EUROPEAN CHEMICALS AGENCY

Decision number TPE-D-0000003068-75-01/F Helsinki, 20 December 2012

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

For Di-tert-butyl 1,1,4,4-tetramethyltetramethylene diperoxide, CAS No 78-63-7 (EC No 201-128-1), 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 in accordance with Articles 10(a)(ix) and 12 (1)(e) thereof for Di-tert-butyl 1,1,4,4-tetramethyltetramethylene diperoxide CAS No 78-63-7 (EC No 201-128-1), by [redacted] (Registrant), latest submission number [redacted] for the tonnage band of [redacted] per year:

- Viscosity (OECD 114)
- 90-day oral toxicity study (OECD 408).
- Developmental toxicity / teratogenicity study (OECD 414) in rats.

This decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band of [redacted] per year. This decision does not take into account any updates after 19 July 2012, 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 22 July 2011, 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 14 October 2011 until 28 November 2011. ECHA did receive information from third parties (see section III below).

On 22 March 2012 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 23 April 2012 ECHA received comments from the Registrant.

ECHA considered the Registrant's comments received. The comments are reflected in the Statement of Reasons (Section III) whereas no amendments to the Testing Required (Section II) were made.

On 19 July 2012 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 to amend the draft decision within 30 days of the receipt of the notification.

Subsequently, one Competent Authority of a Member State submitted a proposal for amendment to the draft decision.

On 22 August 2012 ECHA notified the Registrant of the proposal for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposal for amendment within 30 days of the receipt of the notification.

On 3 September 2012 ECHA referred the draft decision to the Member State Committee.

ECHA reviewed the proposal for amendment received and did not amend the draft decision.

The Registrant did not provide comments on the proposed amendment.

A unanimous agreement of the Member State Committee on the draft decision was reached on 8 October 2012 in a written procedure launched on 26 September 2012 and ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Testing required

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

1. Viscosity (Annex IX, 7.17.; test method: OECD 114);
2. Pre-natal developmental toxicity study in rats or rabbits, oral route (Annex IX, 8.7.2.; test method: EU B.31/OECD 414).

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

3. Sub-chronic toxicity study (90-day) in rats, oral route (Annex IX, 8.6.2.; test method: EU B.26/OECD 408) modified to include urinalysis and 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.

The Registrant shall determine the appropriate order of the studies taking into account the possible outcome and considering the possibilities for adaptations of the standard information requirements according to column 2 provisions of the respective Annex and those contained in Annex XI of the REACH Regulation.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **20 December 2014** an update of the registration dossier containing the information required by this decision.

Data from a second pre-natal developmental toxicity study on another species is a standard

information requirement according to Annex X, 8.7.2. of the REACH Regulation. The Registrant should firstly take into account the outcome of the pre-natal developmental toxicity on a first species and all other relevant available data to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI. If the Registrant considers that testing is necessary to fulfil this information requirement, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species.

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. Viscosity

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

Viscosity is a standard information requirement as laid down in Annex IX, section 7.17 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 generate the data for this endpoint.

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.

Pre-natal developmental toxicity studies are part of the standard information requirements as laid down in Annexes IX and X, 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 proposed the test to be done in rats. However, the Registrant did not specify the route to be used 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

The third party proposes a strategy to be used before deciding whether the pre-natal developmental study should be conducted: read-across to decomposition product should be used.

The third party has proposed a strategy for ECHA to consider before further tests on animals are requested. However, third parties were invited, as specified by Article 40(2) of the REACH Regulation to submit "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal". As the proposal for a strategy as such cannot be regarded information or studies, ECHA concludes that this is not a sufficient basis to fulfil the data/information requirement.

In addition, ECHA acknowledges the information provided by the third party but notes that it is the responsibility of the Registrant to use read across. Furthermore, the registrant has to justify that the criteria set out in Annex XI, 1.2. or 1.5. of the REACH Regulation, respectively, are met and that the information is a sufficient basis to fulfil the data/information requirements.

In addition, as the third party mentions ("TBA [tertiary-butyl alcohol] was anticipated to be the major hydrolytic product but no proof was documented in the dossier"), it is not certain that TBA is the main decomposition product. In fact, tertiary-butyl alcohol could not be detected in samples of the hydrolysis study.

c) Outcome

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

When considering the need for a testing proposal for a prenatal developmental toxicity study in a second species, the Registrant should take into account the outcome of the pre-natal developmental toxicity study on the first species and all available data to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI; for example if the substance meets the criteria for classification as toxic for reproduction Category 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, or alternatively, if Weight of Evidence assessment of all relevant available data provides scientific justification that the study in a second species is not needed.

3. 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, but modifying the conditions under which the test is to be carried out.

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 generate the data for this endpoint.

The Registrant proposed testing by the oral route. In the light of the physico-chemical properties of the substance and the information provided on the uses and human exposure, ECHA considers that testing by the oral route is appropriate.

The Registrant did not specify the species to be tested. According to the test method EU B.26/OECD 408 the rat is the preferred rodent species. ECHA considers this species as being

appropriate. However, in the oral 28-day study in male rats "increased incidence/severity of the hyaline droplet and tubular basophilia were observed at 60 mg/kg/day and 200 mg/kg/day and tubular necrosis was observed at 200 mg/kg/day". 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 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 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.

The Registrant, in his comments submitted according to Article 51(1) of the REACH Regulation, suggests that instead of the proposed immunohistochemical investigation, firstly the results of the standard histopathological examination should be investigated whether there are eosinophilic accumulations in the kidney in male rat only. The Registrant proposes that Mallory-Heidenhain staining investigation would only be carried out, if eosinophilic accumulations are observed in the male rat only.

ECHA considers that since there are strong indications that the observed adverse effects in kidney in male rat (hyaline droplets in renal histopathology, renal tubular necrosis) are mediated through alpha-2u-globulin mechanism, the required immunohistochemical staining and analysis are necessary. Concerning the staining method, the Mallory-Heidenhain stain proposed by the Registrant is not considered appropriate to visualize alpha-2u-globulin in kidney histopathological examination, since it is not specific for alpha-2u-globulin. Instead, immunohistochemical staining of alpha-2u-globulin should be performed. Therefore, the draft decision is not amended.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation.

The third party proposes a strategy to be used before deciding whether a 90-day study should be conducted: 1) the results of the 28-day study should be used and 2) read-across to decomposition product (tertiary-butyl alcohol, TBA) should be used.

The third party has proposed a strategy for ECHA to consider before further tests on animals are requested. However, third parties were invited, as specified by Article 40(2) of the REACH Regulation to submit "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal". As the proposal for a strategy as such cannot be regarded information or studies, ECHA concludes that this is not a sufficient basis to fulfil the data/information requirement.

In addition, ECHA acknowledges the information provided by the third party but notes that it is the responsibility of the Registrant to use read across. Furthermore, the Registrant would have to justify that the criteria set out in Annex XI, 1.2. or 1.5. of the REACH Regulation, respectively, are met and that the information is a sufficient basis to fulfil the data/information requirements.

In addition, as the third party mentions ("TBA was anticipated to be the major hydrolytic product but no proof was documented in the dossier"), it is not certain that TBA is the main decomposition product. In fact, TBA could not be detected in samples of the hydrolysis study.

c) Outcome

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, the Registrant is required to carry out the following modified study: Sub-chronic toxicity study (90-day) in rats, oral route (Annex IX, 8.6.2.; test method: EU B.26/OECD 408) modified to include urinalysis and 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.
At any time, the Registrant shall take into account that there may be an obligation to make every effort to agree on sharing of information and costs with other Registrants.

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

ECHA always 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). National authorities monitoring GLP maintain lists of test facilities indicating the relevant areas of expertise of each facility.

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.

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://echa.europa.eu/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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