EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-2114292449-35-01/F Helsinki, 27 January 2015

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

For bis(4-(1,1,3,3-tetramethylbutyl)phenyl)amine, CAS No 15721-78-5 (EC No 239-816-9), 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 egistration dossier in accordance with Articles 10(a)(ix) and 12(1)(d) thereof for bis(4-(1,1,3,3-tetramethylbutyl)phenyl)amine, CAS No 15721-78-5 (EC No 239-816-9), submitted by [redacted] (Registrant).

- Repeated dose 90-day oral toxicity study (OECD 408);
- 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 30 October 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.

On 20 June 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 18 February 2014 until 4 April 2014. ECHA received information from third parties (see section III below).

On 5 September 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.

By 13 October 2014 the Registrant did not provide any comments on the draft decision to ECHA.

On 30 October 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 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. Sub-chronic toxicity study (90-day) in rats, oral route (Annex IX, Section 8.6.2.; test method: EU B.26/OECD 408);
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 ***3 February 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)

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) via the oral route (EU B.26/OECD 408) with the following justification: *"An OECD Test Guideline 408: Repeated Dose 90-Day Oral Toxicity Study in Rodents is proposed for the substance Bis(4-(1,1,3,3-tetramethylbutyl)phenyl)amine (CAS number 15721-78-5; EC number 239-816-9). The Lead Registrant proposes an OECD 408 study to fulfil the data requirements as specified under REACH for this tonnage level (Annex IX). The lower tonnage bands allow for the completion of an OECD 407: Repeated Dose 28-day Oral Toxicity Study in Rodents or an OECD 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test. Positive results in an OECD 407 or OECD 422, however, would likely result in the need to conduct additional and/or more comprehensive studies. The OECD 408 study is therefore proposed so as to meet the data requirements for REACH Annex IX requirements and to meet the data requirements of the lower tonnage bands. An OECD 408 is more comprehensive study and will assess the repeated dose toxicity of the substance while also reducing animal testing as fewer animals are required by conducting an OECD 408, rather than conducting an OECD 407 and/or OECD 422."*

ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 8.6.2. of the REACH Regulation.

The Registrant proposed testing by the oral route. ECHA notes that the registered substance is a solid with a low vapour pressure and is water insoluble. ECHA observes the Registrant's explanation that exposure of humans via inhalation route is unlikely, taking into account the very low vapour pressure, the low potential of exposure from particles of inhalable size and appropriate Risk Management Measures (RMMs) identified in the Chemical Safety Report. The Registrant explained as well that exposure via skin contact is considered minimal due to appropriate Risk Management Measures (RMM) identified in the Chemical Safety Report. In 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 most appropriate.

The Registrant did not specify the species to be used for testing. 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.

b) Consideration of the information received during third party consultation

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

A third party has indicated that *in vitro* bioavailability studies are recommended before carrying out any (oral) toxicological studies. The proposed oral studies are scientifically not justified if bioavailability studies prove the absence of systemic exposure to the substance. The registrant assessed the physicochemical data of the substance along with use-related exposure and concluded that the absorption capacity through the oral, dermal and inhalation route is low. The substance is predicted by Lipinski rule OASIS not to be bioavailable (OECD Toolbox 3.1).Additionally, the Guidance (Appendix R.7.12-2 - Prediction of toxicokinetics integrating information generated in silico and *in vitro*) points out the possibly of generating additional information on toxicokinetics by means of *in vitro* permeation studies across lipid membranes or a monolayer of cultured epithelial cells, *or in vitro* permeation studies using excised human or animal intestinal tissues (such as the everted gut sac model).

ECHA acknowledges that the third party has proposed a testing strategy based on column 2 of Annex IX, Section 8.6.2 for the Registrant to consider.

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 absorption. However, the third party did not provide sufficient evidence of no absorption. Furthermore, an adaptation would also need to demonstrate that the other conditions of the adaptation possibility are fulfilled. ECHA notes that:

- the granulometric information does not allow concluding that the substance is not inhalable, since 10% of the particles have diameter < 52 μm therefore might be of inhalable size,
- there is no 28-day study available to show that the substance is of low toxicity,
- the substance is not classified and consequently no exposure assessment has been performed to demonstrate limited human exposure; moreover, some uses (spraying and brushing applications) might indicate that exposure is likely to occur.

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 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).

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

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 with the following justification: *"An OECD Test Guideline 414: Prenatal Development Toxicity Study is proposed for the substance Bis(4-(1,1,3,3-tetramethylbutyl)phenyl)amine (CAS number 15721-78-5; EC number 239-816-9).The Lead Registrant proposes an OECD 414 to address this endpoint and meet the data requirements as specified in REACH Annex IX. The Lead Registrant is a multi-national company with world-wide distribution; therefore, study results will be used to meet the data requirements for multiple regulatory programs. Furthermore, if effects were noted in the more screening level studies, OECD 422 or OECD 421, it may be necessary to still conduct an OECD 414. By performing the OECD 414, the data can be used to address the data requirements of multiple regulatory programs and offer a potential reduction on the testing of vertebrate animals while offering an increase in the reliability of the data since the OECD 414 is a more comprehensive study that has sufficient experience in being conducted and historical control data available*".

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 indicated that *in vitro* bioavailability studies are recommended before carrying out any (oral) toxicological studies. The proposed oral studies are scientifically not justified if bioavailability studies prove the absence of systemic exposure to the substance. The registrant assessed the physicochemical data of the substance along with use-related exposure and concluded that the absorption capacity through the oral, dermal and inhalation route is low. The substance is predicted by Lipinski rule OASIS not to be bioavailable (OECD Toolbox 3.1). Additionally, the Guidance (Appendix R.7.12-2 - Prediction of toxicokinetics integrating information generated in silico and *in vitro*) points out the possibly of generating additional information on toxicokinetics by means of *in vitro* permeation studies across lipid membranes or a monolayer of cultured epithelial cells, *or in vitro* permeation studies using excised human or animal intestinal tissues (such as the everted gut sac model). No repeated dose toxicity data for the substance exist but an oral 90-day study has been proposed by the registrant. In any case sequential testing is suggested to be able to assess possible adverse outcomes in terms of morphological changes in reproductive organs in the repeated dose toxicity study first.

ECHA acknowledges that the third party has proposed a testing strategy based on column 2 of Annex IX, Section 8.7.2. for the Registrant to consider.

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 8.7., 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.

However, ECHA observes that the third party comment addressed only the criterion concerning absorption. The third party did not provide proof that no systemic absorption occurs via relevant routes of exposure. Furthermore, an adaptation would also need to demonstrate that the other conditions of the adaptation possibility are fulfilled. ECHA notes that:

- there is no repeated dose toxicity study or reproductive toxicity screening study available to show that the substance is of low toxicological activity,
- it is not proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure,
- the substance is not classified and consequently no exposure assessment has been performed to demonstrate the absence of significant human exposure; moreover, some uses (spraying and brushing applications) might indicate that exposure is likely to occur.

Therefore the criteria listed in Column 2 of Annex IX, section 8.7., third indent are not met and the information requirement for the pre-natal developmental toxicity study cannot be adapted on this basis.

Finally ECHA notes that the time given to the Registrant to perform the required tests already takes into account the possibility for sequential testing.

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 reproductive toxicity study (Annex IX, Section 8.7.3.)

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 at this stage 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.

A third party has indicated that the tonnage level of the registered substance only requires the conduct of a two-generation reproduction toxicity study if the 28-day or 90-day study indicates adverse effects on reproductive organs or tissues.

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. 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.

Therefore, ECHA has rejected the testing proposal for a two-generation reproductive toxicity study.

c) Outcome

ECHA concludes that there is at this stage 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

Once the results from the sub-chronic toxicity study (Section II, 1. above) are available, the Registrant should reconsider the information requirement of Annex IX, Section 8.7.3. If the sub-chronic toxicity study indicates adverse effects on reproductive organs or tissues a new testing proposal for the present endpoint would – in accordance with the REACH Regulation – have to be submitted, unless the information requirement could be adapted.

Guidance in this respect can be found in the ECHA Guidance on information requirements and chemical safety assessment R.7.a, more specifically, chapter 7.6.6.3 (February 2014) outlines the testing strategy for reproductive toxicity.

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 has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

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

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://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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