EUROPEAN CHEMICALS AGENCY

Helsinki, 25 April 2017

Addressee: [redacted]

Decision number: TPE-D-2114359790-42-01/F
Substance name: tris[2-[2-(2-methoxyethoxy)ethoxy]ethyl] orthoborate
EC number: 250-418-4
CAS number: 30989-05-0
Registration number: [redacted]
Submission number: [redacted]
Submission date: 17 December 2015
Registered tonnage band: 1000+T

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA examined your testing proposal(s) and decided as follows.

Your testing proposal is accepted and you are requested to carry out:

1. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rabbit), oral route using the registered substance.**

You 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 and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **1 November 2018**. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals.

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.

Appendix 1: Reasons

The decision of ECHA is based on the examination of the testing proposal(s) submitted by you.

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

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 on two species are part of the standard information requirements for substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The dossier contains a pre-natal developmental toxicity study in rats as first species. However, there is no information available for a pre-natal developmental toxicity study in a second species. Consequently there is an information gap for Annex X, Section 8.7.2. and it is necessary to provide information for this endpoint.

On the results in the rat study you concluded: "*as TEGME (Methyltriglycol or 2-(2-(2-methoxyethoxy)ethoxy)ethanol) was used as a vehicle in all groups, maternal toxicity was masked by which the study on its own is not conclusive for classification. The report needs to be further refined by means of historical control data.*" You derived a NOAEL for developmental toxicity and maternal toxicity of 1000 mg/kg bw/day or lower than 1000 mg/kg bw/day (highest dose) but also stated that this value has to be refined based on historical control data.

Observed effects were:

- Reduced foetal body weights. This might partly be explained by larger litter sizes at 1000 mg/kg bw/day only, but this explanation does not hold at 300 mg/kg bw/day. ECHA considers that reduction of foetal weights at 300 mg/kg bw/day is due to foetotoxicity.
- Skeletal effects at 1000 and 300 mg/kg bw/day. ECHA considers that this may be related to reduced foetal body weights – a consequence of reduced general development due to large litter size or foetotoxicity (reduced foetal body weight).
- Skeletal effects at 300 and 30 mg/kg bw/day. ECHA considers that this may be due to delayed skeletal development (related to reduced foetal body weight/foetotoxicity or specific effect of the substance).
- Foetuses with bilateral/unilateral short 13th rib(s) were observed at 30 mg/kg bw/day. This means that for skeletal variations there was no NOAEL identified. You claim: "*The mean percent value for these litters was comparable to previous control values and in the absence of any associated findings at this level, the intergroup difference was considered not to be of toxicological significance.*" However it is not clear what control values were used to support this claim. The PNDT study conducted with the vehicle did not show such effects.
- Renal effects in foetuses. ECHA considers that this may be related to delayed development or special toxicity to kidneys.

ECHA has doubts on your interpretation based on the observed pre-natal developmental toxicity effects. ECHA cannot confirm that maternal toxicity was observed in this study or in other studies with the vehicle and the study was performed under GLP standards. In summary, on the basis of the current information ECHA considers the observed pre-natal toxicity in the rat as (most likely) test substance related.

In any case, there is a need to further clarify the pre-natal developmental toxicity.

You have submitted a testing proposal for a pre-natal developmental toxicity study in a second species (rabbit) according to EU B.31./OECD TG 414 by the oral route.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (pre-natal developmental toxicity). ECHA notes that you provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

ECHA considers that the proposed study performed with the registered substance is appropriate to fulfil the information requirement of Annex X, Section 8.7.2. of the REACH Regulation.

You proposed testing with the rabbit as a second species. The test in the first species was carried out with rats. According to the test method EU B.31./OECD 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with the rabbit as a second species.

You proposed testing by the oral route. ECHA agrees that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route. The choice of the vehicle in the rat study leaves questions whether other vehicles would not have been a better choice and would not have resulted in a clearer picture. You should consider using another appropriate vehicle for the rabbit study.

In the comments to the draft decision you agreed to perform the Pre-natal developmental toxicity study in a second species.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are thus requested to carry out the proposed study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a second species (rabbit), oral route (test method: EU B.31./OECD TG 414).

Deadline to submit the requested information in this decision

In the draft decision communicated to you, the time indicated to provide the requested pre-natal developmental toxicity study in a second species and submit the study results to ECHA in a dossier update by information was 12 months from the date of adoption of the decision. In your comments on the draft decision, you requested an extension of this timeline to 18 months. You have justified this request by explaining that the following work need to be performed, prior to the conduct of the pre-natal developmental toxicity study in a second species: search for a suitable vehicle including investigation of substance stability and range finding studies (no studies in rabbits available so far). Furthermore you pointed out that laboratory capacities for this type of studies are limited and heavily loaded by ECHA's decisions on testing. The chosen laboratory provided support for this justification. Based on the provided information, ECHA has granted the request and set the deadline for providing the pre-natal developmental toxicity study in a second species to 18 months.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposal(s) for examination pursuant to Article 40(1) on 17 December 2015.

ECHA held a third party consultation for the testing proposal(s) from 29 April 2016 until 13 June 2016. ECHA did not receive information from third parties.

This decision does not take into account any updates after **18 January 2017**, 30 calendar days after the end of the commenting period.

This decision has not examinated the testing proposal on the endpoint, extended one-generation toxicity study. For further details on this testing proposal, please see the communication letter, communication number TPE-C-2114348811-49-01/F.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and amended the deadline.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided in your 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.

2. 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.

3. In relation to the information required by the present decision, the sample of the substance used for the new test(s) must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants. It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new test(s) 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 or imported by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new test(s) 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 test(s) to be assessed.