~~Confidential~~

Helsinki, 26 October 2023

Addressee(s)
Registrant(s) of Reconsile hexamethyldisilazane as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
21 March 2022

Registered substance subject to this decision ("the Substance")
Substance name: 1,1,1,3,3,3-hexamethyldisilazane
EC/List number: 213-668-5

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

DECISION ON TESTING PROPOSAL(S)

Under Article 40 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by ***2 August 2027***.

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

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) by oral route, in a second species (rabbit), with the analogue substance hydroxytrimethylsilane (EC No. 213-914-1)

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) by oral route, in rats, with the analogue substance hydroxytrimethylsilane (EC No. 213-914-1), specified as follows:
   - Ten weeks premating exposure duration for the parental (P0) generation;
   - The highest dose level in P0 animals must be determined based on clear evidence of an adverse effect on sexual function and fertility without severe suffering or deaths in P0 animals as specified further in Appendix 1, or follow the limit dose concept. The reporting of the study must provide the justification for the setting of the dose levels;
   - Cohort 1A and 1B (Reproductive toxicity);
   - Cohorts 2A and 2B (Developmental neurotoxicity).

   You must report the study performed according to the above specifications. Any expansion of the study must be scientifically justified.

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

Information required depends on your tonnage band

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

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

How to comply with your information requirements

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

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

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

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

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

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

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

Appendix 1: Reasons for the decision

Contents

0. Reasons common to several requests

0.1. Assessment of the read-across approach

1 You have used a read-across approach and you have proposed to conduct the following tests with the analogue substance hydroxytrimethylsilane (EC No. 213-914-1):

- Pre-natal developmental toxicity study (Annex X, Section 8.7.2)
- Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3)

2 ECHA has considered the scientific and regulatory validity of your read-across approach in general before assessing the specific testing proposal.

3 Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used.

4 Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and (eco)toxicological properties so that the substances may be considered as a group or category.

5 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.

6 ECHA understands that your read-across hypothesis assumes that the source substance and the Substance have the same type and strength of effects.

7 You justify the read-across based on the lack of hydrolytic stability of the Substance. The Substance hydrolyses rapidly with a half-life of seconds to hydroxytrimethylsilane and ammonia in contact with water. Therefore, the hydrolytic products are the most relevant substances for assessing the reproductive toxicity in a pre-natal developmental toxicity study and an one-generation reproductive toxicity study with the oral route. With regards to potential reproductive effects of ammonia, there is an OECD SIDS report[2] concluding that 1500 mg/kg bw/day of diammonium phosphate causes no reproductive or developmental effects in rats in a reproduction/developmental toxicity screening test (similar to OECD TG 422) with the oral route. The actual dose level of ammonium tested in the study of the OECD SIDS report is higher than the ammonia levels that would be generated in a limit-test with the Substance.

8 Based on your read-across justification and the information available in the dossier, ECHA agrees with your read-across hypothesis. Therefore, you have established that relevant properties of the Substance can be predicted from data on the analogue substance.

9 However, ECHA emphasises that any final determination on the validity of your read-across adaptation will only be possible when the information on the requested studies will be available in the dossier after assessing whether it confirms or undermines the read-across hypothesis.

[2] The OECD agreed conclusions: Microsoft Word - Ammonia.doc (oecd.org)

Reasons for the decision(s) related to the information under Annex X of REACH

1. Pre-natal developmental toxicity study

10 A pre-natal developmental toxicity (PNDT) study (OECD TG 414) in two species is a standard information requirement under Annex X, Section 8.7.2.

1.1. Information provided to fulfil the information requirement

11 Your dossier contains a PNDT study in a first species (2013) conducted with hydroxytrimethylsilane (EC No. 213-914-1) by the oral route.

12 You have submitted a testing proposal for a PNDT study in a second species according to the OECD TG 414 by the oral route with the analogue substance hydroxytrimethylsilane (EC No. 213-914-1).

13 ECHA requested your considerations for alternative methods to fulfil the information requirement for Developmental toxicity. You provided your considerations and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

14 ECHA agrees that a PNDT study in a second species is necessary.

1.2. Specification of the study design

15 You proposed testing in the rabbit as a second species.

16 The study in the first species was conducted in the rat. The rat or the rabbit are the preferred species under the OECD TG 414 (Guidance on IRs & CSA, Section R.7.6.2.3.2.). Therefore, the study must be conducted in the rabbit.

17 You proposed testing by oral route. ECHA agrees with your proposal.

1.3. Outcome

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

2. Extended one-generation reproductive toxicity study

19 The basic test design of an extended one-generation reproductive toxicity study (EOGRTS) is a standard information requirement under Annex X. Furthermore, Annex X, Section 8.7.3., Column 2 defines when the study design needs to be expanded.

2.1. Information provided to fulfil the information requirement

20 You have submitted a testing proposal for an EOGRTS according to OECD TG 443 with the analogue substance hydroxytrimethylsilane (EC No. 213-914-1).

21 ECHA requested your considerations for alternative methods to fulfil the information requirement for Toxicity to reproduction. You provided your considerations and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

22 ECHA agrees that an EOGRTS is necessary.

2.2. Specification of the study design

2.2.1. Species and route selection

23 You proposed testing in the rat. ECHA agrees with your proposal because the rat is the species preferred by OECD TG 443.

24 You proposed testing by oral route. ECHA agrees with your proposal.

2.2.2. Pre-mating exposure duration

25 The length of the pre-mating exposure period must be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

26 You proposed two weeks pre-mating exposure duration. ECHA disagrees with your proposal.

27 Ten weeks pre-mating exposure duration is required to obtain results adequate for classification and labelling and/or risk assessment. There is no substance specific information in the dossier supporting shorter pre-mating exposure duration (Guidance on IRs & CSA, Appendix R.7.6-3).

2.2.3. Dose-level setting

28 You specified that 'a dose-range finding will be conducted' as a basis for dose level selection. ECHA acknowledges your intention to conduct a dose-range finding study prior to the main OECD TG 443 study.

29 The aim of the requested test must be to demonstrate whether the classification criteria of the most severe hazard category for sexual function and fertility (Repr. 1B; H360F) and developmental toxicity (Repr. 1B; H360D) under the CLP Regulation apply for the Substance (OECD TG 443, para. 22; OECD GD 151, para. 28; Annex I Section 1.0.1. of REACH and Recital 7, Regulation 2015/282), and whether the Substance meets the criteria for a Substance of very high concern regarding endocrine disruption according to Art.57(f) of REACH as well as supporting the identification of appropriate risk management measures in the chemical safety assessment.

30 To investigate the properties of the Substance for these purposes, the highest dose level of the test substance must be set on the basis of clear evidence of an adverse effect on sexual function and fertility, but no deaths (i.e., no more than 10% mortality; Annex I, Section 3.7.2.4.4. to the CLP Regulation) or severe suffering such as persistent pain and distress (OECD GD 19, para. 18) in the P0 animals.

31 In case there are no clear evidence of an adverse effect on sexual function and fertility, the limit dose of at least 1000 mg/kg bw/day or the highest possible dose level not causing severe suffering or deaths in P0 must be used as the highest dose level. A descending sequence of dose levels should be selected to demonstrate any dose-related effect and aiming to establish the lowest dose level as a NOAEL.

32 In summary: Unless limited by the physical/chemical nature of the test substance, the highest dose level in P0 animals must be as follows:

(1) in case of clear evidence of an adverse effect on sexual function and fertility without severe suffering or deaths in P0 animals, the highest dose level in P0 animals must be determined based on such clear evidence, or
(2) in the absence of such clear evidence, the highest dose level in P0 animals must be set to be the highest possible dose not causing severe suffering or death, or
(3) if there is such clear evidence but the highest dose level set on that basis would cause severe suffering or death, the highest dose level in P0 animals must be

set to be the highest possible dose not causing severe suffering or death, or

(4) the highest dose level in P0 animals must follow the limit dose concept.

33 You have to provide a justification with your study results demonstrating that the dose level selection meets the conditions described above.

34 Numerical results (i.e. incidences and magnitudes) and description of the severity of effects at all dose levels from the dose range-finding study/ies must be reported to facilitate the assessment of the dose level section and interpretation of the results of the main study.

2.4.4. Cohorts 1A and 1B

35 Cohorts 1A and 1B belong to the basic study design and must be included.

2.4.4.1. Histopathological investigations in Cohorts 1A and 1B

36 In addition to histopathological investigations of cohorts 1A, organs and tissues of Cohort 1B animals processed to block stage, including those of identified target organs, must be subjected to histopathological investigations (according to OECD TG 443, para. 67 and 72) if

- the results from Cohort 1A are equivocal,
- the test substance is a suspected reproductive toxicant or
- the test substance is a suspected endocrine toxicant.

2.4.4.2. Splenic lymphocyte subpopulation analysis

37 Splenic lymphocyte subpopulation analysis must be conducted in Cohort 1A (OECD TG 443, para. 66; OECD GD 151, Annex Table 1.3).

2.4.4.3. Investigations of sexual maturation

38 To improve the ability to detect rare or low-incidence effects, all F1 animals must be maintained until sexual maturation to ensure that sufficient animals (3/sex/litter/dose) are available for evaluation of balano-preputial separation or vaginal patency (OECD GD 151, para. 12 in conjunction with OECD TG 443, para. 47). For statistical analyses, data on sexual maturation from all evaluated animals/sex/dose must be combined to maximise the statistical power of the study.

2.4.5. Cohorts 2A and 2B

39 Annex IX/X, Section 8.7.3., Column 2 provides that the developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity.

40 The test you proposed did not include Cohorts 2A and 2B.

41 Available repeated dose studies with the Substance (OECD TG 413 and OECD TG 412) and with hydroxytrimethylsilane (OECD TG 407), a combined RDT study with reproduction/developmental toxicity screening test with the Substance (OECD TG 422) and a PNDT study with hydroxytrimethylsilane (OECD TG 414) show evidence of functional effects on the nervous system in adult males and females, causing clinical and behavioural signs described as uncoordinated gait/ataxia, staggering, apathy/decreased activity, prostrate appearance, inability to walk. The incidence and severity of the observed effects are dose-related and consistent. Only a limited number of systemic effects such as reduced bodyweight gain in males and females, accompanied with a reduced food consumption, were observed in the studies and do not explain the acute functional effects on the nervous system after exposure. Any other effects were not observed in both sexes. Therefore, the

substance-specific findings are not likely to be secondary to general toxicity and they indicate a particular concern justifying the inclusion of the developmental neurotoxicity cohort (Guidance on IRs & CSA, Appendix R.7.6-2). Furthermore, in the OECD TG 414 study with hydroxytrimethylsilane by the oral route, you considered the clinical signs seen at the highest dose level (450 mg/kg bw/day) to be adverse effects in pregnant rats 'due to the nature, frequency and severity of the findings and the observation that one animal did not fully recover from the symptoms'.

42 the comments to the draft decision, you acknowledge that there is evidence of functional effects of 1,1,1,3,3,3-hexamethyldisilazane and hydroxytrimethylsilane on the nervous system in adult male and female rats, causing clinical and behavioural signs. However, you disagree with the inclusion of the developmental neurotoxicity cohorts 2A/2B in the EOGRT study, since the observed effects are transient in nature, i.e. the effects were recorded after exposure, lasted for a few hours and dissapeared by the next morning or before the next exposure, as indicated by the descriptions of the study reports you provide in your comments. Furthermore, you indicate that there is no evidence of effects on the nervous system from macroscopic and histopathological examinations.

43 The study descriptions you provide in the comments state that there are no relevant findings in the OECD TG 407 study using hydroxytrimethylsilane. This is in conflict with what you have reported in your dossier, where it is stated that '*short lived staggering*' after dosing is observed in the animals exposed to the highest dose level in the OECD TG 407 study.

44 Furthermore, in your comments you consider that the clinical signs in the OECD TG 414 study using hydroxytrimethylsilane are transient. However, ECHA notes that according to your dossier one animal of the high dose group in the OECD TG 414 study did not fully recover from symptoms such as uncoordinated movement, decreased activity and/or prostrate appearance. Importantly, in your dossier you consider these findings to be adverse in pregnant rats due to their nature, frequency and severity.

45 The reported functional effects on the central nervous system such as decreased activity, lack of coordination and ataxia are signs of narcosis (CLP Regulation, Annex I, Section 3.8.2.2.2). The effects are considered persuasive evidence of neurotoxicity as these are consistently observed, independent of the administration route (oral or inhalation) and their severity and incidence are dose-related, capable of reaching a non-transient and adverse nature in pregnant rats. In accordance with the Guidance on IRs & CSA (Appendix R.7.6-2), narcosis is a functional adverse effect on the nervous system and thus is a substance specific finding which may indicate a particular concern justifying inclusion of the developmental neurotoxicity cohorts.

46 Furthermore, the transient nature of the effects may still be of concern as the nervous system possesses reserve capacity which may compensate for the damage, but the resulting reduction in the reserve capacity should be regarded as an adverse effect (Guidance on IRs & CSA, Appendix R.7.5-1).

47 Last, we would like to draw your attention to the findings of the General Court in Case T-868/19, *Nouryon Industrial Chemicals and Others v Commission*[3] where the General Court considered that the developmental neurotoxicity Cohorts 2A and 2B may be triggered on the basis of narcotic effects.

48 In conclusion, the information you provide in the comments to the draft decision does not change the assessment. For the reasons stated above, the developmental neurotoxicity Cohorts 2A and 2B must be conducted.

[3] Judgment of 29 March 2023, *Nouryon Industrial Chemicals and Others v Commission*, T-868/19, EU:T:2023:168, currently under appeal.

2.5. Outcome

49 Under Article 40(3)(b) your testing proposal is accepted under modified conditions, and you are requested to conduct the test with hydroxytrimethylsilane (EC No. 213-914-1), as specified above.

2.5.1. Further expansion of the study design

50 The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B and/or Cohort 3 if relevant information becomes available from other studies or during conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annex IX/X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in Guidance on IRs & CSA, Section R.7.6.

References

The following documents may have been cited in the decision.

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

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

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

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

Read-across assessment framework (RAAF)

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

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

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

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

Appendix 2: Procedure

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 21 April 2022.

ECHA held a third-party consultation for the testing proposal(s) from 16 June 2022 until 1 August 2022. ECHA did not receive information from third parties.

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

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

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

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

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

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

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

- the information specified in Annexes VII 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]
[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[4].

(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:

- its representativeness towards the specified analogue substance,
- it supports the read-across prediction as presented in the read-across justification document,
- the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the analogue 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

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

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 Practical Guide on How to use alternatives to animal testing to fulfil your information requirements (Chapter 4.4., https://echa.europa.eu/practical-guides).

2. General recommendations for conducting and reporting new tests

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