EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000002339-71-08/F Helsinki, 15 June 2012

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

For 2,2'-ethylenedioxyethyl bis(2-ethylhexanoate), CAS No 94-28-0 (EC No 202-319-2), 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 a testing proposal set out in the registration dossier for 2,2'-ethylenedioxyethyl bis(2-ethylhexanoate), CAS No 94-28-0 (EC No 202-319-2), submitted by [redacted] (Registrant), latest submission number [redacted], for 1000 tonnes or more per year.

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

- Annex IX, 8.6.2.: Sub-chronic toxicity study (90-day) in rats via the oral route according EU Method B.26 (OECD Guideline 408).

The examination of the testing proposal was initiated on 14 September 2010.

ECHA opened a third party consultation for the testing proposal including testing on vertebrate animals that was held from 26 January 2011 until 14 March 2011. ECHA received comments from third parties (see section III below).

On 9 August 2011 ECHA notified the Registrant of its draft decision and invited him pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

On 7 September 2011 the Registrant provided to ECHA comments on the draft decision. Both on 6 September 2011 and 8 December 2011 dossier updates were received.

ECHA has taken into account the information received and decided to amend the draft decision.

On 2 March 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, one Competent Authority of a Member State submitted a proposal for amendment to the draft decision.

On 4 April 2012 ECHA notified the Registrant of the proposal for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on that proposal for amendment within 30 days of the receipt of the notification.

ECHA reviewed the proposal for amendment received and decided to amend the draft decision accordingly.

On 16 April 2012 ECHA referred the draft decision to the Member State Committee.

On 27 April 2012 the Registrant provided comments on the proposed amendment. The Member State Committee took the comments of the Registrant into account.

A unanimous agreement of the Member State Committee on the draft decision was reached on 21 May 2012 in a written procedure launched on 10 May 2012.

This decision does not imply that the information provided by the Registrant in his registration dossier is in compliance with the requirements of the REACH Regulation. The decision does not prevent ECHA to initiate a compliance check on the present dossier at a later stage.

II. Testing required

Pursuant to Article 40(3)(b) of the REACH Regulation, the Registrant shall carry out the following test under modified conditions using the indicated test method:

> Sub-chronic toxicity study (90-day) (Annex IX, 8.6.2., test method EU B.26/ OECD Guideline 408) in rat by the oral route; Additional measurements regarding immunotoxicological parameters shall be carried out as detailed in the statement of reasons below.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA **by 16 December 2013** 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 proposal of the Registrant for the registered substance and scientific information submitted by third parties. Pursuant to Article 40(3)(b), ECHA may take a decision requiring the Registrant to carry out the proposed test but modifying the conditions under which the test is to be carried out.

According to Section 8.6.2. of Annex IX to the REACH Regulation, sub-chronic toxicity via the most appropriate route of administration, having regard to the likely route of human exposure is required to fulfil the standard information requirements. As there is a data gap for this endpoint, a sub-chronic toxicity study needs to be present in the technical dossier to meet the information requirements.

In the oral 28-day repeated dose toxicity study, effects were seen in the thymus of the females (decrease in absolute and relative weight (lymphoid atrophy)), in the spleen of the

females (hemosiderin pigment increased, reduced erythroid hematopoietic foci), in the thyroid gland (diffuse follicular hypertrophy/hyperplasia), in the pituitary gland of the males (adenohypophyseal multifocal hypertrophy), whilst there was a decreased proportion of neutrophils in the highest group of females tested. Thus, the 28-day study raises some concern on immunotoxicity that needs to be addressed in the proposed testing.

As part of the EU B26/OECD 408 guideline, the Registrant is requested to include additional measurements in the study protocol concerning:

- Terminal bone marrow and histology (including bone marrow cellularity). Included in paragraphs 35 and 36 of OECD 408 guideline;

- Terminal chemistry measurements of immunoglobulins performed by either the plague-forming cell (PFC) assay or the enzyme-linked immunosorbent (ELISA) assay. Included in paragraph 29 of OECD 408 guideline;

- Distribution of lymphocyte subsets including total B- and T-cell counts, T-cell subpopulations (including CD4 and CD8 cells) depending on the previous results of the investigations above. Included in paragraph 28 of OECD 408 guideline.

In response to ECHA's draft decision, the Registrant agreed to the draft decision and proposed to apply a tiered approach instead of automatically including all the requested additional immunotoxicological measurements in the OECD 408 test. This tiered approach is based on confirming the (ir)relevance of the observed effects in the OECD 408 test and deciding on the necessity of follow up testing. ECHA notes that the tiered approach proposed by the Registrant cannot be endorsed as possible lack of effects in bone marrow (step 1 in the proposed strategy) does not exclude adverse effects in the lymphocyte subsets due to the specialised tasks of the bone marrow as opposed to the thymus. Therefore, it is necessary to perform the lymphocyte subset analysis independent of the outcome of the bone marrow examination, at the end of the experiment, to examine possible changes in the lymphocyte homeostasis i.e. in the mechanisms governing maintenance of a functional and diverse pool of lymphocytes. The requested additional parameters on the potential effects of the immune system will provide information about the different immunological processes that can occur and are therefore necessary information for the evaluation of the immunotoxicological profile of the registered substance.

ECHA has further examined the scientific information submitted by third parties following the public consultation in order to determine whether there is already scientifically valid information that addresses the relevant substance and hazard endpoint. This additional information is not, however, able to change the conclusion that a 90-day repeated dose inhalation toxicity study needs to be requested, as explained below.

Comment 1, Use data from combined repeated dose developmental/reproduction toxicity study (OECD 422) as Weight of Evidence: ECHA notes that the sub-chronic toxicity study (90-day) is a standard data requirement according to Annex IX, 8.6.2., and the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test is a standard data requirement according to Annex VIII, 8.7.1. The screening study is neither an alternative nor does it replace the information requirement for the sub-chronic toxicity study. The dosing period in the screening study (42 – 53 days in males, 53 days in females) is shorter than in the 90-day study. In addition, interpretation of the results may be complicated due to differences in sensitivity between pregnant and non-pregnant animals, and an assessment of the general toxicity may be more difficult especially when serum and

histopathological parameters are not evaluated at the same time in the study. For the repeated dose toxicity part, the screening study (OECD 422) is in concordance with the OECD 407 (Repeated dose 28-day oral toxicity study).

Comment 2, Inclusion in US EPA HPVC and CANADA domestic substance list: The third party refers to US EPA HPVC and Canada domestic substance list according to which the registered substance is not prioritised for risk assessment and management activities. The third party comment does not give any information on the sub-chronic toxicity study of the registered substance, and therefore it cannot constitute an acceptable adaptation to standard data requirement for this endpoint. Furthermore, the purpose for prioritisation between the regulatory framework of the REACH Regulation and US/ CANADA legislative regimes is different.

The third party did not submit scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal as specified by Article 40(2).

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 generation of information is tailored to real information needs in order to prevent unnecessary testing. The information submitted in the registration dossier was sufficient to confirm the identity of the substance for the purpose of assessing the testing proposal. It is noted, 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 test, the sample of substance used for the new study/ies 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 the joint Registrants of the same substance to agree with the test proposed in the testing proposal (as applicable to their tonnage level) and to document the necessary information on its composition. The substance identity information of the registered substance and of the sample tested must enable ECHA to confirm the relevance of the testing for the substance actually registered by each joint Registrant. Finally, the study must be shared by the joint Registrants concerned.

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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Director of Regulatory Affairs