EUROPEAN CHEMICALS AGENCY

Decision number TPE-D-0000002662-76-05/F Helsinki, 30 January 2013

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

For Ethanol, 2-methoxy-, manufacture of, by-products from, esters with boric acid , CAS No 161907-80-8 (EC No 310-290-3), 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 Ethanol, 2-methoxy-, manufacture of, by-products from, esters with boric acid, CAS No 161907-80-8 (EC No 310-290-3), by [redacted] (Registrant).

This 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 6 September 2012, 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.

- Viscosity (OECD 114).
- Sub-chronic toxicity (90-day), oral route using the analogue substance tris[2-[2-(2-methoxyethoxy)ethoxy]ethyl] orthoborate.
- Developmental toxicity / teratogenicity (OECD 414) using the analogue substance tris[2-[2-(2-methoxyethoxy)ethoxy]ethyl] orthoborate.
- Two-generation reproductive toxicity study (OECD 416) using the analogue substance tris[2-[2-(2-methoxyethoxy)ethoxy]ethyl] orthoborate.

The present decision relates to the examination of the testing proposals for viscosity, sub-chronic toxicity (90-day) and pre-natal developmental toxicity studies. 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.

On 29 September 2010, 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 15 September 2011 until 31 October 2011 for the registered substance (noting that the Registrant proposes to perform the tests on the analogue substance tris[2-[2-(2-methoxyethoxy)ethoxy] ethyl] orthoborate). ECHA did receive information from third parties (see section III below).

On 19 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.

By 20 August 2012 the Registrant did not provide any comments on the draft decision to ECHA.

On 6 September 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 10 October 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 reviewed the proposals for amendment received and decided to amend the draft decision.

On 22 October 2012 ECHA referred the draft decision to the Member State Committee.

The Registrant did not provide any comments on the proposed amendments.

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 proposal for viscosity, sub-chronic toxicity (90-day) and pre-natal developmental toxicity studies.

A unanimous agreement of the Member State Committee on the draft decision relating to the testing proposals for viscosity, sub-chronic toxicity (90-day) and pre-natal developmental toxicity studies was reached on 26 November 2012 in a written procedure launched on 14 November 2012. 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 to initiate a compliance check on the present dossier at a later stage.

II. Testing required

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

a) Viscosity (Annex IX, 7.17.; test method: OECD 114).

2. 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 using the analogue substance tris[2-[2-(2-methoxyethoxy)ethoxy]ethyl] orthoborate (CAS No 30989-05-0, EC No 250-

418-4):

a) Sub-chronic toxicity study (90-day) in rats, oral route (Annex IX, 8.6.2.; test method: EU B.26/OECD 408);
b) Pre-natal developmental toxicity study in rats or rabbits, 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 **30 January 2015** 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.

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 and those contained in Annex XI of the REACH Regulation.

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.(a) Viscosity

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.

Viscosity is a standard information requirement as laid down in Annex IX, section 7.17. 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.

b) Outcome

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.

2. Testing proposals for toxicological endpoints

In relation to the testing proposals subject to the present decision, the Registrant has proposed using the read-across approach, in accordance with Annex XI, 1.5, and to perform the relevant tests on another substance than the registered substance. To the extent that the proposed testing relies upon an identical read-across hypothesis, and that all required tests address endpoints for repeated dose toxicity and reproductive toxicity, ECHA has considered first the scientific validity of the proposed read-across approach, before assessing the testing proposed (Sections (a), (b) and (c) below).

Read-across approach

Article 13(1) of the REACH Regulation requires information on intrinsic properties of substances on human toxicity to be generated whenever possible by means other than vertebrate animal tests, including from information from structurally related substances (grouping or read-across), "*provided that the conditions set out in Annex XI are met*".

The Registrant intends to conduct the proposed studies with a read-across substance, tris[2-[2-(2-methoxyethoxy)ethoxy]ethyl] orthoborate (EC no: 250-418-4, CAS no: 30989-05-0) and has provided the following justification:

(i) The read-across substance, tris[2-[2-(2-methoxyethoxy)ethoxy]ethyl] orthoborate (B-TEGME), is one of the main components of the registered substance, B-TTEGME: B-TTEGME is a mixture of three borated glycol esters, B-TEGME (typical concentration [redacted] %), B-TetraEGME ([redacted] %) and B-PentaEGME ([redacted] %). The impurities of B-TEGME are [redacted] (concentration ≥ [redacted] %) and [redacted]. TEGME is one constituent (typical concentration [redacted] %) of ethanol, 2-methoxy-, manufacture of, by-products from (MTTO; CAS No 161907-79-5), which is a non-classified substance, and therefore the Registrant concludes that [redacted] have no toxicological effects.

(ii) The substances share a common functional group, borate ester: the components are different borated glycol esters whose basic chemical structure is identical: one boric acid molecule forms an ester with three polyethylene glycol ethers of different chain length, i.e. three, four or five glycol ether entities. The components thus belong to the same functional class and are homologues.

(iii) The substances have common breakdown products, boric acid and poly-ethylene glycols: the read-across substance, B-TEGME, hydrolyses spontaneously to boric acid ([redacted] % of the starting material) and polyethylene glycol chains (TEGME, tetraEGME and pentaEGME). The three polyethylene glycol chains are constituents in MTTO which is, as stated under (i) above, a non-classified substance. Since the two other components of B-TTEGME are chemical homologues (boric esters with different side chain lengths), it is concluded that B-TTEGME is also hydrolysed spontaneously.

(iv) A physico-chemical, toxicokinetic and toxicological comparative analysis between the registered substance and B-TEGME was provided. According to the analysis, the substances have a comparable toxicological profile. Potentially higher absorption and consequently the worst case scenario is expected from B-TEGME due to lower molecular weight.

Therefore, the Registrant concludes that a close structural, physicochemical and toxicological similarity exists between the three components of the registered substance.

Based on the data presented by the Registrant, ECHA agrees that the proposed test substance (source substance) and the registered substance (target substance) share structural, physicochemical and toxicological similarity.
Therefore, ECHA concludes that the justification for the read-across in the dossier was found sufficient to allow using such an adaptation of standard requirements.

ECHA considers that the justification given demonstrates that it is plausible that the requirements of Annex XI, section 1.5 in conjunction with article 13(1) and Annex IX, third introductory paragraph, of the REACH Regulation may be met. Specifically, adequate and reliable documentation of the applied method has been provided, and ECHA considers that there is, prima facie, a scientific justification that human health effects for repeat-dose, developmental and reproductive toxicity may be predicted from data for the substance ethanol, 2-methoxy-, manufacture of, by-products from, esters with boric acid through the read-across approach. However, a final conclusion on the validity of the suggested approach to adapt the standard information requirements will only be possible when it has been demonstrated on the basis of test results that the conditions set out in Annex XI section 1.5 are met for this endpoint.

ECHA emphasises that it is the Registrant's responsibility to amend and substantiate read-across and category justification according to Annex XI, section 1.5 and to use all relevant available data.

Following the update of the dossier based on the present decision, ECHA will decide whether the documentation provided is sufficient to satisfactorily address the information requirements for the substance subject to this decision as proposed by the Registrant. If, upon further consideration, the proposed approach does not satisfy the conditions set out in Annex XI, ECHA reserves the right to request the information necessary to fulfil the information requirements.

2.(a). Repeated dose toxicity study

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 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.
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.

b) Consideration of the information received during third party consultation

ECHA held a third party consultation for the registered substance and received information concerning the testing proposal. The third party proposes ECHA to check (i) if the IUCLID

dossier contains human data and use this data for risk assessment and classification purposes, (ii) to request the Registrant to provide such data if that is not provided, and (iii) in case the human studies are not reliable enough, use the human data together with the animal and other data for DNEL/DMEL derivation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

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) of the REACH Regulation 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 as such cannot be regarded information or studies, ECHA concludes that this is not a sufficient basis to fulfil the data/information requirement.

c) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD 408) using the analogue substance tris[2-[2-(2-methoxyethoxy)ethoxy]ethyl] orthoborate.

2.(b). Pre-natal developmental toxicity study

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.

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 provide information for this endpoint.

The Registrant states that the only intended use of B-TTEGME is [redacted] and therefore contact with water and subsequent formation of boric acid is incidental. Therefore, classification of B-TTEGME as a reprotoxicant 1B based on boric acid and subsequent adaptation according to Annex IX or X, 8.7 column 2 would be inappropriate and not relevant for the intended use.

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.

b) Consideration of the information received during third party consultation

ECHA held a third party consultation for the registered substance and received information concerning the testing proposal.
For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

Third party information 1:

The third party proposes to evaluate/consider the following data before conducting the pre-natal developmental toxicity study: (i) evaluate the results of the existing 28-day or 90-day study and other toxicological data, (ii) perform an *in vitro* (pre-) validated test and apply QSAR classification models to waive the study, and (iii) use the TTC concept for reproduction toxicity endpoints.

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) of the REACH Regulation 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 as such cannot be regarded information or studies, ECHA concludes that this is not a sufficient basis to fulfil the data/information requirement.

Third party information 2:

The third party has further proposed to use the results of the extended one-generation reproductive toxicity study (EOGRTS) to waive the pre-natal developmental toxicity study. ECHA notes that in EOGRTS the developmental toxicity parameters such as skeletal and visceral malformations are not examined and, thus, EOGRTS do not provide adequate information on developmental toxicity to waive the prenatal developmental toxicity study.

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 rats or rabbits, oral route (test method: EU B.31/OECD 414) using the analogue substance tris[2-[2-(2-methoxyethoxy)ethoxy]ethyl] orthoborate.

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.

d) 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 reproductive toxicity study according to the standard information requirement of Annex X, 8.7.3 of the REACH Regulation. As the testing proposal for 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 24 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 evaluation 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 evaluation of the testing proposal.
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.

Finally there must be adequate information on substance identity for the sample tested and the grade[s] registered to enable the relevance of the study/studies to be assessed.

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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Jukka Malm
Director of Regulatory Affairs