EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-2114295048-42-01/F Helsinki, 24 March 2015

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

For Polyphosphoric acids, esters with triethanolamine, sodium salts, CAS RN 68131-72-6 (EC No 268-625-3), 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 Polyphosphoric acids, esters with triethanolamine, sodium salts, CAS RN 68131-72-6 (EC No 268-625-3), submitted by [redacted] (Registrant).

- Comet Assay - Single cell gel electrophoresis (COMET) assay in the male rat: *In vivo*
- Developmental toxicity / teratogenicity study (OECD 414)

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 30 October 2014, 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 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 4 July 2012.

ECHA held a third party consultation for the testing proposals from 15 April 2014 until 30 May 2014. ECHA received information from third parties (see section III below).

On 30 July 2014 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].

By 05 September 2014 the Registrant did not provide any comments on the draft decision to ECHA.

On 30 October 2014 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 for amendment of the draft decision within 30 days of the receipt of the notification.

Subsequently, proposals for amendment to the draft decision were submitted.

On 5 December 2014 ECHA notified the Registrant of the proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposals for amendment within 30 days of the receipt of the notification.

The ECHA Secretariat reviewed the proposals for amendment received and amended the draft decision.

On 15 December 2014 ECHA referred the draft decision to the Member State Committee.

By 5 January 2015 the Registrant did not provide any comments on the proposals for amendment.

A unanimous agreement of the Member State Committee on the draft decision was reached on 19 January 2015 in a written procedure launched on 9 January 2015.

ECHA took the decision pursuant to Article 51(6) 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) and 13(4) of the REACH Regulation using the indicated test methods and the registered substance subject to the present decision:

1. *In vivo* alkaline single-cell gel electrophoresis assay for DNA strand breaks (Comet assay) (Annex IX, Section 8.4., column 2; OECD 489) in rats, oral route, with examination of liver and either glandular stomach or duodenum/jejunum;
2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31/OECD 414) in rats or rabbits, oral route.

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 requests in this decision, or to fulfil otherwise the information requirements 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 **31 March 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.

Tests required pursuant to Article 40(3)

1. Comet assay (Annex IX, section 8.4, column 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.

"Mutagenicity" is an information requirement as laid down in Annex VIII, Section 8.4. 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."

An appropriate *in vivo* genotoxicity study to follow up the concern on gene mutations and chromosomal aberrations is not available for the registered substance but shall be considered. Consequently, there is an information gap and the Registrant considered necessary to generate information for this endpoint.

Hence, the Registrant has submitted a testing proposal for a Single cell gel electrophoresis (COMET) assay in the male rat: *In vivo* with the following justification: "*In response to the positive mutagenic result (in the absence of metabolic activation) found in the CHO HPRT forward mutation assay, a Single Cell Gel Electrophoresis (Comet) Assay in the male rat is proposed*".

ECHA notes that this test is an appropriate test to investigate further effects on gene mutations and chromosomal aberrations *in vivo* as described in the ECHA Guidance document on information requirements and chemical safety assessment, chapter R.7.7.1. and table R.7.7-3 (August 2013).

The Registrant proposed testing in the rat. According to this test method, the rat is the default species. ECHA considers this species as being appropriate and testing should be performed with the rat. The Registrant did not indicate the route of exposure in his testing proposal. As regards the route of administration, paragraph 39 of the draft OECD test guideline states that "*The anticipated route of human exposure should be considered when designing an assay*" and "*In any case the route should be chosen to ensure adequate exposure of the target tissue(s)*". In light of the physicochemical properties of the substance, ECHA considers that testing by the oral route is appropriate.

ECHA notes that paragraph 42 of the draft OECD test guideline states: "*The liver has been the tissue most frequently studied and for which there are the most data. Therefore, in the absence of any background information, and if no specific tissues of interest are identified, sampling the liver would be justified as this is a primary site of xenobiotic metabolism and is often highly exposed to both parent substance(s) and metabolite(s). In some cases examination of a site of direct contact (for example, for orally-administered substances the glandular stomach or duodenum/jejunum, or for inhaled substances the lungs) may be most relevant.*" Therefore ECHA considers that the Comet assay should be performed in liver and either glandular stomach or duodenum/jejunum. ECHA notes that this is in line with the draft OECD test method to perform the Comet assay (OECD 489).

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: *In vivo* alkaline single-cell gel electrophoresis assay for DNA strand breaks (Comet assay) in accordance with the draft OECD test guideline 489, in rats via oral route, with examination of liver and either glandular stomach or duodenum/jejunum.

Note for consideration by the Registrant

The Registrant is reminded that according to the column 2 of section 8.4 of Annex IX of the REACH Regulation, if positive results from an *in vivo* somatic cell study are available, "*the potential for germ cell mutagenicity should be considered on the basis of all available data, including toxicokinetic evidence. If no clear conclusions about germ cell mutagenicity can be made, additional investigations shall be considered*". ECHA notes that the examination of gonadal cells would optimize the use of animals. Positive results in whole gonad that contains a mixture of somatic and germ cells are not necessarily reflective of germ cell damage, but they indicate that tested substance(s) and/or its metabolites have reached the gonad. This type of evidence may still be relevant for the overall assessment of possible germ cell mutagenicity including classfication and labelling according to the CLP Regulation.

b) 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: *In vivo* alkaline single-cell gel electrophoresis assay for DNA strand breaks (Comet assay) in accordance with the protocol provided by the Registrant in his registration dossier, and attached to this decision.

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

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 has submitted a testing proposal for a pre-natal developmental toxicity study in rats / rabbits according to EU B.31/OECD 414.

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 and 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.

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 may be sufficient to fulfil this information requirement.

Third party information:

The third party has indicated that "*a sequential testing process is recommended which gives priority to the additionally proposed test on genetic toxicity (Comet assay)* in vivo. *If a positive result will be obtained, the substance selfclassified as a germ cell mutagen, and appropriate risk management measures be implemented a prenatal developmental toxicity study will not be required (REACH Guidance R.7.6.6.3)*".

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, second indent. This adaptation specifies that in case the substance is known to be a germ cell mutagen (which correspond to a classification as germ cell mutagen category 1A or 1B) and appropriate risk management measures are implemented, the pre-natal developmental toxicity study does not need to be conducted.

However, ECHA notes that results of a positive *in vivo* comet assay may contribute to a classification as germ cell mutagen, but this test is usually not sufficient on its own for classification as germ cell mutagen category 1B.

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).

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. 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.

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