Helsinki, 14 December 2016

Addressee: [redacted]

Decision number: TPE-D-2114348831-47-01/F
Substance name: N,N'-(methylenedi-p-phenylene)bis[hexahydro-2-oxo-1H-azepine-1-carboxamide]
EC number: 258-981-8
CAS number: 54112-23-1
Registration number: [redacted]
Submission number: [redacted]
Submission date: 23.07.2014

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA has taken the following decision.

Your testing proposal is accepted and you are requested to carry out:

1. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats using the registered substance**

2. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rats or rabbits), oral route using the registered substance**

3. **Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: Daphnia magna reproduction test, EU C.20./OECD TG 211) using the registered substance.**

You are requested to perform as additional tests:

4. **Growth inhibition study aquatic plants (Annex VII, Section 9.1.2; test method: Alga, growth inhibition test, EU C.3./OECD 201) using the registered substance.**

5. **Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210) using the registered substance.**

You 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 and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation. You are required to submit the requested information in an updated registration dossier by **21 December 2018**. You shall also update the chemical safety report, where relevant.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] by Ofelia Bercaru, Head of Unit, Evaluation E3

[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.

Appendix 1: Reasons

The decision of ECHA is based on the examination of the testing proposal(s) submitted by you.

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

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.

You have submitted a testing proposal for a sub-chronic toxicity study (90 day) by the oral route.

You 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. In powder form, the substance has a particle size of which 90% falls in the range of 10-100 µm, which makes it unlikely for the dust to enter the deeper parts of the respiratory system. The uses of the aqueous dispersion do not have potential for aerosol exposure. Therefore, oral administration is the most appropriate route.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are 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.) in a first species

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.

ECHA notes that in the registration dossier you have submitted a data waiving statement, in addition to a testing proposal, where you state the following: "*In accordance with Column 2 of REACH, Annexes VIII the tests do not need to be conducted if the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available) and it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure and there is no significant human exposure. Thus no additional test was required for this endpoint.*"

ECHA notes that the dossier contains insufficient information to draw definite conclusions about the substance's absorption properties. On the contrary, the results of the acute toxicity study where the rats demonstrated clinical signs seem to suggest that the substance is absorbed from the gastro-intestinal tract. Furthermore, from manufacturing exposure scenarios like "Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities" it cannot be concluded that the human exposure will be insignificant. Therefore, with the current evidence the waiver is considered unjustified. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have also submitted a testing proposal for a pre-natal developmental toxicity study according to EU B.31/OECD 414.

You did not specify the species to be used for testing. You 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.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are 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. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

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.

You have submitted a testing proposal for testing the registered substance for long-term toxicity testing on aquatic invertebrates *Daphnia magna* reproduction test, EU C.20/OECD TG 211 with the following justification:*"At greater than or equal to 100 tonnes/year (Annex IX) a long-term aquatic toxicity testing on invertebrates is usually required. The weight of evidence assessment of the available data and QSAR models indicates that further chronic aquatic toxicity testing is warranted. As no in vivo toxicity data is available, and in accordance with recommendations within the technical guidance document, the registrant proposes to commission a chronic study in Daphnia that will be compliant with OECD Guideline for Testing of Chemicals 211:Daphnia magna Reproduction Test. It is anticipated that the study should be completed within 1 year of signing of the study proposal."* 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. As there was no information in the dossier for the short-term toxicity on aquatic species, species sensitivity differences in aquatic toxicity cannot be determined. In the absence of information on short-term toxicity to daphnia and fish, it cannot be concluded if fish or daphnia are shown to be substantially more sensitive. Therefore, there is a data gap for both long-term daphnia and long-term fish (section 4).

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed test using the registered substance subject to the present decision: Long-term toxicity testing on aquatic invertebrates (test method: *Daphnia magna* reproduction test, EU C.20/OECD TG 211).

Notes for your consideration

According to adaptation rules of Column 2 of Annex VIII, section 9.1.3. the short-term tests on daphnia and fish do not need to be conducted if the substance is highly insoluble in water.

Due to the low solubility of the substance in water you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA Guidance, Chapter R7b, table R. 7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested long-term ecotoxicity tests and for calculation and expression of the result of this test.

4. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2)

Pursuant to Article 40(3)(c) of the REACH Regulation, ECHA may require the Registrant to carry out one or more additional tests in case of non-compliance of the testing proposal with Annexes IX, X or XI of the REACH Regulation.

"Growth inhibition study aquatic plants" is a standard information requirement as laid down in Annex VII, Section 9.1.2. 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.

Regarding the standard information requirement for growth inhibition study aquatic plants in Annex VII, Section 9.1.2 of the REACH Regulation, you have provided the following justification: "*In accordance with Column 2 of REACH, Annexes VII the tests do not need to be conducted if the substance is highly insoluble in water (water solubility: 8.22 µg/L). Thus no additional test was required for this endpoint.*" ECHA considers that the justification for waiving provided does not meet the criteria of the specific adaptation rules of Column 2 of Annex VII, section 9.2.

ECHA notes that in the adaptation provided, you have considered the registered substance to be highly insoluble. The water solubility of the registered substace reported in the technical dossier is 8.22 µg/L. ECHA considers that the registered substance is poorly water soluble rather than highly insoluble.

Therefore, your adaptation of the information requirement cannot be accepted.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 3.0, February 2016) Algae growth inhibition test (test method EU C.3. / OECD TG 201) is the preferred test to cover the standard information requirement of Annex VII, Section 9.1.2.

Therefore, pursuant to Article 40(3)(c)of the REACH Regulation, you are requested to carry out the proposed test using the registered substance subject to the present decision: Algae growth inhibition test, EU C.3./OECD TG 201).

Notes for your consideration

Due to the low solubility of the substance in water and the high partition coefficient and adsorption potential, you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA Guidance on information requirements and chemical safety assessment (version 3.0, February 2016), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

5. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

Pursuant to Article 40(3)(c) of the REACH Regulation, ECHA may require the Registrant to carry out one or more additional tests in case of non-compliance of the testing proposal with Annexes IX, X or XI of the REACH Regulation.

"Long-term toxicity testing on fish" is a standard information requirement as laid down in Annex IX, Section 9.1.6. 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.

Regarding the standard information requirement for short-term toxicity on fish in Annex VIII, Section 9.1.3 of the REACH Regulation, you have provided the following justification: *"In accordance with Column 2 of REACH, Annexes VIII the tests do not need to be conducted if the substance is highly insoluble in water (water solubility: 8.22 µg/L). Thus no additional test was required for this endpoint."* ECHA consideres that the justification for waiving provided meets the criteria of the specific adaptation rules of Column 2 of Annex VIII, section 9.1.3.

Regarding the standard information requirement for Annex IX, Section 9.1.6. of the REACH Regulation, you have provided the following justification: *"A long-term toxicity to Daphnia is proposed. As recommended within the technical guidance document 5, the results of chronic Daphnia testing should be considered prior to beginning a chronic fish study. In addition, exposure of environment to the substance is extremely unlikely since during manufacturing, formulation and undustrial processis all wastes, including gas emissions, water and solid waste, are incenerated in approved inceneration plant, as described in section 3.5."* ECHA notes that the justification for waiving provided does not meet the criteria of either the specific adaptation rules of Column 2 of Annex IX, section 9.1.6. or of the general adaptation rules of Annex XI.

In accordance with column 2 of Annex VII, 9.1.1. and column 2 of Annex VIII, 9.1.3. instead of short-term testing, long-term testing on invertebrates and on fish shall be considered if the substance is poorly water soluble. ECHA agrees with the Registrant that short-term testing would not be relevant. In this case long-term testing is more appropriate. Firstly, based on the water solubility (*8.22 µg/*L), high adsorption potential (log Pow 5) and potential persistency (not readily biodegradable), the short-term test would not provide sufficient level of exposure for assessment of the aquatic toxicity of the substance. Secondly, the dossier is at the tonnage level of 100 or more tonnes per year. At this tonnage level long-term test for fish are standard information requirements according to Annex IX, 9.1.6.

Your justification does not fulfil the standard information requirement of Annex IX, Section 9.1.6. of the REACH Regulation. Therefore there is a data gap for both short- and long-term fish toxicity.

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. ECHA notes that no information on short or long-term toxicity to fish or on invertebrates is available in the registration dossier. In the absence of information on short-term toxicity, it cannot be concluded if fish or invertebrates are shown to be substantially more sensitive.

ECHA considers that for the endpoint of long-term toxicity testing on fish pursuant to Annex IX, section 9.1.6.1, the FELS toxicity test according to OECD TG 210 is the most sensitive of the standard fish tests available as it covers several life stages of the fish from the newly fertilised egg, through hatch to early stages of growth and should therefore be used (see ECHA *Guidance on information requirements and chemical safety assessment* (version 2.0, November 2014), Chapter R7b, Figure R.7.8-4 page 26). The test method OECD TG 210 is also the only suitable test currently available for examining the potential toxic effects of bioaccumulation (ECHA Guidance R7b, version 2.0, November 2014, p. 26). For these reasons, ECHA considers the FELS toxicity test using the test method OECD TG 210 as appropriate and suitable.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to perform as additional test with the registered substance for long-term toxicity testing on fish, early-life stage toxicity test, OECD TG 210.

Notes for your consideration

Due to the low solubility of the substance in water you should consult the OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA Guidance, Chapter R7b, table R. 7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested long-term ecotoxicity tests and for calculation and expression of the result of this test.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposal(s) for examination pursuant to Article 40(1) on 23 July 2014.

ECHA held a third party consultation for the testing proposals from 12 December 2014 until 26 January 2015. ECHA did not receive information from third parties.

ECHA held an additional third party consultation for the testing proposal on long-term toxicity to fish from 31 August 2015 until 15 October 2015. ECHA did not receive information from third parties.

This decision does not take into account any updates after **9 June 2016**, 30 calendar days after the end of the commenting period.

ECHA notified you of the draft decision and invited you to provide comments.

ECHA did not receive any comments by the end of the commenting period.

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment.

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-50 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. 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.

2. 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.

3. In relation to the information required by the present decision, the sample of substance used for the new test(s) 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 who manufacture or import the same substance to agree on the appropriate composition of the test material 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 test(s) 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 test(s) 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 test(s) to be assessed.