ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000005474-72-02/F Helsinki, 30 September 2014

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

For 2,6,10-trimethyldodecane, CAS No 3891-98-3 (EC No 622-542-2), 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 2,6,10-trimethyldodecane, CAS No 3891-98-3 (EC No 622-542-2), by [redacted] (Registrant).

- Repeated dose 90-day oral toxicity study (OECD 408) in rats
- Pre-natal developmental toxicity study (OECD 414)
- Two-generation reproduction toxicity study (OECD 416)

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 24 July 2014, 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.

The examination of the testing proposals was initiated upon the date when receipt of the complete registration dossier was confirmed on 8 January 2014.

ECHA held a third party consultation for the testing proposals from 18 February 2014 until 4 April 2014. ECHA received information from third parties (see section III below).

On 28 May 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. That draft decision was based on submission number [redacted].

On 3 July 2014 ECHA received comments from the Registrant on the draft decision. On 1 July 2014 the Registrant updated his registration dossier (submission number [redacted]).

The ECHA Secretariat considered the Registrant's comments and update. The information is reflected in the Statement of Reasons (Section III) whereas no amendments to the Information Required (Section II) were made.

On 24 July 2014 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 amendment 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 proposed/modified tests pursuant to Article 40(3)(a and b) and 13(4) of the REACH Regulation using the indicated test methods and the registered substance subject to the present decision:

1. Sub-chronic toxicity study (90-day) in rats, oral route (Annex IX, Section 8.6.2.; test method: EU B.26/OECD 408) modified to include urinalysis and in case autopsy or the urinanalysis indicate kidney effects, a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2u globulin nephropathy.
2. Pre-natal developmental toxicity study in rats or rabbits, oral route (Annex IX, Section 8.7.2.; test method: EU B.31/OECD 414).

while the originally proposed test for a Two-generation reproduction toxicity study (OECD 416) proposed to be carried out using the registered substance is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

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 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, will 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 **7 October 2016** an update of the registration dossier containing the information required by this decision. 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.

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

a) Examination of the testing proposal

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

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 proposed testing by the oral route. ECHA notes that the registered substance is a liquid with a low vapour pressure. ECHA notes further that the Registrant has carried out a qualitative risk characterisation and therefore no quantitative exposure estimates have been derived, nevertheless no spraying, brushing or roller application is reported. In light of the physic-chemical properties of the substance and the information provided on the uses and human exposure, ECHA considers that testing by the oral route is most appropriate.

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

ECHA notes that the registered substance is a branched hydrocarbon with 3 methyl groups attached to a chain of 12 carbons. Such substances may induce alpha-2u-globin-mediated nephropathy. There is no 28-day study available for the registered substance to evaluate if kidney effects were observed in male rats, but according to chemical profiling performed by ECHA (Lhasa Ltd, Derek Nexus) there is an alert of possibility of this mechanism for the registered substance. Since humans do not excrete alpha-2u-globin, this mode of action is not relevant to humans. For this reason, ECHA decided to modify the Registrant's testing proposal by including urinalysis (which is optional in paragraph 30 of OECD 408, and the relevant part of Section 1.5.2.2. of EU Method B.26) to investigate kidney function, and in case kidney effects (nephropathy) are observed in autopsy/histologically or indicated by urinanalysis then the full histopathological examination (paragraph 36 of OECD 408, Section 1.5.2.4. of EU Method B.26), shall include immunohistochemical investigation of renal pathology to determine if the pathology is indeed mediated by alpha-2u globulin.

In his comments according to Article 50(1) of REACH the Registrant explained that a new *in vitro* study using everted rat small intestine sacs shows no detectable absorption of the registered substance from the rat small intestine. In addition the parallel studies with n-alkanes show diminishing absorption with increased carbon chain length with no evidence of absorption with C16 and C18 alkanes. The apparent lack of absorption following oral ingestion is also supported by results of an oral OECD 422 study in rats with Alkanes C16-C20,iso (aka. tetrabutane).

ECHA notes that "no evidence of absorption" is part of an adaptation in accordance with Annex IX, Section 8.6.2., column 2, fourth indent. This adaptation specifies that a sub-

chronic toxicity study (90-day) does not need to be conducted if "*the substance is unreactive, insoluble and not inhalable and there is no evidence of absorption and no evidence of toxicity in a 28-day study, particularly if such a pattern is coupled with limited human exposure*". ECHA notes that all criteria need to be met.

ECHA observes that the Registrant's comment addresses only the criterion concerning absorption. For the other conditions of column 2 ECHA notes that based on Registrant's toxicokinetic considerations in the dossier the substance is not unreactive, there is no 28-day study available to asses repeated dose toxicity and although the Registrant has not carried out a quantitative exposure assessment there are reported uses that indicate a potential of human exposure (e.g. use as a fuel and fuel additive). ECHA concludes that it is not demonstrated that conditions of Annex IX 8.6.2 column 2 are fulfilled.

Finally ECHA notes that the Registrant, in his comments according to Article 50(1) expressed a wish to discuss those new in vitro data in a dialogue with ECHA. ECHA points out that it is not foreseen in the REACH Regulation to have a dialogue with the Registrant during the decision-making after the Registrant has submitted his formal comments while those formal comments are addressed above.

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 indicated that a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD Guideline 422) would be adequate to fulfil the information requirements for the registered substance for the developmental and repeated dose toxicity endpoints.

ECHA notes that the substance subject to the present registration is registered for the tonnage band 100 to 1000 tonnes per annum. For that tonnage band 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. Therefore, the information submitted does not provide a sufficient basis on which to reject the proposed test.

c) Outcome

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, the Registrant is requested to carry out the proposed 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 408) modified to include urinalysis and in case autopsy or the urinanalysis indicate kidney effects, a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2u globulin nephropathy.

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 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.

In his comments according to Article 50(1) of REACH the Registrant referred to low absorption of the registered substance from the intestine (see section III.1.a above).

ECHA notes that "no evidence of absorption" is part of an adaptation in accordance with Annex IX, Section 8.7., column 2, third indent. This adaptation specifies that a pre-natal developmental toxicity study does not need to be conducted if "*the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure.*" ECHA notes that all three criteria need to be met.

ECHA observes that the Registrant's comment addresses only the criterion concerning absorption. For the other conditions of column 2 ECHA notes that there is no 28-day study or reproductive toxicity screening study available to confirm a "*low toxicological activity*" and although the Registrant has not carried out a quantitative exposure assessment there are reported uses that indicate a potential of human exposure (e.g. use as a fuel and fuel additive). ECHA concludes that it is not demonstrated that conditions of Annex IX 8.7. column 2 are fulfilled.

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 indicated that a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD Guideline 422) would be adequate to fulfil the information requirements for the registered substance for the developmental and repeated dose toxicity endpoints.

ECHA notes that the substance subject the present registration is registered for the tonnage band 100 to 1000 tonnes per annum. For that tonnage band 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. Therefore, the information submitted does not provide a sufficient basis on which to reject the proposed test.

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).

3. Two-generation reproduction toxicity study

a) Examination of the testing proposal

Pursuant to Article 40(3)(d) of the REACH Regulation, ECHA may reject a proposed test.

According to Annex IX, Section 8.7.3., a two-generation reproductive toxicity study is an information requirement if adverse effects on reproductive organs or tissues have been observed in a 28-day or 90-day repeated dose toxicity study. ECHA notes that there is no 28-day or 90-day repeated dose toxicity study available in the registration dossier, while the Registrant has proposed to perform a 90-day study. ECHA notes further that the Registrant has not included any justification why he proposes to perform a two-generation reproductive toxicity study at tonnage level 100 – 1000 tonnes per annum.
ECHA considers that the proposed study is not necessary to fulfil the information requirement of Annex IX, Section 8.7.3. of the REACH Regulation because no adverse effects on reproductive organs or tissues have been observed in a 28-day or 90-day repeated dose toxicity study.

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 might be sufficient to fulfil this information requirement.

A third party has indicated that the tonnage level of the registered substance does not require the conduct of a two-generation reproduction toxicity study.

As already stated under section III.3.a above, ECHA notes that according to Annex IX, Section 8.7.3., a two-generation reproductive toxicity study is an information requirement if adverse effects on reproductive organs or tissues have been observed in a 28-day or 90-day repeated dose toxicity study while for the substance subject to the present decision there is no 28-day or 90-day repeated dose toxicity study available in the registration dossier that could trigger a two-generation reproductive toxicity study.

c) Outcome

ECHA has examined this testing proposal considering all the relevant and available data in the technical dossier and the information submitted by third parties during the public consultation. ECHA concludes that there is no information gap for the standard information requirement of Annex IX, 8.7.3.

Therefore, pursuant to Article 40(3)(d) of the REACH Regulation, the proposed test for a Two-generation reproduction toxicity study (OECD 416) is rejected.

Notes for consideration by the Registrant

ECHA notes that while a pre-natal developmental toxicity study is requested under section II of the present decision and the testing proposal for two-generation reproductive toxicity study is rejected, the endpoint for reproductive toxicity regarding fertility and peri-natal toxicity is not covered in the dossier. ECHA strongly recommends that the Registrant considers how this data gap is best filled and includes this information in the updated dossier.

Guidance on how to fulfil this information requirement can be found in the REACH Guidance on information requirements and chemical safety assessment R.7. More specifically, paragraph 7.6.6.3 outlines the testing strategy for reproductive toxicity.

In his comments according to Article 50(1) of REACH the Registrant explained that the registered substance is not classified for reproductive toxicity, carcinogenicity or mutagenicity and based on available information it is not expected to be absorbed in significant amounts or cause systemic toxicity. The Registrant further explained that (1) straight and branched chain alkenes do not raise structural alerts for reproductive toxicity, (2) data indicate diminishing absorption with increasing chain length and low potential for absorption above C14 and (3) a related material, (Alkanes C16-C20,iso) also showed no effects in an oral 422 study at levels up to 1000 mg/kg. For these reasons, the Registrant believes there is sufficient weight of evidence showing that the registered substance is unlikely to present a hazard to reproduction and should a 90-day repeat dose toxicity study in rats still be required, this would provide additional supporting information for the assessment of reproductive toxicity potential.

ECHA notes that the data supporting the above arguments 1 to 3 as well as the 90-day study subject to the present decision are not yet included in the dossier. Therefore it is not possible for ECHA to assess whether they adequately support the proposed weight of evidence.

IV. Adequate identification of the composition of the tested material

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. If the registration of the substance covers different grades, the sample used for the new studies must be suitable to assess these.

Furthermore, 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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