~~Confidential~~

Helsinki, 08 June 2023

Addressee(s)
Registrant(s) of js_245-589-7 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
08/04/2019

Registered substance subject to this decision ("the Substance")
Substance name: 2-heptadecyl-1h-imidazole
EC number/List number: 245-589-7

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 ***16 December 2024***.

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

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

1. Skin sensitisation (Annex VII, Section 8.3.2; in vivo skin sensitisation test method: EU B.42./OECD TG 429);

2. 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);

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

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 addressees 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 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)

Contents

Reasons related to the information under Annex VII of REACH

1. Skin sensitisation

1 Skin sensitisation is an information requirement under Annex VII, Section 8.3. Under Section 8.3., Column 1, the registrants must submit information allowing (1) a conclusion whether the substance is a skin sensitiser and (2) whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

1.1. Information provided

2 You have provided:

(i) An *in vitro* Direct Peptide Reactivity Assay (DPRA) (2018) with the Substance;

(ii) An *in vitro* KeratinoSens assay (2018) with the Substance;

(iii) An *in vitro* Human Cell Line Activation Test (hCLAT) (2018) with the Substance;

(iv) a Local Lymph Node Assay (LLNA) (2018) with the Substance.

1.2. Assessment of the information provided

1.2.1. Assessment whether the Substance causes skin sensitisation

1.2.1.1. Reliability of the results obtained from the in vitro data (studies i-iii)

3 The OECD TGs 442C and 442E identify limitations in the conclusions which can be derived from negative results obtained from these test methods when performed:

- on a test material which is not soluble at a concentration of up to 100mM in an appropriate solvent (OECD TG 442C).
- on a test material with a log Kow greater than 3.5, which tend to produce false negative results (OECD TG 442E).

4 The OECD TG 442D indicates that the test method is applicable to test chemicals soluble or that form a stable dispersion in the exposure medium. The OECD TG 442D also stresses that "Test chemicals that do not fulfil these conditions at the highest final required concentration of 2 000 µM may still be tested at lower concentrations. In such a case, results fulfilling the criteria for positivity could still be used to support the identification of the test chemical as a skin sensitiser."

5 Negative results have been reported for studies (i) and (iii). Taking into account the low water solubility (<18.7 µg/L) and high log Kow (7.4-8.5), you conclude that the negative results from studies (i) and (iii) should be considered as inconclusive.

6 The study (ii) has returned positive results in 2 out of 3 runs. You have concluded that the Substance has "skin sensitising potential based on the key event "inflammatory response in keratinocytes". You further indicate that "Test chemicals that do not act as a sensitiser but are nevertheless chemical stressors may lead to false positive results. Furthermore, highly cytotoxic test chemicals cannot always be reliably assessed. In addition, the test substance is extremely hydrophobic. Hydrophobic substances with a LogP above 7 are outside the known applicability of the test method."

7 ECHA agrees with your interpretation of the results from studies (i) and (iii) as inconclusive. The results from the study (ii) cannot be entirely dismissed on the basis of the hydrophobicity of the Substance. These positive results do not allow to conclude, on their own, on the skin sensitisation potential of the Substance but can contribute to the identification of the Substance as a skin sensitiser.

8 Based on the outcome of the in vitro assays, in vivo data is required to conclude on the skin sensitising properties of the Substance.

1.2.1.2. The study (iv) does not meet the specifications of the test guideline(s)

9 To fulfil the information requirement, and to enable concluding whether the Substance causes skin sensitisation, a study must comply with the EU Method B.42/OECD TG 429 (Article 13(3) of REACH). Therefore, the following specification must be met: the highest concentration is the highest technically possible concentration that maximises exposure while avoiding systemic toxicity and/or excessive local skin irritation.

10 In study (iv), no dose level selection rationale was provided for selecting the highest dose of 12.5% (w/v) in acetone/olive oil (4:1). You report that "the vehicle was chosen as it was suitable at the highest concentration".

11 The information provided does not cover the specification(s) required by the EU method B.42/OECD TG 429.

12 Even though the substance is insoluble in water, you have not established that the dose of 12.5% (w/v) in acetone/olive oil (4:1) is the highest technically possible concentration that maximises exposure while avoiding systemic toxicity and/or excessive local skin irritation.

13 On this basis, it cannot be concluded whether the Substance causes skin sensitisation.

14 In your comments on the draft decision you have clarified the reasoning for the dose level selection. You report that the solubility of the Substance had been tested in 4 different vehicles acetone/olive oil (4:1), propylene glycol, DMSO and water with 2% carboxymethylcellulose and that the highest applicable concentration of the Substance was found to be 12.5% in acetone/olive oil (4:1).

15 ECHA has assessed the information provided in your comments against the requirement in OECD TG 429. 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.

1.2.2. No assessment of potency

16 To be considered compliant and enable a conclusion in cases where the substance is considered to cause skin sensitisation, the information provided must also allow a conclusion whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

17 As the currently available data does not allow to conclude whether the Substance causes skin sensitisation (see section 1.2.1 above), this condition cannot be assessed.

18 Therefore, the information requirement is not fulfilled.

1.3. Specification of the study design

19 Since no conclusion on the skin sensitisation potency can be made for the Substance based on the existing in vitro/in chemico data, in vivo skin sensitisation study must be performed

and the murine local lymph node assay (EU Method B.42/OECD TG 429) is considered as the appropriate study for the potency estimation.

2. Long-term toxicity testing on aquatic invertebrates

20 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.

2.1. Triggering of the information requirement

21 Poorly water soluble substances require longer time to reach steady-state conditions. As a result, the short-term tests do not give a true measure of toxicity for this type of substances and the long-term test is required.

22 In the provided study on water solubility with the Substance (2018), the saturation concentration of the Substance in water was determined to be <18.7 µg/Lor below the limit of detection of the analytical method (i.e. LOQ = 18.7 µg/L).

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

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

25 In the absence of information on long-term toxicity on aquatic invertebrates, this information requirement is not fulfilled.

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

2.2. Study design and test specifications

27 The Substance is difficult to test due to the low water solubility (< 18.7 µg/L) and adsorptive properties (Log K_{ow} = 7.4-8.5). OECD TG 211 specifies that, for difficult to test substances, you must consider the approach described in the 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.

3. Growth inhibition study aquatic plants

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

3.1. Information provided

29 You have provided a growth inhibition study on aquatic plants/algae (2018) with the Substance.

3.2. Assessment of the information provided

30 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:

Characterisation of exposure

a) if the concentration of the test material has not been maintained within ±20 % of the nominal or measured initial concentration throughout the test, results must be based on the geometric mean of measured concentrations during exposure or on a model describing the decline of the concentration of the test material over the exposure period.

31 In the study provided:

Characterisation of exposure

a) the measured concentrations of the test material were < LOQ, i.e. 18.7 µg/L at the end of the test and thus not within ± 20 % of nominal or measured initial concentration throughout the test. You have expressed the effect values based on nominal concentration only. Therefore, it does not correspond to either the geometric mean of measured concentrations during exposure or a model describing the decline of the concentration of the test material over the exposure period.

32 Based on the above, the Substance is difficult to test due to its low solubility in water and there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, the Substance was not stable during the study and therefore, effect values based on nominal test concentrations underestimate the hazard.

33 In your comments to the draft decision you provide further information on

- Test medium preparation: *"The Substance was applied as saturated solution and the saturated solution was prepared appropriately by stirring for 24hr and filtration through a membrane filter, according to OECD GD 23"*
- Analytical method used to monitor test material stability in the test medium, with a LOD = 1.5 ng/L
- Statement regarding the water solubility of the Substance

34 Taken together you consider the above study to be adequately conducted in accordance with OECD TG 201 as well as GD 23.

35 However, you have not explained how the reported effect values will be updated based on the above. As explained under a) results must not be based on nominal concentrations if the test material was not demonstrated to be stable within +/-20% of nominal or initial measured concentrations.

36 On this basis, the specifications of OECD TG 201 are not met and the information requirement is not fulfilled.

37 Last, please note that 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). In particular, where the water solubility is below the detection limit of the analytical method

for a substance, and toxicity is recorded, the effect concentration for classification purposes may be considered to be less than the analytical detection limit (Guidance on the Application of the CLP Criteria, ANNEX I: AQUATIC TOXICITY, I.4.2 Poorly soluble substances).

38 In the study provided the following % inhibition in growth rate (T0-T72h) were observed at nominal concentrations of 0(control), 9.53, 17.1, 30.9, 55.6, 100 mg/L: 0.0, 0.0, 8.3, 29.6, 55.1, 139.2%, respectively, indicating clear toxicity in a concentration-response related manner.

39 Since the test material was not detectable in any of the test media, more specifically those that caused effects, you must report effect values based on the LOD of the analytical method, i.e. 1.5 ng/L, for classification purposes (Guidance on the Application of the CLP Criteria, I.4.2., particularly bullet c.).

3.3. Study design and test specifications

40 The OECD TG 201 specifies that, for difficult to test substances, the 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 and test specifications' under request 2.

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

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 02 May 2022.

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 6 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations (CROs).

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

In the comments on the draft decision, you requested an extension of the deadline due to limitations in CROs availabilities. As already explained above, the deadline of this decision already takes into account the potential constraints in this regards.

ECHA took into account your comments did not amend the request(s) / the deadline.

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 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 and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

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.

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

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

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.

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

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).