~~Confidential~~

Helsinki, 20 May 2024

Addressee
Registrant of JS_448-300-4 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
15 July 2020

Registered substance subject to this decision ("the Substance")
Substance name: Reaction mass of trans-Cyclohexadecen-8-one, cis-Cyclohexadecen-8-one, trans-Cyclohexadecen-7-one, cis-Cyclohexadecen-7-one
EC/List number: 448-300-4

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 ***27 May 2027***.

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 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. Screening 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

4. 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 of the decision and its 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.

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 (2005), the saturation concentration of the Substance in water was determined to be 0.982 mg/L.

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

4 In your comments to the initial draft decision, you point out that long-term testing would only be needed under the condition that it is unlikely that short-term toxicity testing can provide a true measure of the intrinsic aquatic toxicity of the substance, and that ECHA would not have shown that this is the case.

5 However, the legal provision in Annex VII, Colum 2, last paragraph, explicitly mentions two scenarios in which it is legally presumed that it is unlikely that short-term toxicity testing can provide a true measure of the intrinsic aquatic toxicity of the substance, and the first of these is "*if the substance is poorly water soluble (solubility below 1 mg/L)*". As explained above, the available data show that this condition is met.

1.2. Information requirement not fulfilled

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

7 In the comments to the draft decision, you indicate that you intend to adapt this information requirement by means of grouping and read-across according to Annex XI, Section 1.5, of the REACH Regulation.

8 You propose to predict the long-term toxicity on aquatic invertebrates of the Substance from new study(ies) on source substance "mixture of cis- and trans-Cyclohexadecen-8-one isomers" (EC number 401-70).

9 As this strategy relies on a read-across approach that has not yet been fully described and justified, as well as on data which is not yet to be provided for the proposed source substance, no conclusion on the compliance of the proposed adaptation can be made.

10 Therefore, on the basis of the available information, the information requirement is not fulfilled.

1.3. Study design

11 The Substance is difficult to test due to the low water solubility and/or adsorptive properties (log K_{oc} 4.36). 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.

2. Growth inhibition study aquatic plants

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

2.1. Information provided

13 You have provided:

(i) Growth inhibition study on aquatic plants/algae (2008) with the Substance.

2.2. Assessment of the information provided

2.2.1. The provided study does not meet the specifications of the test guideline(s)

14 To fulfil the information requirement, a study must comply with OECD TG 201 and the specifications of OECD GD 23 if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following specifications must be met:

Technical specifications impacting the sensitivity/reliability of the test

a) the pH of the control medium does not increase by > 1.5 units;

Reporting of the methodology and results

b) the results of algal biomass determined in each flask at least daily during the test period are reported in a tabular form;

15 In study (i):

Technical specifications impacting the sensitivity/reliability of the test

a) the pH increase in the controls was 2.2 units;

Reporting of the methodology and results

b) tabulated data on the algal biomass determined daily for each treatment group and control are not reported;

16 Based on the above,

- As tabulated raw data are missing, it is not possible to verify that the validity criteria of OECD TG 201 are met
- There are critical methodological deficiencies resulting in the rejection of the study results. More specifically, on the basis of your reporting, pH appears to be increased in the controls by more than 1.5 units. High pH could have limited the algae growth in the controls by the end of the test. If the growth of the algae was reduced in the controls, then the calculation of the inhibition percentages for the different test concentrations could have been underestimated. Since no information is provided on the growth curves, we cannot rule out this phenomenon and we cannot verify that the validity criteria are met.

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

18 In the comments to the draft decision, you agree with the shortcomings in the reporting of the study. You indicate your intention to provide the missing information in a future update of your registration dossier.

19 However, you do not provide specific information addressing the issues identified above. Therefore, the information provided in your comments does not change the assessment outcome.

20 Therefore, the information requirement is not fulfilled.

2.3. Study design

21 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. Screening study for reproductive/developmental toxicity

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

3.1. Information provided

23 You have adapted this information requirement by using Annex XI, Section 1.5. (Grouping of substances and read-across approach) and by using Annex VIII, Section 8.7.1., Column 2. To support the adaptations, you have provided the following information:

(i) Pre-natal developmental toxicity study (2002) with the analogue substance [redacted], EC 422-320-3;

(ii) read-across justification document in IUCLID section 13.

24 You provide the following reasoning for the prediction of this information requirement: "*The comparable structural characteristics and similar functional groups of the target and the source substance are responsible for similar physicochemical and toxicological properties. Consequently, target and source substances are considered suitable for the analogue approach based on structural similarity"*.

25 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.

3.2. Assessment of the information provided

3.2.1. Read-across adaptation rejected

26 Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group.

27 Additional information on what is necessary when justifying a read-across approach can be found in the Guidance on IRs and CSA, Chapter R.6. and related documents (RAAF, 2017; RAAF UVCB, 2017).

3.2.1.1. Read-across hypothesis/prediction contradicted by existing data

28 Annex XI, Section 1.5. requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information must strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6., Section R.6.2.2.1.f.).

29 The observation of differences in the toxicological properties between the source substance(s) and the Substance would contradict the hypothesis that the properties of the Substance can be predicted from the data on the source substance(s). An explanation why

such differences do not affect the read-across hypothesis must to be provided and supported by scientific evidence.

30 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar Substance and source substance(s) cause the same type of effect(s).

31 Based on the information in your dossier, however, the results of the repeated dose toxicity study on the source substance (a sub-chronic (90-day) repeated dose toxicity study (1998) included in your registration dossier) differ from the repeated dose toxicity study results obtained with the Substance (a sub-acute (28-day) repeated dose toxicity study (2007) included in your registration dossier). Specifically, treatment related effects were noted in the 28-day study with the Substance concerning liver weights in both sexes that remained after recovery in the female animals. In addition, increases were noted in cholesterol values following treatment in both sexes and increased absolute spleen weights in recovery female animals. Such observations were not noted in the 90-day study performed with the source substance, despite a threefold treatment period which should result in higher sensitivity. Moreover, the Substance has been classified for skin irritation (Cat 2 of CLP) and the source substance is considered not to be irritating to the skin.

32 These observations underline differences in the chemical bond type and metabolism between the two substances (ester vs. ketone).

33 In your comments on the draft decision you provide explanations on some of these observations, that the "*marginal changes observed […] are considered to be a non-specific metabolic adaptation caused by the high workload on the liver with the test item*" and "*The potential slight difference for local compatibility does not compromise a read across for repeated dose toxicity for which a bridging study […] exists and demonstrates that the test and source substance have quantitatively equal properties*". However, you did not explain the differences in effects on spleen weights.

34 Furthermore, you noted but did not explain the structural chemical differences between the two different bond types of the source- and target substance (ester vs. ketone). You did not explain the impact of these differences, in e.g. metabolism, on the prediction.

35 ECHA assesses read-across as endpoint-specific (as also explained in the reply to your comment in section 3.2.1.2 below). However, significant differences which lead to different classification outcomes are indications for differences in the overall toxicity profiles of source and target substances.

36 The available set of data on the Substance and on the source substances indicates differences in the (eco)toxicological properties of the substances. This contradicts your read-across hypothesis whereby the Substance and source substances cause the same type of effect(s). However, you have not supported and scientifically justified why such differences in the (eco)toxicological properties do not affect your read-across hypothesis.

3.2.1.2. Missing supporting information to compare properties of the substances(s)

37 Annex XI, Section 1.5. requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6., Section R.6.2.2.1.f.).

38 Supporting information must include (bridging) studies to compare properties of the the Substance and the source substance that are relevant for the endpoint, in this case reproduction and development.

39 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar source substance(s) cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the source substance(s) is necessary to confirm that the substances cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance(s).

40 You have provided information on repeated dose toxicity studies for both the Substance (a sub-acute (28-day) repeated dose toxicity study (2007)) and source substance (a sub-chronic (90-day) repeated dose toxicity study (1998)) and information on developmental toxicity for the source substance (study i). In addition, you have referred to a one-generation reproduction toxicity study (OECD TG 415) that has been perfomed with the source substance in your read-across justification document, but which is not available in the dossier for an independent assessment. In particular, you have not provided a study on the Substance that would investigate toxicity to reproduction and/or development and thereby be relevant to the adapted information requirement.

41 In your comments on the draft decision you provide explanations on some of these observations, that the "*the available repeated dose toxicity studies show no adverse effects up to the limit dose of 1000 mg/kg including parameters for a potential reproductive toxicity*" and "*If this information is deemed not sufficient and the bridging data required are meant in the sense, that an OECD 421/422 is always required for a valid read across, then this should be clearly stated by ECHA in the respective guidance documents and the decision*."

42 ECHA assesses read-across adaptations as endpoint specific, especially when performing a thorough analysis of whether parameters have been measured or not for those cases in which the prediction is "absence of effects". While a 28-day sub-acute repeated dose toxicity study provides limited information, e.g. on the reproductive organs and e.g. sperm parameters, there is no mating of female and male animals, no possibility to investigate mating efficiency, pre- or post-implantation losses, gestation index, post-natal malformations, and other parameters which contribute to the hazards that are investigated by the adapted information requirement.

43 Other information that allows comparison of parameters that are relevant to the adapted information requirement, may serve to support your hypothesis. If, for instance, the metabolisation rates and metabolites of target- and source substances were (very) similar, this could support the hypothesis. On the basis of the available information, the present choice of the source substance does not make it likely that metabolism rates e.g. by hydrolysis are likely to be similar enough to support your hypothesis. This is because of the generally known differences in hydrolysis rates between cyclic esters and cyclic ketones.

44 In the absence of information that allows a comparison of properties relevant to the adapted information requirement, you have not established that the Substance and the source substance(s) are likely to have similar properties. Therefore you have not provided sufficient supporting information to scientifically justify the read-across.

3.2.2. Column-2 adaptation rejected

45 For the same reasons as those provided in Section 3.2.1, the provided information is unreliable and cannot be used in an adaptation according to Annex VIII Section 8.7.1 column 2.

3.2.3. Conclusion

46 Therefore, the information requirement is not fulfilled.

3.3. Study design

47 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.

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

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

4. Long-term toxicity testing on fish

50 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.

4.1. Triggering of the information requirement

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

4.2. Information requirement not fulfilled

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

53 In the comments to the draft decision, you disagree to perform the requested study because you claim that it is not mandatory, not a standard information requirement and for animal welfare reasons.

54 However, similar to what is explained already in section 1.1. above, under Annex IX, section 9.1.3, Column 2 ECHA may require long-term toxicity testing on fish when it is unlikely that short-term toxicity testing can provide a true measure of the intrinsic aquatic toxicity of the substance, which among others is presumed when the substance is poorly water soluble (below 1 mg/L), as it is for the Substance.

55 Furthermore, minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under the general rules of Annex XI, and you do not provide any documentation on any general adaptation.

56 In the comments to the draft decision, you indicate that you might adapt this information requirement by a (Q)SAR approach in accordance with Annex XI, Section 1.3 of the REACH Regulation by using VEGA software. However, you do not provide any other information on the QSAR prediction. Therefore, no conclusion on the compliance of the proposed adaptation can be made. You remain responsible for complying with this decision by the set deadline.

57 Therefore, you have not demonstrated that this information can be omitted.

58 Therefore, the information requirement is not fulfilled.

4.3. Study design

59 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.).

60 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 22 November 2022.

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) but amended the deadline.

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

In your comments on the draft decision, you requested an extension of the deadline to provide the information. You provided a letter from a testing laboratory to support your request. On this basis, ECHA has extended the deadline to 36 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 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/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.

With that detailed information, ECHA can confirm 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 (https://echa.europa.eu/manuals).