EUROPEAN CHEMICALS AGENCY

Helsinki, 21 June 2012

Decision number: TPE-D-0000002283-80-04/F

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

**For 2-Butyne-1,4-diol, polymer with 2-(chloromethyl)oxirane, brominated, dehydrochlorinated, methoxylated, CAS No [redacted] (List No 614-503-3), 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)(e) thereof for 2-Butyne-1,4-diol, polymer with 2-(chloromethyl)oxirane, brominated, dehydrochlorinated, methoxylated, CAS [redacted] (List No 614-503-3) by [redacted] (Registrant), latest submission number [redacted], for over 1000 tonnes per year.

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 Annexes IX and X:

- Sub-chronic repeated dose toxicity study (90-days) in male rat by the inhalation route on the registered substance that contains in addition 6-7% of triethyl phosphate according to the OECD test guideline 413
- Pre-natal developmental toxicity study by the oral route on the registered substance that contains in addition 6-7% of triethyl phosphate according to the OECD test guideline 414
- Two-generation reproductive toxicity study by the oral route on the registered substance that contains in addition 6-7% of triethyl phosphate according to the OECD test guideline 416.

The present decision relates solely to the examination of the testing proposal for a sub-chronic toxicity study (90-day) and pre-natal developmental toxicity study. The testing proposal for the two-generation reproductive toxicity study is addressed in a separate decision although all testing proposals were initially addressed together in the same draft decision.

The examination of the testing proposals was initiated on 17 November 2010.

ECHA opened a third party consultation for the testing proposals including testing on vertebrate animals that was held from 15 April 2011 until 30 May 2011. ECHA did not receive any comments by the deadline from third parties.

On 9 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 8 December 2011 ECHA received comments from the Registrant agreeing to ECHA's draft decision.

On 20 January 2012 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 23 February 2012 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 has reviewed the proposals for amendment received and decided not to amend the draft decision.

On 5 March 2012 ECHA referred the draft decision to the Member State Committee.

On 26 March 2012 the Registrant provided comments on the proposed amendments. The Member State Committee took the comments of the Registrant into account and amended the draft decision.

The draft decision was split into two draft decision documents: one relating to the testing proposal for a two-generation reproductive toxicity study and one relating to the testing proposals for a sub-chronic repeated dose toxicity study and a pre-natal developmental toxicity study.

The Member State Committee reached unanimous agreement on the modified draft decision relating to the testing proposal for a sub-chronic repeated dose toxicity study and a pre-natal developmental toxicity study in a written procedure launched on 2 April and closed on 12 April 2012.

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 to initiate a compliance check on the present dossier at a later stage.

## II. Testing required

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

- Sub-chronic repeated dose toxicity study (90-days) in rats, both sexes, inhalation route, on the substance 2-Butyne-1,4-diol, polymer with 2-(chloromethyl)oxirane, brominated, dehydrochlorinated, methoxylated (Annex IX, 8.6.2, test method: EU B.29/OECD 413).
- Pre-natal developmental toxicity study in rats, oral route on the substance 2-Butyne-1,4-diol, polymer with 2-(chloromethyl)oxirane, brominated, dehydrochlorinated, methoxylated (Annex IX and X, 8.7.2, test method: EU B.31/OECD 414).

while pursuant to Article 40(3)(d) the proposed tests sub-chronic repeated dose toxicity and pre-natal developmental toxicity on the registered substance that contains in addition 6-7% of triethyl phosphate are rejected.

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.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **23 June 2014** an update of the registration dossier containing the information required by this decision.

Data from a second pre-natal developmental toxicity study on another species is a standard information requirement according to Annex X, 8.7.2. of the REACH Regulation. The Registrant should firstly take into account the outcome of the pre-natal developmental toxicity on a first species and all other relevant available data to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI. If the Registrant considers that testing is necessary to fulfil this information requirement, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposal of the Registrant for the registered substance.

- Sub-chronic toxicity study (90-days), inhalation route

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 generate the data for this endpoint.

The Registrant has based his testing proposal on the findings observed in the 28-day repeated dose toxicity study, where the registered substance showed concentration dependent increase in squamous metaplasia in the larynx. A LOAEC was established for local effects in the males, therefore the Registrant proposes to conduct the 90-day study with male animals only. However, the Annex IX, 8.6.2 of the REACH Regulation specifies that a sub-chronic toxicity study shall be conducted in one species, rodent, male and female. The Registrant did not specify the species to be used for testing. According to the test method EU B.29/OECD 413 the rat is the preferred rodent species. ECHA considers this species as being appropriate.

Additionally, the Registrant proposes to perform the test by using a mixture containing the registered substance with 6-7% triethyl phosphate, without adding any sound justification for such proposal. According to the REACH Regulation, in particular Article 6 and 10, the information to be submitted to the Agency relate to the registered substance(s), and not to mixtures. REACH applies to any manufacturer, importer "*of a substance, either on its own or in a mixture*". Accordingly, the information and tests proposed to ECHA should refer to the registered substance and not to a mixture which is not object of the registration dossier.

Therefore, pursuant to Article 40(3)(c)of the REACH Regulation, the Registrant is required to carry out the following study: 90-day repeated dose toxicity study in rats, inhalation route using both sexes (test method: EU B.29/OECD 413) using the registered substance, while the proposed test on the registered substance that contains in addition 6-7% of triethyl phosphate is rejected pursuant to Article 40(3) (d).

- Pre-natal developmental toxicity study

Pre-natal developmental toxicity studies are part of the standard information requirements as laid down in Annexes IX and X, 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 generate the data for this endpoint.

The Registrant included an additional justification in their testing proposal stating "As the current data set of the substance does not contain a repeated dose toxicity study by the oral route, a two week oral dose range finding study will also be performed." The Registrant did not specify the species 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. The rat should be the first species to be used.

Additionally, the Registrant proposes to perform the test by using a mixture containing the registered substance with 6-7% triethyl phosphate, without adding any sound justification for such proposal. According to the REACH Regulation, in particular Article 6 and 10, the information to be submitted refers to the registered substance. REACH applies to any manufacturer, importer "*of a substance, either on its own or in a mixture*". Accordingly, the information and tests proposed to ECHA should refer to the registered substance and not to a mixture which is not object of the registration dossier.

Therefore, pursuant to Article 40(3) (c) of the REACH Regulation, the Registrant is required to carry out the proposed study: Pre-natal developmental toxicity study in rats, oral route (test method: EU B.31/OECD 414) using the registered substance, while the proposed test on the registered substance that contains in addition 6-7% of triethyl phosphate is rejected pursuant to Article 40(3) (d).

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, 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.

- Deadline for submitting the information

In the draft decision communicated to the Registrant the time indicated to provide the requested information was 36 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested a 2-generation reproductive toxicity study. As the testing proposal for this study is not addressed in the present draft decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated IUCLID5 dossier is 24 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

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

ECHA always 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). National authorities monitoring GLP maintain lists of test facilities indicating the relevant areas of expertise of each facility.

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.

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://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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Jukka Malm
Director of Regulatory Affairs