

Decision number: TPE-D-2114309871-50-01/F

Helsinki, 19 October 2015

DECISION ON TESTING PROPOSAL(S) SET OUT IN A REGISTRATION PURSUANT TO ARTICLE 40(3) OF REGULATION (EC) NO 1907/2006**For N,N'-hexane-1,6-diylbis(hexahydro-2-oxo-1H-azepine-1-carboxamide), EC No 227-563-7 (CAS No 5888-87-9), 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 registration dossier in accordance with Articles 10(a)(ix) and 12(1)(d) thereof for N,N'-hexane-1,6-diylbis(hexahydro-2-oxo-1H-azepine-1-carboxamide), EC No 227-563-7 (CAS No 5888-87-9), submitted by [REDACTED] (Registrant).

- *In vivo* mammalian erythrocyte micronucleus test (OECD Guideline 474); and
- Long-term toxicity testing on aquatic invertebrate (OECD Guideline 211; *Daphnia magna* Reproduction Test).

This decision is based on the registration 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 6 June 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 23 May 2013.

ECHA held a third party consultation for the testing proposal from 18 September 2014 until 3 November 2014. ECHA did not receive information from third parties.

On 30 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.

By 6 May 2015 the Registrant did not provide any comments on the draft decision to ECHA.

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.

Subsequently, a proposal for amendment to the draft decision was submitted.

On 17 July 2015 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.

The ECHA Secretariat reviewed the proposal for amendment received and amended the draft decision.

On 27 July 2015 ECHA referred the draft decision to the Member State Committee.

By 17 August 2015 the Registrant did not provide any comments on the proposal for amendment.

A unanimous agreement of the Member State Committee on the draft decision was reached on 31 August 2015 in a written procedure launched on 20 August 2015.

ECHA took the decision pursuant to Article 51(6) 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. *In vivo* mammalian erythrocyte micronucleus test (Annex IX, Section 8.4., column 2; test method B.12./OECD 474); and
2. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211).

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 **26 October 2016** an update of the registration dossier containing the information required by this decision, including, where relevant, an update of the Chemical Safety Report.

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.

A. Tests required pursuant to Article 40(3)

1. *In vivo* mammalian erythrocyte micronucleus test (OECD Guideline 474; Annex IX, 8.4, column 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.

"Mutagenicity" is an information requirement as laid down in Annex VIII, Section 8.4. of the REACH Regulation. Column 2 of Annex IX, Section 8.4. provides that "If there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII and there are no results available from an *in vivo* study already, an appropriate *in vivo* somatic cell genotoxicity study shall be proposed by the Registrant."

The technical dossier contains two *in vitro* studies conducted with the registered substance: i) a bacterial reverse mutation assay performed according to OECD Guideline 471 that show negative results; and ii) an *in vitro* mammalian cell micronucleus test performed according to OECD Guideline 487 that show positive results with and without metabolic activation. The positive results indicates that the substance is inducing chromosomal aberrations under the conditions of the test.

An appropriate *in vivo* genotoxicity study to follow up the concern on chromosomal aberrations is not available for the registered substance but shall be proposed by the Registrant. Consequently, there is an information gap and the Registrant proposed to generate information for this endpoint.

Hence, the Registrant has submitted a testing proposal for a *in vivo* mammalian erythrocyte micronucleus test according to OECD 474 in order to further investigate the effects observed in the *in vitro* studies.

ECHA notes that this test is an appropriate test to investigate further effects on chromosomal aberrations *in vivo* as described in the ECHA Guidance document on information requirements and chemical safety assessment R.7a, chapter R.7.7.1. and figure R.7.7-1 (August 2014).

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: *In vivo* mammalian erythrocyte micronucleus test (test method: EU B.12./OECD 474).

Notes for consideration by the Registrant :

According to paragraph 10 of the OECD 474 (Mammalian Erythrocyte Micronucleus Test, updated on 26 Sept 2014) "If there is evidence that the test substance(s), or its metabolite(s), will not reach the target tissue, it may not be appropriate to use this test". Additionally, according to paragraph 48 (d) of the OECD 474, a test chemical is considered

clearly negative if "Bone marrow exposure to the test substance(s) occurred". Accordingly, if a substance is negative in this test, and if it is not possible to demonstrate that bone marrow exposure to the substance occurred, then ECHA will consider any remaining uncertainty concerning the mutagenic potential of the substance and whether to request any further information.

The Registrant is reminded that according to Annex IX, Section 8.4., column 2 of the REACH Regulation, if positive results from an *in vivo* somatic cell study are available, "the potential for germ cell mutagenicity should be considered on the basis of all available data, including toxicokinetic evidence. If no clear conclusions about germ cell mutagenicity can be made, additional investigations shall be considered".

2. Long-term toxicity testing on aquatic invertebrates (OECD Guideline 211; Annex IX, Section 9.1.5.)

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.

"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. 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 long-term toxicity testing on aquatic invertebrates [*Daphnia magna* reproduction test, EU C.20/OECD 211] with the following statement, under the adaptation argumentation for the long-term toxicity to fish endpoint: "*According to the results of the Chemical Safety Assessment, there is only a very limited exposure to the aquatic environment conceivable. Since the short term results of aquatic toxicity of all tested species did not show significant deviations, the long-term testing of the toxicity of aquatic invertebrates is considered to be sufficient. Therefore a long-term fish toxicity study is not required.*". ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 9.1.5 of the REACH Regulation.

According to ECHA Guidance on information requirements and chemical safety assessment (version 2.0, November 2014), Chapter R7b (Section R.7.8.5 including Figure R.7.8-4), if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially more sensitive, long-term studies may be required on both. There were no indications in the dossier from the short-term toxicity studies on aquatic species that the fish would be substantially more sensitive than aquatic invertebrates. In such case, according to the integrated testing strategy, the *Daphnia* study is to be conducted first. If based on the results of the long-term *Daphnia* study and the application of a relevant assessment factor no risks are observed (PEC/PNEC<1), no long-term fish testing may need to be conducted. However, if a risk is indicated, long-term fish testing may need to be conducted.

b) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study using the registered substance subject to the present decision: Long-term toxicity testing on aquatic invertebrates (Annex IX, 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211).

Notes for consideration by the Registrant:

Once results of the proposed test on long-term toxicity to aquatic invertebrates are available, the Registrant shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation. If the revised chemical safety assessment indicates the need to investigate further the effects on aquatic organisms, the Registrant shall submit a testing proposal for a long-term toxicity test on fish in order to fulfil the standard information requirement of Annex IX, 9.1.6. If the Registrant comes to the conclusion that no further investigation of effects on aquatic organisms is required, he shall update his technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex IX, 9.1.6.

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.

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. 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.

Authorised¹ by Guilhem de Seze, Head of Unit, Evaluation E1

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.