EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000002593-73-05/F Helsinki, 7 June 2013

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

**For 2-ethyl-N,N-bis(2-ethylhexyl)hexylamine, CAS No 1860-26-0 (EC No 217-461-0), 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 2-ethyl-N,N-bis(2-ethylhexyl)hexylamine, CAS No 1860-26-0 (EC No 217-461-0), by [redacted] (Registrant).

- **Testing proposed by the Registrant:**

  Annex IX, 8.6.2: Sub-chronic toxicity study (90-day), following the oral route of application
  Annex IX, 8.7.2: Pre-natal developmental toxicity study
  Annex IX, 9.1.5: Long-term toxicity testing on invertebrates
  Annex IX, 9.4.1: Short-term toxicity to invertebrates, for which, in view of the properties of the substance, a long-term test was proposed using earthworms.

This decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band [redacted] per year. This decision does not take into account any updates after 18 January 2013, 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 present dossier at a later stage.

On 29 November 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 16 January 2012 until 01 March 2012. ECHA received information from third parties (see section III below).

On 17 July 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 14 August 2012 ECHA received comments from the Registrant.

ECHA considered the Registrant's comments received and amended Section III accordingly to reflect the comments.

On 18 January 2013 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, Competent Authorities of the Member States submitted proposals for amendment to the draft decision.

On 21 February 2013 ECHA notified the Registrant of proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on those proposals for amendment within 30 days of the receipt of the notification.

ECHA reviewed the proposals for amendment received and decided to amend the draft decision.

On 4 March 2013 ECHA referred the draft decision to the Member State Committee.

By 25 March 2013 the Registrant did not provide any comments on the proposals for amendment but only comments on the draft decision which were not requested at this stage of the decision making process.

A unanimous agreement of the Member State Committee on the draft decision was reached on 8 April 2013 in a written procedure launched on 27 March 2013. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

## II. Testing required

The Registrant shall carry out the following 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, 8.6.2.; test method: EU B.26/OECD 408);
2. Pre-natal developmental toxicity study in the rat or the rabbit, oral route (Annex IX, 8.7.2.; test method: EU B.31/OECD 414);
3. Long-term toxicity testing on aquatic invertebrates (Annex IX, 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211);
4. Long-term toxicity to terrestrial invertebrates (Annex IX, 9.4.1. and Column 2 of 9.4.); test method Earthworm reproduction test (*Eisenia fetida/Eisenia andrei*), OECD 222);

Pursuant to Article 40(3)(c) of the REACH Regulation the Registrant shall carry out the following tests using the indicated test method and the registered substance subject to the present decision:

5. Effects on soil micro-organisms (Annex IX, 9.4.2.; test method: Soil microorganisms: nitrogen transformation test, EU C.21/OECD 216); and

6. Long-term toxicity testing on plants (Annex IX, 9.4.3. and Column 2 of 9.4.); test method: Terrestrial plants, growth test (OECD 208), with at least six species tested (with as a minimum two monocotyledonous species and four dicotyledonous species); or test method: Soil Quality – Biological Methods – Chronic toxicity in higher plants (ISO 22030).

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 1 or 2 provisions of the relevant Annexes of the REACH Regulation.

More specifically, 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. If the revised chemical safety assessment indicates the need to investigate further the effects on aquatic organisms, the Registrant shall consider submitting 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.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **7 June 2015** an update of the registration dossier containing the information required by this decision.

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.

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. Sub-chronic toxicity study (90-day)**

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 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. Furthermore, 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.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the testing proposal is accepted and the Registrant is requested to carry out the following test: Sub-chronic toxicity study (90-day) (Annex IX, 8.6.2) in rat by the oral route (EU Method B.26 or OECD 408).

## 2. Pre-natal developmental toxicity study

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 did not specify the species and 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.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the testing proposal is accepted and the Registrant is requested to carry out the following test: Pre-natal developmental toxicity study (Annex IX, 8.7.2) in rat or rabbits by the oral route (EU Method B.31 or OECD 414).

Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal for the pre-natal developmental toxicity endpoint 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 proposed a weight-of evidence approach for ECHA to take into account before further tests on vertebrate animals are required. As part of this approach, the third party provided results from pre-natal developmental studies or screening tests (OECD 422) for a variety of similar tertiary amines with different alkyl chain lengths and with an unbranched or branched chemical structure that indicated that these tertiary amines are not teratogenic and induce retardation of offspring development secondary to maternal toxicity. Moreover, a negative QSAR prediction for developmental toxicity, based on the Consensus method, was included.

ECHA has taken the information provided into account and concludes that it is insufficient for demonstrating that the conditions of Annex XI, Section 1.2 and 1.5 of the REACH Regulation are met. More specifically, the proposed weight-of-evidence approach is not sufficient to assume that the substance has or has not a particular dangerous property after gestational exposure and that the standard information requirement for a pre-natal developmental study could be adapted. Furthermore, the proposed read-across approach as an element of the weight of evidence justification did not demonstrate that human health effects of the registered substance may be predicted from data on the reference substances. Especially the similarity of the substances was not demonstrated. Although ECHA recognises that the information as provided by the third party might be scientifically valid, it does not fulfil Annex XI requirements and is therefore not sufficient to allow ECHA to reject the testing proposal.

Nevertheless, ECHA acknowledges that the Registrant may himself supplement under its own responsibility the argumentation and information provided by the third party in order to make use of adaptation possibilities. This would require that the Registrant documents, using several independent sources of information, that there is a sufficient weight-of-evidence leading to the assumption/conclusion that a substance has or has not particular dangerous properties, according to the criteria laid down in Annex XI of the REACH Regulation.

**3. Long-term toxicity testing on aquatic invertebrates**

According to column 1 of Section 9.1.5. of Annex IX of the REACH Regulation, long-term toxicity testing on invertebrates is required to fulfil the standard information requirements. 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.

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

According to ECHA Guidance on information requirements and chemical safety assessment (version 1.1, August 2008), Chapter R7b, Figure R.7.8-4 page 53, 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. 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, a testing proposal for a long-term fish study needs to be submitted.

**4-6. Effects on terrestrial organisms (Annex IX, section 9.4 of the REACH Regulation)**

Pursuant to Article 40(3)(c) ECHA may take a decision permitting the registrant to carry out the proposed test in accordance with Article 40(3)(a) but requiring the Registrant to carry out one or more additional tests in cases of non-compliance of the testing proposal with Annexes IX, X, and XI of the REACH Regulation.

In order to fulfil the standard information requirements set out in Annex IX, section 9.4., registrants should provide the following studies: (i) short-term toxicity to invertebrates (section 9.4.1.), (ii) effects on soil micro-organisms (section 9.4.2.) and (iii) short-term toxicity to plants (section 9.4.3.). Column 2 of Annex IX, section 9.4. advises the Registrant to consider long-term toxicity testing instead of short-term in particular for substances that have a high potential to adsorb to soil or that are very persistent.

a) Acceptance of the proposed test (Annex IX, 9.4.1. and Column 2 of Annex IX, 9.4.)

The Registrant proposed a long-term toxicity test on terrestrial invertebrates. As the substance has a high potential to adsorb to soil (Log $K_{OC}$ = 4.58 for the charged molecule; Log $K_{OC}$ = 6.29 for the uncharged molecule) and is expected to be persistent (about 20-40% degradation in 28 days), ECHA agrees that long-term testing is required (Column 2 of Section 9.4. of Annex IX). The proposed test is suitable to address the information requirement of Annex IX, section 9.4.1.

Therefore pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study Long-term toxicity to terrestrial invertebrates (Annex IX, 9.4.1., column 2 of section 9.4.); test method: Earthworm reproduction test (Eisenia fetida/Eisenia andrei), OECD 222, using the registered substance.

b) Testing for the two remaining taxonomic groups

The proposed test that ECHA accepted under subsection 4-6 a) above can only address the information requirement of Annex IX, section 9.4.1. It is not sufficient by itself to address the information requirements for the two remaining taxonomic groups specified within section 9.4. of Annex IX.

The Registrant has proposed to waive the two other information requirements for effects on terrestrial organisms claiming negligible direct and indirect exposure due to the low water solubility and *risk characterisation ratios <1.* Additionally, during the 30-day commenting period after the original draft decision was sent to the Registrant, it was argued by the Registrant that the uncertainties surrounding the PNEC aquatic calculations might lead to the withdrawal of these values from the technical dossier.

Based upon these comments, a thorough review of the available information was undertaken, in relation to section R.7.11.6., Chapter R.7c of the ECHA *Guidance on information requirements and chemical safety assessment* (May 2008). ECHA agrees with the Registrant that the PNEC aquatic values currently present in the technical dossier (using nominal concentration above the water solubility limit) cannot be considered as valid and, as a result, it is not possible to allocate the substance to a soil hazard category.

Consequently, as it is not meaningful to perform an initial screening assessment for the terrestrial compartment based upon the Equilibrium Partitioning Method (EPM) in the absence of reliable PNEC aquatic values, it is not possible to waive the standard information requirements for the terrestrial compartment mentioned in Annex IX, section 9.4.

Furthermore, the Registrant's argumentation on negligible indirect exposure cannot be accepted, due to uncertainties in water solubility and adsorption. The Registrant has concluded that "*Under environmental conditions (pH from 5 to 9) the test substance is almost completely present in its charged form*" and has proposed, under toxicokinetics, an estimated water solubility of 0.1031 mg/L for the charged form; while he is using the water solubility of the uncharged molecule in the ecotoxicological assessment. In comparison, the Registrant is using the $K_{OC}$ value for the charged molecule in the ecotoxicological assessment. Thus, in summary the Registrant's argumentation cannot be accepted.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant is required to carry out the following additional studies, using the registered substance:

- Long-term toxicity testing on plants (Annex IX, 9.4.3., column 2 of Annex IX 9.4.); test method: Terrestrial plants, growth test (OECD 208), with at least six species tested (with as a minimum two monocotyledonous species and four dicotyledonous species) or test method: Soil Quality – Biological Methods – Chronic toxicity in higher plants (ISO 22030), using the registered substance; and

- Effects on soil micro-organisms (Annex IX, 9.4.2.; test method: Soil microorganisms: nitrogen transformation test, EU C.21/OECD 216).

If the results of the proposed toxicity test on aquatic invertebrates allow the subsequent derivation of a PNEC aquatic, the Registrant may consider the Integrated Testing Strategy as recommended in section R.7.11.6., Chapter R.7c of the ECHA Guidance on information requirements and chemical safety assessment (May 2008), and determine the need for further testing on terrestrial organisms.

Concerning the information requirement for terrestrial plants, OECD guideline 208 (Terrestrial plants, growth test) considers the need to select the number of test species according to relevant regulatory requirements, and the need for a reasonably broad selection of species to account for interspecies sensitivity distribution. For long-term toxicity testing, ECHA considers six species as the minimum to achieve a reasonably broad selection. The long-term toxicity testing shall be conducted with species from different families, as a minimum with two monocotyledonous species and four dicotyledonous species, selected according to the criteria indicated in the OECD 208 guideline. The Registrant should consider if testing on additional species is required to cover the information requirement.

Concerning the information requirement for soil microorganisms (Annex IX, 9.4.2.), ECHA notes that the intrinsic properties of soil microbial communities are not addressed through the EPM extrapolation method. Thus, the hazard to soil microbial communities needs to be evaluated as a standard information requirement under Annex IX, section 9.4.2. of the REACH Regulation. ECHA concludes that the effects on soil microorganisms need to be ascertained by performing a relevant test (EU Method C.21 or OECD 216).

**7. Registrant's request to extend deadline for update submission**

Apart from the other comments submitted by the Registrant during the 30-day commenting period that have been addressed above, the Registrant has also requested an extension of the deadline for the submission of the updated dossier to 30 months to account for the sequential approach for the toxicological testing. In accordance with other draft decisions where sequential testing of the sub-chronic and pre-natal developmental toxicity endpoints was proposed and in the absence of substance-specific argumentation, ECHA did not accept the Registrant's request for a six-month extension as 24 months is deemed an adequate period for the performance of both tests.

IV. Adequate identification of the composition of the tested material

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 registered to enable the relevance of the studies to be assessed.

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

ECHA 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).

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.

VI. 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.

[redacted]
Jukka Malm
Director of Regulatory Affairs