Decision number: TPE-D-2114307740-59-01/F Helsinki, 28 August 2015

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

For α,α,α',α'-tetramethylxylene-α,α-diol, EC No 248-256-4 (CAS No 27138-01-8), 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 α,α,α',α'-tetramethylxylene-α,α-diol, EC No 248-256-4 (CAS No 27138-01-8), submitted by [redacted] (Registrant).

- 90-day oral toxicity study (OECD 408) with inclusion of urinalysis and a full histopathological examination of the testes, weights of reproductive organs and assessor glands as well as immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2u globulin nephropathy.

- Developmental toxicity / teratogenicity study (OECD 414).

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 27 May 2015, i.e. 30 calendar days after the end of the commenting period .

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.

ECHA received the registration dossier containing the above-mentioned testing proposals for further examination pursuant to Article 40(1) on 16 April 2013.

ECHA held a third party consultation for the testing proposals from 14 August 2014 until 29 September 2014. ECHA received information from third parties (see section III below).

On 20 March 2015 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 24 April 2015 ECHA received comments from the Registrant agreeing to ECHA's draft decision.

On 11 June 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 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 tests pursuant to Article 40(3)(a) 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), oral route (Annex IX, Section 8.6.2.; test method: EU B.26/OECD 408) in rats, modified to include urinalysis and immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2u globulin nephropathy. It is at the Registrant's discretion to perform the intended additional examinations to better evaluate reproductive effects as well as the immunohistochemical investigation during the testing program.

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 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 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.

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 **4 September 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.

A. Tests required pursuant to Article 40(3)

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

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 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 rats via the oral route (EU B.26/OECD 408) with the following justification *"A 90-day oral toxicity study in rats is proposed. In order to better evaluate reproductive effects of repeated dose exposure, histopathology of the testes, as well as weights of reproductive organs and accessory glands will be taken (i.e. testis, epididymis, prostate, seminal vesicle). In addition, immunohistochemical analysis of kidney should be performed in order to characterize alpha-2-microglobuline in male kindey."*

ECHA however notes that the proposed test guideline in the IUCLID technical dossier and the CSR is *"OECD Guideline 409 (Repeated Dose 90-Day Oral Toxicity in Non-Rodents) rat"* whereas in the header of the IUCLID endpoint the Registrant indicated *"90-day toxicity by oral route in rats".*

ECHA reminds that the OECD test guideline 409 (90d oral study in non-rodents) should only be used:
- where effects observed in other studies indicate a need for clarification/characterisation in a second, non-rodent species, or
- where toxicokinetic studies indicate that the use of a specific non-rodent species is the most relevant choice of laboratory animal, or
- where other specific reasons justify the use of a non-rodent species.

ECHA notes that there is no indication in the dossier motivating the use of the 90d study in non-rodents.

ECHA considers that the sub-chronic toxicity study (90 day) study via the oral route is appropriate to fulfil the information requirement of Annex IX, Section 8.6.2. of the REACH Regulation because the proposed route is the most appropriate route of administration having regard to the likely route of human exposure due to the following reasons.

The Registrant proposed testing by the oral route. In light of the physico-chemical properties of the substance, that is, low vapour pressure, not classified as corrosive/ irritating to the skin and/or damaging/irritating to the eyes, water soluble, solid crystalline powder, and the information provided on the uses and human exposure (i.e., no uses with spray application), ECHA considers that testing by the oral route is most appropriate. It is also noted that the information provided on granulometry indicates that the substance does not include a significant proportion of particles of an inhalable size.
Therefore, ECHA agrees with the Registrant that the oral route is the most appropriate route of administration for testing to fulfil the standard information requirement for Annex IX, Section 8.6.2.

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.

The Registrant proposed to extend the sub-chronic toxicity study (90 day) by including additional examinations/parameters: *"histopathology of the testes, as well as weights of reproductive organs and accessory glands will be taken (i.e. testis, epididymis, prostate, seminal vesicle)"and "in addition, immunohistochemical analysis of kidney should be performed in order to characterize alpha-2-microglobuline in male kindey".*

ECHA notes, that it is at the Registrant's discretion to perform the intended additional histopathology examinations (i.e. testis, epididymis, prostate, seminal vesicle) during the testing program and use the results to ensure the safe use of the substance.
However, the Registrant is reminded that, if the condition of Annex IX, Section 8.7.3., Column 1 is fulfilled, the proposed extension of the study presently requested does not fulfil the standard information requirement in the registration dossier for reproductive toxicity set out in Annex IX, Section 8.7.3.

In the repeated dose toxicity 28 day (OECD 407) study microscopic findings in kidney (hyaline droplets in 4/5 and 5/5 males at 300 and 1000 mg/kg/day, respectively, together with an increase in tubular basophilia in 3/5 males at 1000 mg/kg/day considered as adverse, tubular dilation and infiltrate of mononuclear cells), and in adrenals (non adverse increased vacuolation in 2/5 males at 1000 mg/kg/day) were observed in male rats. The fact that these effects were only observed in male rats indicates that the registered substance may induce alpha-2u-globulin-mediated nephropathy. Since humans do not excrete alpha-2u-globulin, this mode of action is not relevant to humans.
For this reason, ECHA decided to include in the request for a sub-chronic toxicity study 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 a full histopathological examination (paragraph 36 of OECD 408, Section 1.5.2.4. of EU Method B.26), which is to include immunohistochemical investigation of renal pathology to determine if the pathology is indeed mediated by alpha-2u globulin.

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 *"Treatment-related findings in an oral sub-acute study (compliant to OECD Test Guideline 407) at 100, 300 and 1000 mg/kg bw/d were largely confined to signs of male-rat specific nephropathy. An LD50 value of 4655 mg/kg obtained with an isolated isomer of the substance and further registration data are indicative of a 'low toxicity profile'.*
A review on more than 40 low toxicity chemicals has shown that the results of the 28-day study are predictive of low toxicity in the 90-day repeated dose toxicity study. Under these circumstances waiving the proposed oral sub-chronic toxicity study in a weight-of-evidence approach may be considered."

ECHA notes that it is the Registrant's responsibility to consider and justify in the registration dossier any adaptation of the information requirements 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 third party comment addressed only the criterion concerning low toxicity. However, the third party did not provide sufficient evidence of no toxicity. Furthermore, an adaptation would also need to demonstrate that the other conditions of the adaptation possibility are fulfilled.

Therefore the criteria listed in Column 2 of Annex IX, section 8.6.2., fourth indent are not met and the information requirement for the sub-chronic toxicity study (90-day) cannot be adapted only on this basis.

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 : Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD 408) including urinalysis (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 a full histopathological examination (paragraph 36 of OECD 408, Section 1.5.2.4. of EU Method B.26), which is to include immunohistochemical investigation of renal pathology to determine if the pathology is indeed mediated by alpha-2u globulin.

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

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 in rats according to EU B.31/OECD 414 with the following justification: "There is no information available. A developmental toxicity study in rats on the meta isomer alone has been performed but has been invalidated due to severe protocol deficiencies". Furthermore, the registrant waives the OECD 421 screening study: *"No effects on reproductive organs were found in the 28-day OECD 407 study summarized elsewhere. These results suggest a low risk for reproductive toxicity; therefore, we are waiving the requirement for a reproductive toxicity study. An extended 90-day subchronic toxicity study and an OECD 414 developmental toxicity study are also* proposed, and this proposed data waiver may be re-evaluated when the results of those studies are available. *This is in line with fact sheet ECHA-09-FS-05-EN".*

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 proposed testing in rats. 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) 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. 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.

Authorised[1] by Guilhem De Seze, Head of Unit, Evaluation

[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.