances, OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in "Study design" under request 1.

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 (2023).
***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

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.

The compliance check was initiated on 16 November 2022.

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

ECHA did not receive any comments within the commenting period.

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 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 and VIII to REACH, for registration at 10-100 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 (https://echa.europa.eu/practical-guides).

(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/group of constituents on the test results for the endpoint to be assessed. For example, if a constituent/group of constituents of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/group of constituents.

(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 the careful identification and description of the characteristics of the Tests Materials in accordance with OECD GLP (ENV/MC/CHEM(98)16) and EU Test Methods Regulation (EU) 440/2008 (Note, Annex), namely all the constituents must be identified as far as possible as well as their concentration. Also any constituents that have harmonised classification and labelling according to the CLP Regulation must be identified and quantified using the appropriate analytical methods.

With that detailed information, ECHA can confirm whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers (https://echa.europa.eu/manuals).