~~Confidential~~

Helsinki, 13 April 2022

Addressees
Registrants of JS_Heptanal as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
18/06/2019

Registered substance subject to this decision ("the Substance")
Substance name: Heptanal
EC number: 203-898-4
CAS number: 111-71-7

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 the deadline of ***18 January 2024***.

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

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

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: EU B.13/14. / OECD TG 471)

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

1. If negative results are obtained in test performed for the information requirement of Annex VIII, Section 8.4.2. then: In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490)

2. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: OECD TG 203)

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

1. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: EU C.20./OECD TG 211)

2. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: OECD TG 210)

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

- Appendix entitled "Reasons common to several requests";
- Appendices entitled "Reasons to request information required under Annexes VII to X of REACH", respectively.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

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 testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

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

[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 A: Reasons to request information required under Annex VII of REACH

1. In vitro gene mutation study in bacteria

An *in vitro* gene mutation study in bacteria is an information requirement under Annex VII to REACH (Section 8.4.1.).

You have provided key studies in your dossier with the Substance:

i. *In vitro* gene mutation study in bacteria (Zeiger, 1992), equivalent or similar to OECD 471, not GLP specified with the following strains, TA 98, TA 100, TA 1535, TA 1537 which all gave negative results,

ii. *In vitro* gene mutation study in bacteria (Florin, 1980), equivalent or similar to OECD 471, not GLP, with the following strains, TA 98, TA 100, TA 1535, TA 1537 which all gave negative results.

We have assessed this information and identified the following issues:
To fulfil the information requirement, the study has to meet the requirements of OECD TG 471[2] (1997). The key parameters of this test guideline include:

a) The test must be performed with 5 strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101)
b) The maximum dose tested must induce a reduction in the number of revertant colonies per plate compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test dose must correspond to 5 mg/plate or 5 ml/plate.
c) At least 5 doses must be evaluated, in each test condition.
d) Triplicate plating must be used at each dose level.
e) One positive control must be included in the study. The positive control substance must produce a statistically significant increase in the number of revertant colonies per plate compared with the concurrent negative control.
f) The number of revertant colonies per plate for the concurrent negative control must be inside the historical control range of the laboratory.
g) The mean number of revertant colonies per plate must be reported for the treated doses and the controls.

The reported data for the studies (i-ii) you have provided did not include:

a) the required fifth strain, *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101).
b) a maximum dose of 5 mg/plate or 5 ml/plate or that induced a reduction in the number of revertant colonies per plate compared to the negative control, or the precipitation of the tested substance.
c) the evaluation of at least 5 doses in each test condition, only one dose in the study ii
d) triplicate plating at each dose level.
e) a positive control that produced a statistically significant increase in the number of revertant colonies per plate compared with the concurrent negative control.
f) a negative control with a number of revertant colonies per plate inside the historical control range of the laboratory.
g) data on the number of revertant colonies per plate for the treated doses and the controls.

The information provided does not cover the key parameters required by OECD TG 471.

Therefore, the information requirement is not fulfilled.

[2] ECHA Guidance R.7a, Table R.7.7–2, p.557

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

Appendix B: Reasons to request information required under Annex VIII of REACH

1. In vitro gene mutation study in mammalian cells

An *in vitro* gene mutation study in mammalian cells is an information requirement under Annex VIII to REACH (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.

i. Triggering of the study

Your dossier contains (i) a negative result for *in vitro* cytogenicity study in mammalian cells and (ii) inadequate data for the *in vitro* gene mutation study in bacteria.

The *in vitro* gene mutation study in bacteria provided in the dossier is rejected for the reasons provided in section A.

The result of the request for information in Appendix A.1 will determine whether the present requirement for an *in vitro* mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3 is triggered.

ii. Assessment of information provided

You have provided a key study in your dossier:

i. *in vitro* gene mutation in mammalian cells ([redacted], 1981), equivalent or similar to OECD TG 476, not GLP

We have assessed this information and identified the following issues:

To fulfil the information requirement, the *in vitro* gene mutation study on mammalian cells has to meet the requirements of OECD TG 476 or OECD TG 490[3]. The key parameter(s) of these test guidelines include:

a) The maximum concentration tested must induce 80-90% of cytotoxicity compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test concentration must correspond to 10 mM, 2 mg/mL or 2 µl/mL, whichever is the lowest.
b) At least 4 concentrations must be evaluated, in each test condition.
c) One positive control must be included in the study. The positive control substance must produce a statistically significant increase in the response compared with the concurrent negative control.
d) The response for the concurrent negative control must be inside the historical control range of the laboratory.

The reported data for the studies you have provided do not include:

a) a maximum tested concentration of 10 mM, 2 mg/mL or 2 µl/mL, or that induced 80-90% of cytotoxicity compared to the negative control, or the precipitation of the tested substance. However, the cytotoxicity reported is higher than 90% starting at 50 nL/mL and up, in the assay without metabolic activation.
b) the evaluation of at least 4 concentrations in each test condition. However, due to the excessive cytotoxicity in the assay without metabolic activation, only 3 test concentrations, instead of 4, meet the acceptability criteria (appropriate cytotoxicity) to be evaluated
c) one positive control that produced a statistically significant increase in the number of revertant colonies per plate compared with the concurrent negative control. However,

[3] ECHA Guidance R.7a, Table R.7.7–2, p.557

there is no data reported on the positive control.

d) a negative control with a response inside the historical control range of the laboratory. However, there is no information on the historical control data.

Based on the above, the information provided does not cover key parameters required by OECD TG 476/490.

Therefore, the information requirement is not fulfilled.

Consequently, you are required to provide information for this endpoint, if the *in vitro* gene mutation study in bacteria provides a negative result.

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

Study design

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

2. Short-term toxicity testing on fish

Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH (Section 9.1.3.).

You have provided the following information:

i. TG 203, key study, Heptanal: Acute toxicity to *Salmo gairdneri, Daphnia magna* and *Selenastrum capricornutum*. [redacted] 1982.

We have assessed this information and identified the following issue[s]:

To fulfil the information requirement, a study must comply with OECD TG 203 and the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following specifications must be met:

Validity criteria

- the analytical measurement of test concentrations is conducted.

  However, no analytical measurement of test concentrations was conducted.

Technical specifications impacting the sensitivity/reliability of the test

- although not generally recommended, if a solvent is used, its concentration in the test water is below its critical micelle concentration (if relevant) and, in all case, ≤ 100 mg/L (or 0.1 mL/L).

  However, the concentration of solvent present in the test solutions was 0.5 mL/L i.e. 0.05% v/v.

- the photoperiod is adequate for the selected test species.

  However, the photoperiod is not known.

Based on the above, the validity criteria of OECD TG 203 are not met, since there is no analytical monitoring of exposure concentrations. In addition, there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, the applied solvent concentration exceeds the recommended maximum in

the TG 203. Also, the photoperiod during the test is not known. Therefore, the requirements of OECD TG 203 are not met.

On this basis, the information requirement is not fulfilled.

In your comments to the draft decision, you acknowledge that the provided study "*is not entirely reliable nor fully compliant with the standard requirements*". Instead of performing a new OECD TG 203 study as requested, you propose to perform the long-term toxicity to fish study (OECD TG 210) requested in Appendix C.2.

REACH Annex VIII section 9.1.3., column 2 specifies that the short-term toxicity study does not need to be conducted if a long-term aquatic toxicity study on invertebrates is available. At present no long-term toxicity study on fish is provided in the IUCLID dossier, therefore no conclusion on the compliance can currently be made. Please note that this decision does not consider updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation). You remain responsible for complying with this decision by the set deadline.

Study design

The Substance is difficult to test due to the relatively high vapour pressure 660 Pa at 25 °C. OECD TG 203 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 203. 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.

Appendix C: Reasons to request information required under Annex IX of REACH

1. Long-term toxicity testing on aquatic invertebrates

Long-term toxicity testing on aquatic invertebrates is an information requirement under Annex IX to REACH (Section 9.1.5.).

You have provided the following information:

i. TG 211, *Daphnia magna* reproduction test, key study, [redacted] 2016.

We have assessed this information and identified the following issue:

To fulfil the information requirement, a study must comply with the OECD TG 211 and the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following specifications must be met:

Characterisation of exposure

- a reliable analytical method for the quantification of the test material in the test solutions with reported specificity, recovery efficiency, precision, limits of determination (i.e. detection and quantification) and working range must be available.

  However, you have not provided performance parameters of the analytical method (i.e. recovery efficiency).

- the nominal test concentrations and the results of all analyses to determine the concentration of the test substance in the test vessels are reported.

  However, the detailed results of the analyses to determine the concentration of the test substance in the test vessels are not provided.

- water quality monitoring within the test vessels (*i.e.* pH, temperature and dissolved oxygen concentration, and TOC and/or COD and hardness where applicable) is reported.

  However, water quality monitoring within the test vessels (pH, temperature and dissolved oxygen concentration) are not reported.

- the full record of the daily production of living offspring during the test [by each parent animal/in each replicate] is provided.

  However, the full record of the daily production of living offspring during the test by each parent animal is not provided.

- the coefficient of variation for control reproductive output is reported.

  However, the coefficient of variation for control reproductive output is not reported.

Based on the above, the reporting of the study is not sufficient to conduct an independent assessment of its reliability. The missing information includes recovery efficiency of the analytical method and detailed results of the analyses to determine the concentration of the test substance in the test vessels. In addition, water quality monitoring within the test vessels and the full record of the daily production of living offspring during the test by each parent animal are not provided. Also, the coefficient of variation for control

reproductive output is not reported. Therefore, the requirements of OECD TG 211 are not met.

On this basis, the information requirement is not fulfilled.

In your comments, you submitted the missing information identified above, supported by the original study report. ECHA has assessed the information against the requirement in OECD TG 211. The information you have provided in your comments addresses the incompliances identified in this decision for this information requirement. However, as the information is currently not available in your registration dossier, the data gap remains. You should therefore submit this information in an updated registration dossier by the deadline set out in the decision.

Study design

OECD TG 211 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 Appendix B.2.

2. Long-term toxicity testing on fish

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

You have provided the following information:

- a justification to omit the study which you consider to be based on Annex IX, Section 9.1., Column 2. In support of your adaptation, you provided the following justification:
    - *In accordance with column 2 of REACH Annex IX, long-term toxicity testing on fish does not need to be proposed by the registrant as the chemical safety assessment according to Annex I indicates no need to investigate further the effects on aquatic organisms, as indicated in the integrated testing strategy of ECHA's Guidance on information requirements and chemical safety assessment, chapter R7b (v3.0 ; Feb 2016 ; p. 59).*

We have assessed this information and identified the following issue:

Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to fish under Column 1. It must be understood as a trigger for providing further information on long-term toxicity to fish if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

Your adaptation is therefore rejected.

On this basis, the information requirement is not fulfilled.

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

Study design

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 Appendix B.2.

Appendix D: 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[4].

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 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[5].

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

Appendix E: 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 4 May 2021.

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).

In your comments on the draft decision, you requested an extension of the deadline to provide the requested information from 12 to 18 months from the date of adoption of the decision. You justify the extension by the limited lab capacity to conduct studies according to OECD TG 210 and you provide a letter from a Contract Research Organisation (CRO) in support of your request.

On this basis, ECHA has extended the deadline to 18 months.

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 F: List of references - ECHA Guidance[6] 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)[7]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[8]

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[9]

[6] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[7] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[8] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[9] 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 G: Addressees of this decision and their corresponding information requirements

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]
[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.