EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000002969-56-04/F Helsinki, 13 February 2014

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

For Polyethylenepolyamine/CAS 68131-73-7 (EC No 268-626-9), 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 testing proposals set out in the registration dossier for **Polyethylenepolyamine CAS 68131-73-7 (EC NO 268-626-9)** submitted [redacted] (Registrant)

In accordance with Articles 10(a)(ix) and 12(1)(e) of the REACH Regulation, the Registrant submitted the following testing proposals as part of the registration dossier to fulfil the information requirements set out in Annex IX and X:

- Annex IX, 7.16 Dissociation constant, OECD Guideline 112 (Dissociation constant in water).
- Annex IX, 7.17 Viscosity, OECD Guideline 114 (Viscosity of liquids).
- Annex IX, 8.7.2: Pre-natal developmental toxicity study, OECD Guideline 414.
- Annex X, 8.7.3: Two-generation reproductive toxicity study, OECD Guideline 416.

The present decision relates only to the examination of the first three testing proposals whereas the fourth testing proposal for fulfilling the information requirement for a reproductive toxicity study (Annex X, 8.7.3.) is addressed in a separate decision although all these were initially addressed together in the same draft decision.

The present decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band of 1000 tonnes or more per year. This decision does not take into account any updates after 20 June 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.

The examination of the testing proposals was initiated on 28 September 2010.

ECHA opened a third party consultation for the testing proposals including testing on vertebrate animals that was held from 28 February 2011 until 14 April 2011. ECHA received comments from third parties for an endpoint addressed by the present decision (see section III.3.b below).

On 25 November 2011 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 22 December 2011 ECHA received comments from the Registrant. While the initial testing proposal did not specify the test substance, the Registrant clarified in the follow-up communication with ECHA in 2012 that the proposed test substance for all four endpoints referred to above is the registered substance Polyethylenepolyamine CAS 68131-73-7. In addition, in the follow-up communication it became clear the Registrant no longer proposed to conduct a study with test method OECD 422 (Combined Repeated Dose Toxicity with the Reproduction/Developmental Toxicity Screening Test) to cover for both the developmental toxicity and reproductive toxicity information requirement. This study was initially included in the Registrant's testing proposal. The Registrant later updated its dossier to reflect the change in the test method.

ECHA considered the Registrant's comments received. The comments are reflected in the Statement of Reasons (Section III with amendments made to the Testing Required (Section II).

On 20 June 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 no proposals for amendment to the draft decision concerning the endpoints covered by the present decision but only for the endpoint of two-generation reproductive toxicity.

On 26 July 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.

The draft decision was split into two draft decision documents: one relating to the testing proposal for a two-generation reproduction toxicity study (Annex X, 8.7.3), and one relating to the testing proposals addressed in this decision.

On 5 August 2013 ECHA referred the draft decision to the Member States Committee.

By 26 August 2013 the Registrant did not provide comments on the proposed amendments.

A unanimous agreement of the Member State Committee on the draft decision relating to dissociation constant, viscosity and pre-natal developmental toxicity was reached on 9 September 2013 in a written procedure launched on 28 August 2013. ECHA took the decision pursuant to Article 51(6) 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 registration at a later stage.

II. Testing required

Pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant shall carry out the following proposed tests using the indicated test methods and the registered substance Polyethylenepolyamine CAS 68131-73-7 (EC No 268-626-9):

1. Annex IX, 7.16 Dissociation constant, OECD Guideline 112;
2. Annex IX, 7.17 Viscosity, OECD Guideline 114;
3. Pre-natal developmental toxicity study in rat or rabbit, oral route (Annex IX, 8.7.2., test method: EU B.31/OECD 414).

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **13 February 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 of the Registrant for the registered substance and scientific information submitted by third parties.

1. Dissociation constant

According to Annex IX, 7.16 of the REACH Regulation, Dissociation constant is required to fulfil the standard information requirements. As the proposed test is not available for the registered substance but need to be present in the technical dossier to meet the information requirement, it is necessary to generate the data and to perform the test.

The Registrant has proposed that the test is carried out according to OECD Guideline 112. The Registrant will use Polyethylenepolyamine CAS 68131-73-7 as the test substance. ECHA considers these parameters as appropriate.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: Dissociation constant (test method: OECD 112) using the registered substance Polyethylenepolyamine CAS 68131-73-7 (EC NO 268-626-9).

2. Viscosity

According to Annex IX, 7.17 of the REACH Regulation, Viscosity is required to fulfil the standard information requirements. As the proposed test is not available for the registered substance but need to be present in the technical dossier to meet the information requirement, it is necessary to generate the data and to perform the test.

The Registrant has proposed that the test is carried out according to OECD Guideline 114. The Registrant will use Polyethylenepolyamine CAS 68131-73-7 as the test substance. ECHA considers these parameters as appropriate.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: Viscosity (test method: OECD 114) using the registered substance Polyethylenepolyamine CAS 68131-73-7 (EC NO 268-626-9).

3. Pre-natal developmental toxicity study

a) Examination of the testing proposal

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, but referred to OECD guideline 414 in his updated registration dossier concerning the testing proposals. 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 third party information

ECHA received third party information concerning vertebrate animal testing during the consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

Third party information 1

A third party has proposed to evaluate the need to conduct a Prenatal Developmental Toxicity in light of the results of the existing 28-day or 90-day study and other toxicological data.

ECHA assessment

According to the information submitted in the dossier on a related substance (triethylene tetramine hydrochloride) it cannot be excluded that toxicity in repeated dose toxicity studies may occur. No toxicity is reported on the gonads.

According to Annex IX, 8.7, Column 2 of the REACH Regulation, the study does not need to be conducted if the substance is of low toxicological activity or if it can be proven that no systemic absorption occurs via relevant routes of exposure and if there is no or no significant human exposure. First, the Registrant has not proposed to adapt the information requirement on this basis. Second, there is information in the IUCLID dossier, which indicates that the substance is absorbed and becomes systemically available via relevant routes of exposure. Given the intended use of the substance, there is also potential for widespread human exposure. Therefore, at this level of supply (1000 tonnes or more per year), the column 2 specific rules for adapting the requirement for a Prenatal Developmental Toxicity Study are not fulfilled. Unless the information requirement can be adapted justifiably by other means such as those of Annex XI of the REACH Regulation and claimed by the Registrant in the registration dossier, an acceptable prenatal developmental toxicity study remains the regulatory requirement.

Therefore, ECHA concludes that the information provided is not sufficient to fulfil the information requirement.

Third party information 2

A third party has proposed the use of In vitro tests, QSAR models, and Exposure.

ECHA assessment

The third party has proposed a strategy for ECHA to consider before further tests on animals are requested. However, third parties were invited, as specified by Article 40(2) to submit "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal". As the proposal for a strategy cannot be regarded as such information or studies, ECHA concludes that this is not a sufficient basis for rejecting the Testing Proposals.

Additionally, ECHA notes the following:

For *in vitro* tests (embryonic stem cell test, the limb bud micromass culture and the whole embryo culture), ECHA notes the Guidance on information requirements and chemical safety assessment R.7, chapter R.7.6, which states these tests have limited value in a regulatory context. Considering the possibility of establishing a weight of evidence approach on the basis of such tests and existing *in vivo* data, which could fulfil the information requirements of REACH, is the registrant's responsibility and can only be questioned by ECHA if it is not tailored to real information needs. It is noted that the European Centre for Validation of Alternative Methods maintains a list of test protocols that have regulatory acceptance.

For QSARs, a model and prediction for the registered substance should be provided that complies with Annex XI, 1.3, and should be compliant with the ECHA Guidance on information requirements and chemical safety assessment R.6.

Regarding the exposure argument, exposure based waiving must essentially be based on the information for the manufactured/imported substance and comply with specific adaptations in the REACH text, e.g. Annex XI, 3.2(a).

c) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: Pre-natal developmental toxicity study in rat or rabbit, oral route (test method: EU B.31/OECD 414) using the registered substance Polyethylenepolyamine CAS 68131-73-7 (EC NO 268-626-9).

d) Notes for consideration by the Registrant

In addition, a pre-natal developmental toxicity study on a second species is part of the standard information requirements as laid down in Annex X, Section 8.7.2. for substances registered for 1000 tonnes or more per year (see sentence 2 of introductory paragraph 2 of Annex X).

When considering the need for a testing proposal for a prenatal developmental toxicity study in a second species, the Registrant should take into account the outcome of the pre-natal developmental toxicity study on the first species and all available data to determine if the conditions are met for adaptations according to Annex X, Section 8.7. column 2, or according to Annex XI; for example if the substance meets the criteria for classification as toxic for reproduction Category 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, or alternatively, if Weight

of Evidence assessment of all relevant available data provides scientific justification that the study in a second species is not needed. If the Registrant considers that the conditions for adaptations are not fulfilled, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species. If the Registrant comes to the conclusion that the conditions for these adaptations can be fulfilled, he should update his technical dossier by clearly stating the reasons for proposing to adapt the standard information requirement of Annex X, Section 8.7.2. of the REACH Regulation.

4. Deadline for submitting the information

In the draft decision communicated to the Registrant the time indicated to provide the requested information was 24 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested another study (reproductive toxicity study, Annex X, 8.7.3.). As this study is not addressed in the present decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated IUCLID5 dossier is 12 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

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, or the information submitted by other registrants of the same substance, has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

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. 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.

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