ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 19 July 2018

Addressee: [redacted]

Decision number: TPE-D-2114428349-43-01/F
Substance name: dimethoxydimethylsilane
EC number: 214-189-4
CAS number: 1112-39-6
Registration number: [redacted]
Submission number: [redacted]
Submission date: 06.05.2015
Registered tonnage band: 100 to 1000 tonnes per year

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA has taken the following decision.

While your originally proposed test for

- **a Sub-chronic toxicity study (90-day), inhalation route (Annex IX, Section 8.6.2.; test method: OECD TG 413) in rats, using the registered substance**

is rejected, you are requested to perform:

1. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats using the registered substance, including measurements of the specific hormones thyroxine (T4), tri-iodothyronine (T3) and thyroid stimulating hormone (TSH) in serum at termination.**

   It is at your discretion to perform the intended additional examinations on additional reproductive parameters during the testing program.

Your testing proposal is modified and you are requested to carry out:

2. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rats or rabbits), oral route using the registered substance.**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **27 January 2020**. You shall also update the chemical safety report, where relevant.

The timeline has been set to allow for sequential testing of the requests in this decision and the request made in a separate, decision of **19 July 2018** (**communication number CCH-D-2114428794-40-01/F** on a Compliance Check on the registered substance .

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals.

Authorised[1] by Ofelia Bercaru, Head of Unit, Evaluation E3

[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

The decision of ECHA is based on the examination of the testing proposals submitted by you.

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

Examination of the testing proposal

A sub-chronic toxicity study (90 day) is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements.

You have submitted a testing proposal for a sub-chronic toxicity study (90 day) in rats by the inhalation route according to OECD TG 413 with the registered substance. You also indicate that you intend to perform additional reproductive parameters such as the examination of reproductive organs, sperm parameters and oestrous cycle.

You proposed testing by the inhalation route and provided the following justification:

"No adequate information about specific organ toxicity after subchronic repeated inhalation exposure is available for dimethoxydimethylsilane (CAS 1112-39-6). Therefore, a testing proposal is included into this dossier. However, to conduct a quantitative risk assessment, reliable data from a closely related substance trimethoxymethylsilane (CAS 1185-55-3) was used as interim measure."

ECHA notes, that the read-across to the analogue substance is intended to be used only as an interim measure to conduct a quantitative risk assessment. Furthermore, the available repeated dose inhalation study (OECD TG 413, [redacted] 2008) on the analogue substance trimethoxy(methyl)silane (CAS 1185-55-3, EC 214-685-0), indicates different systemic toxicity effects (i.e. kidney toxicity, effects on urinary bladder and adrenal gland) than the available oral study (OECD TG 422, [redacted] 2010) with the registered substance (i.e. toxicity to liver, thyroid gland, adrenal glands, kidney and reproductive toxicity). Thus there is no adequate information present in the technical dossier on the sub-chronic repeated dose toxicity of the registered substance. Consequently there is an information gap and it is necessary to provide information for this endpoint.

It is noted that the inhalation route has to be considered for testing. The registered substance is reported to be a liquid at ambient temperature of vapour pressure 7400 Pa at 25°C. Hence, inhalation exposure of humans to vapours is likely.

However, judging from the information you provided, the oral route is considered the more appropriate route of administration for testing.

More specifically, even though the information in the technical dossier and/or in the chemical safety report indicates that human exposure to the registered substance by the inhalation route is likely, the exposure concentrations reported in the chemical safety report for the inhalation route is low. Furthermore, the registered substance is not eye or skin

irritant and a non-sensitizer therefore there is no concern for local effects following inhalation exposure, and there is no need to further address the inhalation route.
In your comments you argue that inhalation route should be further pursued, because exposure to vapour of the registered substance cannot be disregarded. However, ECHA observes that for all uses where exposure to vapour of the registered substance may occur you have already performed quantitative risk characterisations, resulting in RCRs far below 1. Hence, ECHA considers that there is no need to further assess the inhalation route.

In order to decide on the most appropriate route of exposure, ECHA also took into account the available oral study with the registered substance (OECD TG 422, [redacted] 2010) which indicates a concern for systemic toxicity such as toxicity to liver, thyroid gland, adrenal glands and reproductive toxicity (e.g. effects on testes and epididymides), at 1000 mg/kg bw/day dose level. ECHA considers that these findings require further investigation and therefore requests information on repeated dose toxicity by the oral route.

In your comments you challenge the relevance of the above listed effects (i.e. being secondary effects). ECHA observes the data are relying on short exposure. ECHA is of the opinion that the observed systemic toxicity effects and the effects on reproductive organs / in relation with reproductive toxicity are observed in the provided OECD 422 oral screening study giving rise to concern. ECHA confirms that these findings need further investigation and the further investigation has to be carried out via the same route of administration *i.e.* via oral route.

Consequently, taken all the above into account and after balancing the benefits of information resulting from either of the two likely routes of exposure, information on the inhalation route is considered to be less relevant than information obtained by the oral route to further investigate oral systemic toxicity.

Therefore, ECHA considers that the oral route is the most appropriate route of administration for testing. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

You have proposed that "*Additional reproductive endpoints will be covered. These could include but are not limited to "Examination of reproductive organs, sperm parameters, and oestrus cycle*". Firstly, ECHA considers that you are not addressing an 'endpoint', in the sense of an information requirement, but that rather you wish to add additional examinations, or parameters, to the 90-day study. ECHA refers to these additional examinations as 'parameters'. Secondly, ECHA notes that it is at your discretion to perform the intended additional examinations during the testing program to thereby ensure the safe use of the substance. However, you must ensure that those additional examinations do not interfere with full compliance to OECD TG 408. Thirdly, you are reminded that the proposed additional parameters for this study do not fulfil the standard information requirement in the registration dossier for reproductive toxicity set out in Annex X, Section 8.7.3.

Following a proposal for amendment (PfA) from one of the Member State Competent Authority (MSCAs) it was noted that follicular cell hypertrophy is seen in the thyroid in both sexes at high dose in the OECD 422 study in the dossier, and that such hypertrophic effects may be adverse. It is necessary to study the role of thyroid hormones in order to understand their role in causing this effect on the thyroid. In accordance with OECD TG 408, paragraph 31, "Other determinations that should be carried out if the known properties of the test substance may, or are suspected to, affect related metabolic profiles include calcium, phosphorus, fasting triglycerides, specific hormones, methaemoglobin and

cholinesterase. These need to be identified for chemicals in certain classes or on a case-by-case basis." Accordingly, it is necessary to measure the specific hormones thyroxine (T4), tri-iodothyronine (T3) and thyroid stimulating hormone (TSH) in serum at termination, since these hormone levels are suspected to be affected by the known properties of the substance (thyroid hypertrophy), and also in order to understand the basis and consequences of the observed follicular cell hypertrophy in thyroid. Blood samples specifically intended for hormone determination should be obtained at a comparable time of the day.

According to the test method EU B.26/OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Outcome

Based on the above considerations your testing proposal for an inhalation study for repeated dose toxicity (90 day) has to be rejected in accordance with Article 40(3)(d) of the REACH Regulation. Instead, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the following study with the registered substance subject to the present decision: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD TG 408), including measurements of the specific hormones thyroxine (T4), tri-iodothyronine (T3) and thyroid stimulating hormone (TSH) in serum at termination. It is at your discretion to perform the intended additional examinations on additional reproductive parameters during the testing program.

Notes for your consideration

ECHA notes that a revised version of OECD TG 408 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters which make the method more sensitive. You should test in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

Pursuant to Article 40(3)(b) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test under modified conditions.

Examination of the testing proposal

A pre-natal developmental toxicity study for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a pre-natal developmental toxicity study in rats according to EU B.31/OECD TG 414 by the inhalation route with the registered substance.

ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

According to the test method EU B.31/OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with rats or rabbits as a first species.

You proposed testing by the inhalation route. ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) R.7a, chapter R.7.6.2.3.2. In additon, as explained under section 1, the available oral study with the registered substance (OECD TG 422, [redacted] 2010) indicates a concern for reproductive toxicity that requires further information from studies conducted by oral route. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

In your comments to the draft decision you provided considerations on the route of administration of the requested study.

As mentioned above, ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) R.7a, chapter R.7.6.2.3.2.

ECHA took into account your comments and did not change the route of administration for the requested study.

Outcome

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, you are requested to carry out the modified study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a first species (rats or rabbits), oral route (test method: EU B.31/OECD TG 414).

Notes for your consideration

For the selection of the appropriate species you are advised to consult ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6.2.3.2 (July 2015).

ECHA notes that a revised version of OECD TG 414 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. You should test in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

Deadline to submit the requested information

In the draft decision communicated to you the time indicated to provide the requested information was 24 months from the date of adoption of the decision. Following a proposal for amendment from one of the Member State Competent Authorities, it was proposed to reduce the time to 18 months, considering that the information to be generated from the present decision is required before the extended one-generation reproductive toxicity study, requested in a separate decision on a Compliance Check of the registered substance **19 July 2018** (CCH-D-2114428794-40-01/F), can be initiated. The reduced time is considered as sufficient to perform the studies required in the present decision. Hence, ECHA has modified the deadline of the decision to 18 months.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposal(s) for examination pursuant to Article 40(1) on 23 April 2013.

ECHA held a third party consultation for the testing proposal(s) from 16 October 2014 until 1 December 2014. ECHA did not receive information from third parties.

This decision does not take into account any updates after 1 March 2016, 30 calendar days after the end of the commenting period.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation:

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).

You did not update the dossier by the given deadline.

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

ECHA received proposals for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendments.

ECHA referred the draft decision to the Member State Committee.

You did not provide any comments on the proposed amendment(s).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-60 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided by you in your registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the registration at a later stage.

2. Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the Enforcement Authorities of the Member States.

3. In relation to the information required by the present decision, the sample of the substance used for the new test(s) must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants. It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new test(s) is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new test(s) must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.

4. Your dossier has also been investigated in a compliance check and the decision CCH-D-2114428794-40-01/F requests In vitro gene mutation study in mammalian cells and Extended one-generation reproductive toxicity study. The timelines given in the two decisions allow for sequential testing.

   You may take into consideration the new information which becomes available after you generate the information specified in this decision in order to determine if there are adaptation possibilities according to column 2 or Annex XI in respect of the information required in the separate compliance check decision.

   When submitting the study results required by this decision you are invited to provide your considerations whether changes in the study design of the Extended one-generation reproductive toxicity study (test method EU B.56/ OECD TG 443) are needed based on the results of the repeated-dose toxicity and pre-natal developmental toxicity studies.