ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-2114300905-56-01/F Helsinki, 20 May 2015

DECISION ON TESTING PROPOSAL(S) SET OUT IN A REGISTRATION PURSUANT TO ARTICLE 40(3) OF REGULATION (EC) NO 1907/2006

For N-(3-(trimethoxysilyl)propyl)ethylenediamine, CAS No 1760-24-3 (EC No 217-164-6), registration number: [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 40(1) of the REACH Regulation, ECHA has examined the following testing proposals submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(d) thereof for N-(3-(trimethoxysilyl)propyl)ethylenediamine, CAS No 1760-24-3 (EC No 217-164-6), submitted by [redacted] (Registrant).

- Repeated dose toxicity study according to OECD 408 (OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents));
- Developmental toxicity/teratogenicity study according to OECD Guideline 414 (Prenatal Developmental Toxicity Study).

This decision is based on the registration dossier as submitted with submission number [redacted] for the tonnage band of 100 to 1000 tonnes per year. This decision does not take into account any updates after 5 March 2015, the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) of the REACH Regulation.

This decision does not imply that the information provided by the Registrant in his 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.

On 7 May 2013 pursuant to Article 40(1) of the REACH Regulation, ECHA initiated the examination of the testing proposals set out by the Registrant in the registration dossier for the substance mentioned above.

ECHA held a third party consultation for the testing proposals from 3 March 2014 until 17 April 2014. ECHA received information from third parties on the proposed developmental toxicity study (see section III below).

On 2 July 2014 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision.

On 8 August 2014 ECHA received comments from the Registrant.

On 21 November 2014 the Registrant updated his registration dossier (submission number [redacted]).

The ECHA Secretariat considered the Registrant's comments and update. On basis of this information the Statement of Reasons (Section III) was changed.

On 5 March 2015 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals for amendmends of the draft decision within 30 days of the receipt of the notification.

As no proposal for amendment was submitted, ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

II. Testing required

A. Tests required pursuant to Article 40(3)

The Registrant shall carry out the following test pursuant to Article 40(3)(c) of the REACH Regulation using the indicated test method and the registered substance subject to the present decision:

1. Sub-chronic toxicity study (90-day), inhalation route (Annex IX, Section 8.6.2.; test method: OECD 413) in rats

while the originally proposed test for a sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD 408) proposed to be carried out using the registered substance is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

The Registrant shall carry out the following proposed test pursuant to Article 40(3)(a) of the REACH Regulation using the indicated test method and the registered substance subject to the present decision:

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31/OECD 414) in rats or rabbits, oral route.

Note for consideration by the Registrant:

The Registrant 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 sound scientific justification, referring to and conforming with the appropriate rules in the respective Annex, and an adequate and reliable documentation.

Failure to comply with the requests in this decision, or to fulfil otherwise the information requirements with a valid and documented adaptation, shall result in a notification to the Enforcement Authorities of the Member States.

B. Deadline for submitting the required information

Pursuant to Articles 40(4) and 22(2) of the REACH Regulation, the Registrant shall submit to ECHA by **29 May 2017** an update of the registration dossier containing the information

required by this decision, including, where relevant, an update of the Chemical Safety Report. The timeline has been set to allow for sequential testing as appropriate.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposals submitted by the Registrant for the registered substance and scientific information submitted by third parties.

Tests required pursuant to Article 40(3)

1. Sub-chronic toxicity study (90-day)

a) Examination of the testing proposal

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.

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. Consequently there is an information gap and it is necessary to provide information for this endpoint.

The Registrant has submitted a testing proposal for a sub-chronic toxicity study (90-day) in rodents by the oral route (EU B.26/OECD 408). In his comments and in the dossier update subject to the present decision the Registrant provided justifications for his route selection.

The Registrant uses two lines of arguments to support the oral route instead of the inhalation route:

1. Overestimation of the exposure potential via inhalation;
2. Technical feasibility of conducting a 90-day repeated dose study via inhalation.

ECHA analysed the information in the CSR included in the updated dossier to support these arguments and balanced them to come to a conclusion on the most appropriate administration route:

Oral route

The registered substance is a liquid at ambient temperature and pressure, with a predicted boiling point of 240°C. According to the Registrant, the substance has a vapour pressure of 0.3 – 0.4 Pa at 20°C, therefore exposure to vapour is regarded as not likely.

The repeated dose toxicity study available for the registered substance (according to OECD 422) administered at 25, 125 and 500 mg/kg bw/day did not reveal obvious adverse effects. A 90-day study with oral administration would provide a more definitive toxicity profile after oral administration due to the higher statistical power and the more thorough investigations compared with a screening study according to OECD 422. Therefore the oral route is considered as an appropriate route for testing.

Inhalation route

Aerosol exposure is a likely route of exposure to workers and, at lower levels, to consumers.

In the CSR, two industrial scenarios describe the use of the substance in industrial spray applications as [redacted] PROC 7 (industrial spraying) with LEV and optional RPE,

where aerosol is released. These are ES 6: Preparation and use of non-metal surface treatment solution/dispersion (p 196, Table 9.6.4 of the CSR) and ES 8: Use in polymer preparation (p 217, Table 9.8.4 of the CSR) calculated to result in inhalation exposures of 19 mg/m3.

Non-industrial spraying applications are indicated for use in coatings and in masonry products for professional workers. The concentration of the registered substance in formulations is indicated as [redacted] (worst case assumption by the Registrant). For instance, in table 9.4.4, p 174 of the CSR, PROC 7 (industrial spraying with no respiratory protection) results for workers in a maximum exposure estimates (ECETOC TRA) of 6.5 mg/m^3. In table 9.5.4, p 185 of the CSR, PROC 11 (non-industrial spraying with no respiratory protection) results for professional use in maximum exposure estimates (Stoffenmanager) of 3.1 mg/m^3. For professional use of masonry products in table 9.14.4, p 274, PROC 11 (high pressure) an inhalation exposure of 11 mg/m^3 is calculated.

The Registrant uses a report on an occupational monitoring study conducted with isobutyltriethoxysilane as argument to use a 90% percentile value in the Stoffenmanager for the registered substance. The Registrant states on page 273 of the CSR: "*Results from a spray application occupational monitoring study with isobutyltri-ethoxysilane, a substance with a higher vapour pressure (49 Pa) than the registration substance ([redacted], 2010) with personal sampling (short time measurement; without re-filling of the storage vessel, no interruption of spraying procedure and overhead spraying, close to two walls) gave a measured total concentration (aerosol+vapor) of 269 mg/m^3 for outdoor use during a short application time.*" This evidence suggests a rather high potential for exposure, if such result is applied to the registered substance. Much of this exposure will be aerosol.

In the update of the dossier, the Registrant has added an additional good practice advice to operational conditions and risk management measures associated with potential aerosol exposure: "*The use of RPE where potential for generation of aerosol and high exposure to aerosol that may contain the substance (e.g. from spraying).*" ECHA considers this as an unreliable measure to reduce aerosol exposure. It is optional and leaves it to the user to determine what high exposure means.

When the registered substance is inhaled, systemic uptake is likely. The Registrant reports on page 59 of the CSR and in section 7.1 of the IUCLID dossier on the estimation of the blood:air partition coefficient: "*Using these values for the parent and hydrolysis products results in very high blood:air partition coefficients of approximately 4.4E+06:1 and 1.9E+09:1 respectively, meaning that, if lung exposure occurred there would be significant uptake in to the systemic circulation. However, their high water solubility may lead to some them being retained in the mucus of the lungs therefore limiting absorption.*" ECHA concludes that the inhalation route is appropriate to also investigate the systemic effects of the registered substance thereby clarifying if possible route specific systemic effects occur, which may not be observed when the substance is administered orally.

In an acute aerosol inhalation study conducted with measured concentrations of 0.515, 1.06, 1.49, 2.44 and 5.75 mg/l 9 out of 10 test animals in the highest dose group and 8 out of 10 in the second highest dose group died. The following observations were reported: "*Severely congested lungs were observed in all deceased animals. The observation is considered to be associated with the cause of death. Areas of severe congestion together with pale raised hardened areas were also observed in the surviving female exposed to 5.75 mg/l. Pale raised lungs were also observed in the lungs of a proportion of surviving rats of both sexes in all other groups exposed to the test aerosol.*" On the basis of these findings the registered substance is classified as "Acute Tox. 4". ECHA considers the results as indication of a specific interaction of the registered substance with the respiratory tract

which can be expected to be expressed at much lower concentrations in a repeated dose toxicity study conducted via the inhalation route.

The substance is characterised as mildly irritating in skin irritation studies and is classified as Eye damage 1 (H318: Causes serious eye damage). Also on this basis, local effects on the respiratory tract after prolonged exposure cannot be excluded and cannot be extrapolated from other routes.

The outcome of this analysis demonstrates that exposure to aerosols is likely. Such exposure might lead to local effects and once inhaled also systemic uptake of the substance is likely. Therefore, the inhalation route is also an appropriate route for testing.

Conclusion on the most appropriate route of administration
In Annex IX, Section 8.6.2 column 2 it is stated that "*testing by the inhalation route is appropriate if exposure of humans via inhalation is likely taking into account the vapour pressure of the substance and/or the possibility of exposure to aerosols, particles or droplets of an inhalable size*" (emphasis added). The Registrant did not provide information on the droplet size of the aerosols formed. In absence of this information, exposure via spraying application indicates a likelihood for inhalation exposure via aerosols of an inhalable size.

The Registrant states in the CSR: "*All applications/PROCs, including spray applications, have been shown in the assessment to be safe, based on systemic DNELs, without use of respiratory protective equipment (RPE) (see Sections 9 and 10). Use of RPE are however specified as additional good practise, in addition to the present assessment, where there is potential for generation and high exposures to aerosol that may contain the substance. Therefore, based on the above qualitative assessment, it is considered that there is limited potential of exposure to the registration substance from aerosol generation. Hence, there is no immediate risk to any potential local effects of the substance from uses assessed.*"

The Registrant has not derived a DNEL for long-term inhalation, local effects. The DNEL for long-term inhalation, systemic effects, of 35.3 mg/m^3 for workers and 8.7 mg/m^3 for the general population is based on an extrapolated NOAEC of 882 mg/m^3 for workers and 435 mg/m^3 for the general population based on the NOAEL of 500 mg/kg bw/d from the oral OECD screening study. For long term inhalation, local effects, the conclusion is "no hazards identified", however no experimental information is presented that would support this conclusion. The derived DNEL for long-term inhalation, systemic effects, appears not suitable to demonstrate that workers are protected against long term local respiratory tract effects possibly occurring specifically after inhalation exposure. Reasons for this conclusion are the expected potential of the substance for respiratory tract irritation, the results obtained in the acute study conducted with aerosol in rats, and the properties of the substance facilitating systemic uptake after inhalation. The good practice advice (added to the updated CSR) of using RPE, if potential for high aerosol exposure is expected, is optional and leaves it to the user to determine what high exposure means. It is not clear, how this would lead to safe use of the substance in the absence of quantitative information.

Having considered all these aspects ECHA regards the inhalation route as the most appropriate route for testing since an inhalation study is expected to provide more critical information for the hazard profile and the safe use of the registered substance when compared with a study with oral administration.

Technical feasibility of conducting a 90-day repeated dose study via inhalation
The other argument of the Registrant to support the proposed oral route of administration is related to the substance properties. "*The oral route is proposed due to the technical*

challenges expected with the conduct of a 90-day repeat dose study by the inhalation route". The main reasons provided are related to the assumed unstable nature of the registered substance in aqueous solutions. "*Furthermore, in an acute inhalation toxicity study presented in the dossier, the test substance was aerosolized (Key Acute toxicity: [redacted], 2000a, section 5.2.1.2), with a lowest tested concentration of 0.515 mg/L (515mg/m3). In the study report it was noted that the test substance was observed to form a solid substance on contact with moisture. It was considered that the water vapour produced by the animals during exposure resulted in most of the test substance being converted to an aerosol of this solid. It was technically challenging to achieve a standardized testing atmosphere with the required substance concentrations. The ratio between nominal and analysed concentration varied by a factor of 3 to 4.3 over the dose range. Similar condensation reactions with water are described in the Chemical Safety Report (section 2.2.3.2), for water-based coating spray applications.*"

The Registrant concludes: "*Therefore, based on the known physicochemical behaviour of the test substance and the observations made during the acute inhalation study, it is considered that the generation of a meaningful, standardised and stable test atmosphere concentration for 6 hours daily for 90-days is technically not possible. Therefore to investigate the systemic toxicity profile of the substance the oral route of administration is proposed.*"

ECHA considers the arguments presented as not convincing.
(1) ECHA considers that the test atmosphere concentrations may well be determined even if there are technical difficulties in generating a stable aerosol concentration of the registered substance. The presented acute inhalation study used a gravimetric method to determine the total exposure concentration derived from the test substance, including possibly formed condensation products.
(2) The generation of a test atmosphere for concentrations applicable in a repeated dose toxicity study has not been proven to be technically not possible. It is not clear what fraction of the registered substance would form condensation products at which exposure concentrations and at which kinetics when coming into contact with moisture exhaled by the animals in the experimental setup. So it is not known whether at the lower exposure concentrations of a 90-day study such reactions would concern a minor or major fraction of the registered substance and would be complete during the formation of the aerosol or not. Moreover, under the IUCLID section 4.8 (Water solubility) it is stated that the hydrolysis products are N-(3 -trihydroxysilyl)propyl)-ethylenediamnine and methanol. Neither the speed of the hydrolysis under exposure conditions for a 90-day study nor the speed of any subsequent condensation reactions is provided. In conclusion, it is not clear why and how such reactions would make it impossible to conduct an aerosol study.
(3) It is not known whether the hydrolysis products and/or the condensation compounds add to the possible toxicity of the registered substance. Moreover, such condensation reaction may also occur with biological molecules in the respiratory tract and thereby could be viewed as possible mechanism for toxicity.
(4) The possible formation of a solid from the test substance when coming into contact with water did not prevent the animals in the acute inhalation study to show severe respiratory tract effects leading to death at high concentrations.

ECHA therefore does not accept the argument that the conduct of an aerosol study is technically not possible.

The Registrant did not specify the species to be used for testing. According to the test method OECD 413 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

b) Outcome

Therefore, pursuant to Article 40(3)(d) and (c) of the REACH Regulation, the Registrant is requested to carry out the following study with the registered substance subject to the present decision: Sub-chronic toxicity study (90-day) in rats, inhalation route (test method: OECD 413).

2. Pre-natal developmental toxicity study

a) Examination of the testing proposal

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

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.

The Registrant has submitted a testing proposal for a pre-natal developmental toxicity study according to EU B.31/OECD 414.

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

The Registrant did not specify the species to be used for testing. He did not specify the route for testing. According to the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

A third party has commented that combined repeated dose toxicity study with the reproduction/developmental toxicity screening test indicated a low potential for systemic and reproductive toxicity. The substance rapidly hydrolyses to methanol and trisilanols which are reactive and polymerise at concentrations > 500 ppm forming not bioavailable resins. Consequently the registrant may consider fulfilling the information requirements in accordance with Annex XI of Regulation 1907/2006 by read-across to the hydrolysis product methanol.

ECHA acknowledges that the third party has proposed for the Registrant to consider a read across approach to methanol. This is based on the hydrolysis of the registered substance to methanol and to trisilanols.

ECHA notes that it is the Registrant's responsibility to consider and justify any adaptation of the information requirements in accordance with Annex XI. This would require that the Registrant documents to a sufficient extent that the properties of the substances are likely to be similar according to the criteria laid down in Annex XI, Section 1.5. of the REACH

Regulation and following ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.6: QSAR and grouping of chemicals (version May 2008).

However, ECHA notes that the information provided by the third party in its current form is insufficient for demonstrating that the conditions of Annex XI, Section 1.5. of the REACH Regulation are met. For example, the third party does not take into account the trisilanol toxicity (in this case N-(3-(trihydroxysilyl)propyl)ethylenediamine) or intermediate hydrolysis products in the read across approach since these are claimed to polymerize, although such polymerisation has not been demonstrated to occur under physiological conditions.

Therefore, based on the information provided, the criteria of Annex XI, Section 1.5. are not met to adapt the pre-natal developmental toxicity study.

c) Outcome

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

IV. Adequate identification of the composition of the tested material

The process of examination of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the new studies meet real information needs. Within this context, the Registrant's dossier was sufficient to confirm the identity of the substance to the extent necessary for examination of the testing proposal. The Registrant must note, however, that this information, or the information submitted by other registrants of the same substance, has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.
In relation to the proposed tests, the sample of substance used for the new studies must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is within the specifications of the substance composition that are given by the joint registrants. It is the responsibility of all joint registrants of the same substance to agree to the tests proposed (as applicable to their tonnage level) and to document the necessary information on their substance composition.

In addition, it is important to ensure that the particular sample of substance tested in the new studies 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 by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new studies 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 studies to be assessed.

V. General requirements for the generation of information and Good Laboratory Practice

ECHA reminds registrants of the requirements of Article 13(4) of the REACH Regulation that ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP).

According to Article 13(3) of the REACH Regulation, tests that are required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or the European Chemicals Agency as being appropriate. Thus, the Registrant shall refer to Commission Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 as adapted to technical progress or to other international test methods recognised as being appropriate and use the applicable test methods to generate the information on the endpoints indicated above.

VI. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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