~~Confidential~~

Helsinki, 30 May 2024

Addressees
Registrants of RECONSILE EC# 220-099-6 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
05 October 2020

Registered substance subject to this decision ("the Substance")
Substance name: 1,1,3,3-tetramethyl-1,3-divinyldisiloxane
EC/List number: 220-099-6

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 ***6 September 2027***.

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

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

1. Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.; test method: OECD TG 443) in rats, oral route, 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 in section 1.2.3., 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); and
    - 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 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
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.

~~Confidential~~

Appendix 1: Reasons for the request

Reasons related to the information under Annex IX of REACH

1. Extended one-generation reproductive toxicity study

1 An extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is an information requirement under Annex IX, Section 8.7.3., if the available repeated dose toxicity studies indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. Furthermore Column 2 defines the conditions under which the study design needs to be expanded.

1.1. Triggering of the information requirement

2 You claim that "*the available repeated dose toxicity studies do not indicate adverse effects on reproductive organs or tissues, or reveal other concerns in relation with reproductive toxicity*."

3 However, the available studies conducted with the Substance reported in your dossier indicate concerns in relation with reproductive toxicity. More specifically, effects of concern are reported in the thyroid:

- histopathological findings in the thyroid are reported in a sub-chronic repeated dose toxicity study (2020, report number [redacted]). More specifically, epithelial cell hypertrophy (minimal-mild) was noted in the thyroid in the two highest dose groups of males and the highest group of females. Furthermore, minimal colloid alteration was reported for the high-dose males. You did not consider these findings as adverse based on severity but you do not exclude that these findings may raise a concern.
- effects on thyroid hormone levels were observed in a sub-chronic (90d) repeated dose toxicity study (2020, report number [redacted]) and a prenatal developmental toxicity (PNDT) study in rats (2020, report number [redacted]). In the 90d study, your report that "[t]*est substance-related effects on thyroid hormone parameters were noted in the 65 mg/kg bw/day group females and 300 mg/kg bw/day group male and females. The 300 mg/kg bw/day group males had lower T4 levels at the terminal necropsy relative to the control group, coupled with thyroid gland hypertrophy observed microscopically. T3 levels were lower in a dose-responsive manner in the 65 and 300 mg/kg bw/day group females relative to the control group. TSH levels were unaffected by the administration of the test substance*". In the PNDT study, you report a statistically significant increase in TSH concentrations in females in the two highest dose groups, and a decreased T3 concentration at the highest dose level. Changes in thyroid hormone levels or signs of thyroid toxicity have been closely linked to developmental neurotoxic effects (Chapter R.7a, Appendix R.7.6–2).

4 In addition, a screening study for reproductive/developmental toxicity (2011, report number [redacted]) with the Substance showed adverse effects on post-natal survival of offspring, with two complete losses of litter reported on PND 1 and 3. You consider these to be test substance-related and adverse.

5 Therefore, the information requirement is triggered.

1.2. Information requirement not fulfilled

6 You have provided no information to fulfil this information requirement.

7 Therefore, this information requirement is not fulfilled.

8 In your comments to the draft decision, you agree to perform a OECD TG 443 study.

1.3. Study design

1.3.1. Species and route selection

9 According to the test method OECD TG 443, the rat is the preferred species. Therefore, the study must be conducted in the rat.

10 As the Substance is a liquid, the study must be conducted with oral administration of the Substance (Annex X, Section 8.7.3., Column 1).

1.3.2. Pre-mating exposure duration

11 The length of 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.

12 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 premating exposure duration (Guidance on IRs and CSA, Section R.7.6.).

13 In this specific case, ten weeks exposure duration is supported by the lipophilicity of the Substance (Log K_{ow} of 5.4) to ensure that the steady state in parental animals has been reached before mating.

14 Therefore, the requested pre-mating exposure duration is ten weeks.

1.3.3. Dose-level setting

15 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, paragraph 22; OECD GD 151, paragraph 28; introductory part of Annex IX/X to REACH; Annex I, Section 1.0.1. to 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.

16 To investigate the properties of the Substance for these purposes, the highest dose level 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. of the CLP Regulation) or severe suffering such as persistent pain and distress (OECD GD 19, paragraph 18) in the P0 animals.

17 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.

18 In summary: unless limited by the physical/chemical nature of the 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.

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

20 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.

1.3.4. Cohorts 1A and 1B

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

1.3.4.1. Histopathological investigations in Cohorts 1A and 1B

22 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, paragraph 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.

1.3.4.2. Splenic lymphocyte subpopulation analysis

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

1.3.4.3. Investigations of sexual maturation

24 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, paragraph 12 in conjunction with OECD TG 443, paragraph 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.

1.3.5. Cohorts 2A and 2B

25 The developmental neurotoxicity Cohorts 2A and 2B must be conducted in case of a particular concern on (developmental) neurotoxicity.

26 Existing information on the Substance from in vivo studies (i.e., a prenatal developmental toxicity study in rat and a repeated dose toxicity study) show evidence of thyroid toxicity, i.e. relevant changes in thyroid hormone levels and histopathological findings.

27 The prenatal developmental toxicity study shows statistically significant changes in thyroid hormones in pregnant rats: lower (-30.0%) mean T3 concentration in the highest dose compared to the control animals and higher mean concentrations (+72.7% and + 69.7%) of thyroid stimulating hormone (TSH) were noted in the mid and high dose groups, compared to the control animals.

28 Also, in the sub-chronic repeated dose toxicity study changes in hormone levels coupled with thyroid gland hypertrophy (i.e., lower T4 levels (-20.1%) at necropsy in high dose group males and lower T3 levels (-16.5% and -20.8%, respectively) in the mid and high dose group females relative to the control group was observed.

29 In your comments, you do not agree that the thyroid-related findings justify the conduct of Cohorts 2A and 2B. You acknowledge the changes in T3 and TSH in the prenatal developmental toxicity study but note that "*No effect on T4 level, on thyroid weight or histopathology was seen in any exposure group. The study report concluded that the thyroid hormones changes were test material-related but not adverse"*. Furthermore, you note that "*In the 90-day study, absolute and relative thyroid weights were not affected in any exposure groups"* and that "*The thyroid results (hormone or microscopic) are not reported as adverse in the report conclusion, nor as the basis for the study NOAEL"*.

30 According to the ECHA/EFSA Guidance[2] for the identification of endocrine disruptors, substances inducing histopathological changes in the thyroid as well as substances that alter the circulating levels or T3 and/or T4 present a potential concern for neurodevelopment.

31 ECHA acknowledges your comment on lack of effects observed in thyroid gland weights but notes that the changes observed in thyroid hormone levels and thyroid histopathology are indicative of thyroid toxicity. Changes in thyroid hormone levels is considered a specific mode of action with an association to developmental neurotoxicity (OECD GD 150).

32 Specifically, ECHA notes that changes in thyroid hormone levels were observed in the two following studies. Decreased T3 levels were consistently observed in females in the sub-chronic repeated dose toxicity study as well as in the prenatal developmental toxicity study which investigates pregnant females. According to the ECHA/EFSA Guidance[2] for the identification of endocrine disruptors, substances that alter the circulating levels or T3 and/or T4 present a potential concern for neurodevelopment. You have not provided any study which investigates neurodevelopment of offspring after exposure to the Substance. The aim of Cohorts 2A and 2B is to investigate and characterise the Substance's potential effects on the developing nervous system.

33 Furthermore, in the sub-chronic repeated dose toxicity study, 7/9 males and 5/10 females at the high dose showed histopathological changes (epithelial cell hypertrophy) in the thyroid gland (described in IUCLID as "*increase in size and height of epithelial cells lining the follicles"*). The thyroid glands of 3/9 males at high dose also showed colloid alteration. Histopathologic changes in the thyroid gland, such as follicular cell height increase (hypertrophy) and colloid area decrease, are indicative of thyroid-related activity (OECD GD 150, see e.g. pages 64-65 for thyroid-related activity / histopathologic changes within repeated-dose studies).

34 For the reasons stated above, the developmental neurotoxicity Cohorts 2A and 2B must be conducted.

1.3.6. Further expansion of the study design

35 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

[2] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5311
ECHA emphasises that even though the ECHA/EFSA Guidance was developed for hazard identification for endocrine-disrupting properties for other regulatory purposes, the same scientific principles apply also under the REACH Regulation.

which are described in Annex IX, Section 8.7.3., Column 2. 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 (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 February 2023.

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.

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]
[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 (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

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, including the nature and concentration values of impurities.

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

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