ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-2114330167-56-01/F Helsinki, 11 May 2016

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

For (Z)-N-octadec-9-enylhexadecan-1-amide, CAS No 16260-09-6 (EC No 240-367-6), 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 (Z)-N-octadec-9-enylhexadecan-1-amide, CAS No 16260-09-6 (EC No 240-367-6, submitted by [redacted] (Registrant).

- Developmental toxicity / teratogenicity study (OECD 414).;
- Earthworm long term toxicity test (OECD 222);

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 9 July 2015.

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 30 May 2013.

ECHA held a third party consultation for the testing proposal from 14 August 2014 until 28 September 2014. ECHA received information from third parties (see section III below).

On 23 February 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. That draft decision was based on submission number [redacted].

On 27 March 2015 ECHA received comments from the Registrant on the draft decision. On 08 July 2015 the Registrant updated his registration dossier [redacted].

The ECHA Secretariat considered the Registrant's comments and update.
The information is reflected in the Statement of Reasons (Section III) whereas no amendments to the Information Required (Section II) were made.

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment(s) on 03 March 2016.

As no amendments were proposed, ECHA took the decision according 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. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31/OECD 414) in rats or rabbits, oral route.
2. Long-term toxicity on terrestrial invertebrates (Annex IX, 9.4.1., column 2); test method: Earthworm reproduction test (*Eisenia fetida/Eisenia andrei*) OECD 222);

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

3. Long-term toxicity testing on plants (Annex IX, 9.4.3., column 2); 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);

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

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 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.

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 **20 November 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. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

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.

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 in rats according to EU B.31/OECD 414 with the following justification:

"There are no data available on the (pre)natal developmental toxicity of the test substance. In order to meet the standard information requirements of Regulation (EC) 1907/2006, Annex IX, 8.7.2, column 1, a GLP-compliant pre-natal developmental toxicity study according to OECD Guideline 414 via the oral route as most relevant route of exposure in humans is proposed. The results of the study will be used to determine the following steps in the testing regime. The study will be conducted after a decision on the requirement to carry out the proposed test has been taken in accordance with the procedure laid down in Regulation (EC) 1907/2006, and a deadline to submit the information required has been set by the Agency. No information is available on this endpoint in the dossier, and therefore there is a data gap for this endpoint"

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 proposed testing by the oral route. 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.

Third party information :

A third party has indicated : *'Physicochemical properties of the substance and the absence of adverse effects at the limit dose in oral acute, sub-acute and sub-chronic toxicity tests suggest that the substance is not absorbed from the gastro-intestinal tract (prediction by Lipinski rule OASIS: not bioavailable). Alternatively, the toxicity of absorbed hydrolysis products may be very low. The proposed study is therefore not expected to add significant information to the risk assessment and may scientifically not be justified' e.g. that based on physicochemical properties the substance is predicted to be not absorbed in the gastrointestinal tract.'*

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.

ECHA observes that the third party comment addressed only the criterion concerning absorption and did not prove 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 are fulfilled.

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.

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).

2 - 4 Effects on terrestrial organisms

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

The Registrant must address the standard information requirements set out in Annex IX, section 9.4., for different taxonomic groups: short-term toxicity testing on invertebrates (Annex IX, section 9.4.1.), effects on soil micro-organisms (Annex IX, section 9.4.2.) and short-term toxicity testing on plants (Annex IX, section 9.4.3.). Column 2 of section 9.4 of Annex IX specifies that long-term toxicity testing shall be considered by the Registrant instead of short-term, in particular for substances that have a high potential to adsorb to soil or that are very persistent.

2) Long-term toxicity on terrestrial invertebrates (Annex IX, 9.4.1. and Column 2 of Annex IX, 9.4.)

The Registrant proposed a long-term toxicity test on terrestrial invertebrates (OECD 222), with the following justification:
'Terrestrial data of (Z)-N-Octadec-9-enylhexadecan-1-amide (CAS No. 16260-09-6) are not available but due to the properties of (Z)-N-Octadec-9-enylhexadecan-1-amide (CAS No. 16260-09-6) a hazard to soil organisms is assumed to be low but in order to fulfil the standard information required according to Regulation (EC) 1907/2006, Annex IX (9.4), an earthworm long term toxicity test (OECD 222) is proposed for this substance. The test substance is characterized by a high log Koc (log Koc > 5.6) indicating a potential for adsorption to the soil particles. Therefore, tests with soil-dwelling organisms like earthworm which allows potential uptake via surface contact, soil particle ingestion and pore water (ECHA, 2012), are most relevant for the evaluation of soil toxicity. In addition, in the absence of a clear indication of selective toxicity, an invertebrate (earthworm) test is preferred, as outlined in ECHA guidance section R.7.11.5.3, page 122. Thus, it can be assumed that earthworms would be highly exposed to toxicants in soil and hence are most sensitive to the potential adverse effects of the substance. The study is not yet available since a testing proposal according to OECD 222 was submitted for (Z)-N-Octadec-9-enylhexadecan-1-amide (CAS No. 16260-09-6). In conclusion, the substance is unlikely to pose a risk for terrestrial plants based on the lack of exposure and the lack of effects in aquatic ecotoxicity tests but the Chemical Safety Assessment according to Annex I of Regulation (EC) No 1907/2006 will be re-evaluated based on the outcome of the proposed earthworm study.'

According to section R.7.11.5.3., Chapter R.7c of the ECHA *Guidance on information requirements and chemical safety assessment* (version 2.0 November 2014), substances that are ionisable or have a log K_{ow}/K_{oc} >5 are considered highly adsorptive, whereas substances with a half-life >180 days are considered very persistent in soil.

According to the evidence presented within the registration dossier, the substance has a high potential to adsorb to soil ($logK_{ow}$ >5,7) and is likely to be very persistent which is the default setting for not readily biodegradable substances, when value of the half-life in soil is not available, as is the case with the current registration. Therefore, ECHA agrees that long-term testing is indicated within the meaning of 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.

In his comments to the draft decision, the Registrant agreed on the need for further soil toxicity testing as the screening assessment based on EPM is not in this case reliable. He proposed to conduct an OECD 222 earthworm reproduction test. However, as ECHA points out in the draft decision, there is no valid PNEC aquatic and the soil hazard category table as per Table R.7.11-2 (Chapter R.7c of the ECHA Guidance on information requirements and chemical safety assessment (version 1.1, November 2012) cannot thus be applied. Moreover, ECHA considers that based on the substance properties, water solubility < 1 mg/L, aquatic acute toxicity information cannot be considered reliable indicator for low toxicity in soil.

Furthermore, ECHA notes that the Registrant has not provided valid arguments to adapt the standard information requirements for Annex IX, section 9.4 column 2 and therefore the proposed testing strategy cannot be accepted. The basis for the need for further testing is further justified under the individual requests below.

In the updated dossier [redacted], the Registrant has updated to the endpoint summary the justifications field with adaptations according to their comments.

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 : Earthworm reproduction test (*Eisenia fetida/Eisenia andrei*), OECD 222.

3) Long-term toxicity testing on plants (Annex IX, 9.4.3 and Column 2 of Annex IX, 9.4)

The proposed test on terrestrial invertebrates, which ECHA accepted above, can only address the information requirement of Annex IX, section 9.4.1. It is not sufficient by itself to address the standard information requirement of Annex IX, section 9.4.3. ECHA notes that the registration dossier does not contain data for this endpoint.

The Registrant proposed to adapt the standard information requirement of toxicity to plants by:

'However, no additional test with soil organisms will be proposed for (Z)-N-Octadec-9-enylhexadecan-1-amide (CAS No. 16260-09-6). In accordance with Regulation (EC) No. 1907/2006, Annex IX, column 2, 9.4 further studies on the effects on terrestrial organisms do not have to be conducted since the chemical safety assessment indicates that there is no need. The Chemical Safety Assessment according to Annex I of Regulation (EC) No 1907/2006 will be re-evaluated
As the test substance is highly insoluble in water, only low concentrations are expected in the pore water, which is the main exposure route for terrestrial plants. Data from acute studies afford that there is no toxicity in the range of water solubility for aquatic organisms. Moreover, chronic and acute studies for mammals result in no toxic effects as well. The test substance is not classified and considering the very low water solubility (< 0.01 mg/L) no further soil toxicity data should be generated. Regarding the very low water solubility (< 0.01 mg/L) it is also not likely that the test substances can be found in the aquatic environment in high concentrations and therefore an application due to floods and irrigation can be ruled out.

Moreover, (Z)-N-Octadec-9-enylhexadecan-1-amide (CAS No. 16260-09-6) shows no inhibition to aquatic microorganisms up to a concentration of [redacted] mg/L. The applied test concentration is in the range of concentrations that can be expected in the influent of a sewage treatment plant, as the substance is highly insoluble in water (< 0.01 mg/L). The ECHA Guidance DocumentR.7c (ECHA, 2012) states that a test on soil microbial activity will only be additionally necessary for a valid PNEC derivation if inhibition of sewage sludge microbial activity has occurred. Therefore, toxicity to soil microorganisms is considered to be unlikely.'

ECHA points out, that contrary to the Registrant's argument, Column 2, Section 9.4 of Annex IX, contains no adaptation under which the present standard information requirement could be adapted on the basis of 'no toxicity' and 'low water solubility', as cited above.

ECHA notes that the Registrant has considered that invertebrates soil testing would suffice for the soil testing while arguing about the non-selective toxicity not to perform any plants testing. However, ECHA notes that there is no valid PNEC aquatic and the soil hazard category table as per Table R.7.11-2(Chapter R.7c of the ECHA *Guidance on information requirements and chemical safety assessment* (version 1.1, November 2012) cannot thus be applied. Therefore, it is not possible, within the meaning of column 2, section 9.4 of Annex IX, to waive the standard information requirements for the terrestrial compartment through an initial screening assessment based upon the Equilibrium Partitioning Method (EPM) and PNEC aquatic derivation to obtain a PNEC on soil compartment. Consequently, there is an information gap in the standard information requirement of Annex IX, Section 9.4.3.

Moreover, ECHA considers that only a long-term toxicity test on plants will provide the necessary information on the properties of the substance. At this tonnage level, according to column 2 of Section 9.4. of Annex IX, the registrant shall consider long-term testing for substances that have a high potential to adsorb in soil or that are very persistent. Based on the substance properties as discussed under subsection (2) above, there is an indication for high adsorption potential and high persistence of the substance in soil. That indicates the need for long-term testing to be performed.

It is also noted that the ECHA Guidance on information requirements and chemical safety assessment Chapter R10, section R.10.6.2. (version May 2008) allows the potential application of a lower assessment factor (AF) if information on additional long-term terrestrial toxicity test of two trophic levels were available. In contrast, the Guidance does not allow for a lower AF to be applied if information on a short-term study were to become available in addition to the long-term invertebrate study, which ECHA accepted under subsection (2) above. For all these reasons, ECHA concludes that, only a long-term toxicity test on plants (and not the short-term) will provide the necessary information.

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. 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.

In his comments to the draft decision and subsequent updated dossier [redacted], in the robust study summary for this endpoint the Registrant states that one single long-term test on a suitable species would be adequate to meet the requirements of Annex IX, where there is no toxicity (LC50 in the standard acute toxicity tests > 10 mg/L) and the substance is highly adsorptive (log Kow > 5).

However, ECHA Guidance (R.7.11.5.3) also describes that when water solubility of the substance is < 1 mg/l, the absence of acute toxicity cannot be considered reliable indicator for potential effects on soil organisms. In addition to the acute aquatic toxicity data there is no long term information available on the aquatic toxicity and no PNEC aquatic could be derived. In case where one long-term study on soil would be acceptable there is a need for valid information on aquatic toxicity (chronic information on aquatic toxicity would be needed when water solubility is low). In this case, the Registrant has not provided adequate evidence on low aquatic toxicity.

Therefore, the proposed testing strategy based solely on effects on Earthworm reproduction cannot be accepted.

Outcome

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant is required to carry out one of the following additional studies using the registered substance subject to the present decision: Terrestrial plants, growth test (OECD 208), with at least six species tested (with as a minimum two monocotyledonous species and four dicotyledonous species), or Soil Quality – Biological Methods – Chronic toxicity in higher plants (ISO 22030).

4) Effects on soil microorganisms (Annex IX, 9.4.2.)

The hazard to soil microbial communities is a standard information requirement under Annex IX, section 9.4.2. of the REACH Regulation. ECHA notes that the registration dossier does not contain data for this endpoint as the Registrant has sought to adapt the information requirement by submitting that there is no no toxicity in sewage treatment plants bacterai inhibition test and the substance has a low water solubility, as desribed under subsection (3) above.

ECHA considers that the proposed test that ECHA accepted under subsection (2) above is not sufficient to address the present standard information requirement. ECHA also states that, as explained under subsection (3) above, testing of toxicity to soil microorganisms cannot be omitted using 'no toxicity' or 'low water solubility' argument. Furthermore, as also explained in subsection (3) above, it is not possible to adapt the standard information requirement through an initial screening assessment based upon EPM. Therefore, the adaptation does not fulfill the column 2 of Annex IX 9.4.

In his update of 08 July, [redacted], following his comments to the draft decision, the Registrant further explained in the endpoint justification why he considered that no further terrestrial toxicity testing is needed.

ECHA still considers based on Registrant arguments that the low aquatic toxicity approach based on acute data can not be applied when the water solubility of the substance is below 1 mg/L. Furthermore, the WoE on low toxicity on microorganisms does not fulfil the Annex XI section 1.2 information and corresponds to one line of evidence on low potential for microbial toxicity as both tests quoted by the Registrant have been performed with same activated sludge inocula.

ECHA concludes that the effects on soil microorganisms need to be ascertained by performing a relevant test (test method: EU C.21 or OECD 216) as no EPM approach can be used as part of TGD (2003).

Outcome

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant is required to carry out the following additional study using the registered substance subject to the present decision: Soil microorganisms: nitrogen transformation test, EU C.21/OECD 216).

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.

In relation to the proposed tests, the sample of substance used for the new studies 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 of the same substance to agree to the tests proposed (as applicable to their tonnage level) 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 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 by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new studies 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 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.

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.