ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 24 June 2019

Addressee: [redacted]

Decision number: TPE-D-2114471589-32-01/F
Substance name: 4,4'-methylenebis[2,6-diethylaniline]
EC number: 237-185-4
CAS number: 13680-35-8
Registration number: [redacted]
Submission number: [redacted]
Submission date: 15/12/2017
Registered tonnage band: 100-1000

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation ((EC) No 1907/2006) (the REACH Regulation), ECHA examined your testing proposal(s) and decided as follows.

Your following testing proposal is rejected:

1. In vivo mammalian erythrocyte micronucleus test (Annex IX, Section 8.4., column 2; test method: OECD TG 474) in mice or rats, oral route using the registered substance.

Your originally proposed test for Long-term toxicity testing on fish (Annex IX, Section 9.1.6.3.; test method: Fish, juvenile growth test, EU C.14./OECD TG 215) using the registered substance is also rejected, and you are requested to perform:

2. 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 are additionally requested to perform:

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 have to submit the requested information in an updated registration dossier by **31 March 2021.** You also have to update the chemical safety report, where relevant.

The reasons for this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and 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 Claudio Carlon, Head of Unit, Hazard Assessment

[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 proposals submitted by you and scientific information submitted by third parties.

1. **In vivo mammalian erythrocyte micronucleus test (Annex IX, Section 8.4., column 2)**

a) Examination of the testing proposal

Pursuant to Article 40(3)(d) of the REACH Regulation, ECHA may reject a proposed test.

"Mutagenicity" is an information requirement as laid down in Section 8.4. of Annexes VII to X 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 three *in vitro* studies with the registered substance that show negative results: the *in vitro* gene mutation study in bacteria (OECD TG 471 / GLP complaint / reliability score of 1); the *in vitro* chromosome aberration study (OECD TG 473 / GLP complaint / reliability score of 1); and, the *in vitro* gene mutation study in mammalian cells (OECD TG 476 / GLP complaint / reliability score of 1).

You have submitted a testing proposal for an *in vivo* mammalian erythrocyte micronucleus test (test method: OECD TG 474) in mice, oral route, since "*an existing MNT in-vitro study does not allow a final assessment of this endpoint due to quality reasons (Klimisch 4)*".

ECHA firstly notes that the "*inconclusive*" "*existing MNT in-vitro study*" is not available in the technical dossier. Hence, the validity of this study cannot be assessed by ECHA.

Consequently, an *in vivo* micronucleus study with the registered substance is not required at this point since there are no positive results in the technical dossier that might indicate that the substance induces chromosomal aberrations and/or gene mutations.

Hence, in view of the above, Annex IX, Section 8.4., column 2, does not apply due to the absence of positive results in the technical dossier.

b) Consideration of the information received during third party consultation

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

Third party information: "*According to the public Registration Dossier, the genotoxicity of the substance has been investigated in an appropriate battery of three in vitro studies, in line with ECHA Guidance. Negative results are reported in an Ames test (Klimisch 1), in a mammalian cell mutation (HPRT) assay (Klimisch 1) and in a mammalian cell chromosomal aberration assay (Klimisch 1). The Registrant also refers to an additional in vitro micronucleus assay; however this study is not presented in the public Registration Dossier. This study is not considered by the Registrant to be reliable (Klimisch 4) for quality reasons. As the Registration Dossier contains an adequate set of negative (and reliable) in vitro studies, there does not appear to be any requirement for additional testing in vivo. If*

additional testing is considered to be required on the basis of the unreliable in vitro micronucleus test, it is suggested that generating data in a reliable study in vitro is more appropriate than conducting a test in vertebrate animals."

ECHA acknowledges the third party comments and has considered these comments as indicated above, within this section.

c) Outcome

Therefore, pursuant to Article 40(3)(d) of the REACH Regulation, you shall not perform the proposed *In vivo* mammalian erythrocyte micronucleus test (test method: OECD TG 474) in mice, oral route, since ECHA has rejected the proposed test.

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

a) Examination of the testing proposal

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

"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.

You have submitted a testing proposal for testing the registered substance for long-term toxicity testing on fish Fish, juvenile growth test - OECD 215, EU Method C.14 (Fish Juvenile Growth Test) with the following justification: "*The test item had significant toxic effects on fish. The 96-h LC50 value was determined to be 1.32 mg/l. Therefore, it is suggested to conduct a long-term toxicity study on the same species.*" ECHA considers that the proposed study is in principle appropriate to fulfil the information requirement of Annex IX, Section 9.1.6 of the REACH regulation.

However, ECHA notes that the proposed guideline OECD 215 measures only the effects of prolonged exposure to chemicals on the growth of juvenile fish and it is not of sufficient duration to examine all the sensitive points in the fish life-cycle. You have not provided evidence to demonstrate that fish growth is the key effect relevant to be measured in a long term toxicty test.

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 more sensitive 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 4.0, June 2017), Chapter R7b, Section R.7.8.4.1.). Test method OECD TG 210 is also a suitable test for examining the potential toxic effects of bioaccumulation (ECHA Guidance R7b, version 4.0, June 2017). For these reasons, ECHA considers the FELS toxicity test using the test method OECD TG 210 as more appropriate and suitable than the test proposed by the Registrant.

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b (Section R.7.8.5 including Figure R.7.8-4), if based on acute aquatic toxicity fish or invertebrates is shown to be substantially more sensitive than the other, a long-term study on the more sensitive species is required. ECHA notes that based on the acute aquatic data in the registration dossier, fish is more sensitive than aquatic invertebrates (fish LC50 1.32 mg/L, daphnia LC50 > 1.69 mg/L (no effects observed) with the solubility of the substance limiting range of concentrations). You have also considered the long-term fish study necessary and submitted the testing proposal.

ECHA requested your considerations for alternative methods to fulfil the information requirement for long-term toxicity testing on fish. ECHA notes that you provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

b) Outcome

Therefore, pursuant to Article 40(3)(d) and (c) of the REACH Regulation, while your originally proposed test for Long-term toxicity testing on fish (Annex IX, Section 9.1.6.3.; test method: Fish, juvenile growth test, EU C.14./OECD TG 215) using the registered substance is rejected, you are requested to carry out the: Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.; test method: Fish, early-life stage toxicity test, OECD TG 210) using the registered substance.

3. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

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

"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. ECHA notes that the information on this endpoint is not available for the registered substance but may need 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 adapted this endpoint requirement providing a justification*: "Study scientifically not necessary / other information available. Substance was found to be non-toxic at the solubility limit in the acute daphnia toxicity study; it's planned to conduct a long-term toxicity study on fish, the most sensitive species, based on the results of the acute test."*

As discussed above in section 2. above ECHA agrees with your assessment that based on acute data fish appear to be the more sensitive species. You are hence first to carry out the long-term fish study requested in section 2. above. The need to conduct the long-term Daphnia study requested here is then to be determined based on the results of the fish study and the consequent risk assessment, as further explained in the *Notes for your consideration* section below.

Therefore, pursuant to Article 40(3)(c)of the REACH Regulation, you are requested to carry out the additional test using the registered substance subject to the present decision: *Daphnia magna* reproduction test (test method: EU C.20/OECD TG 211).

Notes for your consideration

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b (Section R.7.8.5 including Figure R.7.8-4), if based on acute aquatic toxicity data fish or invertebrates is shown to be more sensitive, a long-term study on the more sensitive species is to be conducted first. ECHA notes that therefore the long-term fish study requested under Section 2 is to be conducted first. The need to conduct the long-term Daphnia study requested here is then to be determined based on the results of the fish study and the consequent risk assessment.

If you come to the conclusion that no further investigation of effects on aquatic organisms is required, you shall update your technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex IX, 9.1.5. taking into account the new data generated by the fish study requested by the present decision.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 15 December 2017.

ECHA held a third party consultation for the testing proposals from 26 March 2018 until 11 May 2018. ECHA received information from third parties (see Appendix 1).

This decision does not take into account any updates after **19 November 2018**, 30 calendar days after the end of the commenting period.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

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

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request(s).

ECHA notified the draft decision to the competent authorities of the Member States for proposals 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-64 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 in your 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 requests in this decision, or to otherwise fulfil the information requirements 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 the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported 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 the substance tested in the new tests 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 or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.