EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000001849-61-05/F Helsinki, 18 June 2012

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

For 3,4,5,6,7,8,9,10,11,12,13,14-dodecahydro-2H-cyclododeca[b]pyran, CAS No 32539-83-6 (EC No 251-090-5), 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 **3,4,5,6,7,8,9,10,11,12,13,14-dodecahydro-2H-cyclododeca[b]pyran**, CAS No. 32539-83-6 (EC No. 251-090-5), submitted by [redacted] (Registrant), latest submission number [redacted], for a transported isolated intermediate at 1000 tonnes or more per year.

In accordance with Article 18(3) and, by analogy, Article 10(a)(ix) 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, in conjunction with Annexes VII and VIII:

> IX, 8.4. Mutagenicity (*In vivo* Mammalian Erythrocyte Micronucleus test, OECD Guideline 474)

The examination of the testing proposal was initiated upon the date when receipt of the complete registration dossier was confirmed on 30 September 2010.

ECHA opened a third party consultation for the testing proposals including testing on vertebrate animals that was held from 14 February 2011 until 31 March 2011. ECHA received the following comments from third parties:

- Expert judgement on results from existing *in vitro* tests on mutagenicity/genetoxicity and on the possibility to conduct further *in vitro* testing first
- Software tools for chemicals profiling and QSARs for genetoxicity prediction
- Exposure and the TTC concept
- Reduced information requirements for an intermediate used under strictly controlled conditions

ECHA examined the testing proposal and the information received from third parties and drafted a decision in accordance with Article 40 of REACH Regulation.

On 10 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.

The Registrant did not provide any comments on the draft decision.

On 4 November 2011 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. Subsequently, Competent Authorities of the Member States submitted proposals for amendment to the draft decision. ECHA reviewed the proposals for amendment received and decided not to modify the draft decision.

On 8 December 2011 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 those proposals for amendment within 30 days of the receipt of the notification.

On 19 December 2011, the draft decision was referred to the Member State Committee.

On 9 and 17 January 2012 the Registrant provided comments on the proposals for amendment. The Member State Committee took the comments of the Registrant into account.

After discussion in the Member State Committee meeting on 6-10 February 2012, a unanimous agreement of the Member State Committee on the draft decision was reached on 8 February 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)(a) of the REACH Regulation, the Registrant shall carry out the following test using the indicated test method:

- *In vivo* Mammalian Erythrocyte Micronucleus test, (Annex IX, 8.4., EU Method B.12, OECD testing guideline 474) by gavage

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **18 June 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 comments submitted by third parties.

1. Examination of the testing proposal of the Registrant

The technical dossier includes the results of an *in vitro* gene mutation study in bacteria (Ames test) submitted in accordance with Annex VII 8.4., showing positive results. Pursuant to column 2 of Annex VII 8.4., further mutagenicity studies shall be considered in the case of a positive result in the *in vitro* gene mutation study in bacteria.

In accordance with this obligation, the dossier thus contains the results of an *in vitro* gene mutation study in mammalian cells (Mouse Lymphoma Assay) submitted in accordance with Annex VIII 8.4.3., showing small colonies exclusively, which is indicative of a clastogenic effect. Furthermore, pursuant to column 2 of Annex VIII, 8.4.3., appropriate *in vivo* mutagenicity studies shall be considered in case of a positive result in any of the mutagenicity studies in Annex VII or VIII.

Additionally, pursuant to Annex IX, 8.4. of the REACH Regulation, if there is a positive result in any of the *in vitro* genetoxicity studies in Annex VII or VIII and there are no results available from an *in vivo* study already, an appropriate *in vivo* somatic cell genetoxicity study shall be proposed by the registrant.

The Registrant has applied these provisions in conjunction by proposing an *in vivo* Mammalian Erythrocyte Micronucleus test.

Based on the above and on Article 40(1) of the REACH Regulation, ECHA shall examine a testing proposal set out in a registration dossier for provision of information specified in Annexes IX and X. The results of the Annex VII and VIII *in vitro* studies indicate the need for further investigation of this endpoint. The results of the public consultation did not yield scientifically relevant information that addresses the registered substance and the hazard end-point addressed in this testing proposal. Therefore, ECHA accepts the testing proposal, and the Registrant is requested to carry out the test by gavage, using OECD Guideline 474.

2. Examination of the comments submitted by third parties

During the public consultation, ECHA received the following comments from third parties on the testing proposals:

- Expert judgement on results from existing *in vitro* tests on mutagenicity/genetoxicity and on the possibility to conduct further *in vitro* testing first:

Based on an analysis of the available information, this third party recommended the Registrant to conduct an *in vitro* Mammalian Chromosome Aberration Test (OECD Guideline 473) first, for a weight of evidence assessment. The third party has proposed a strategy for the Registrant to consider before further tests on animals are requested. However, third parties were invited, as specified by Article 40(2) to submit "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal". The proposal for a strategy as such cannot be regarded information or studies. Furthermore, column 2 of Annex VIII, 8.4.3. states that appropriate *in vivo* mutagenicity studies shall be considered in the case of a positive resut in any of the mutagenicity studies in Annex VII or VIII. Given the positive results in the *in vitro* studies, ECHA concludes that this is not a sufficient basis for rejecting the testing proposal.

- Software tools for chemicals profiling and QSARs for genetoxicity prediction

The third party presents the results of QSARs for genetoxicity prediction. According to Annex XI, 1.3 of the REACH Regulation, the results of the QSARs may be used instead of testing when the following conditions are met: a) the results are derived from a QSAR model whose scientific validity has been established; b) the substance falls within the applicability domain of the QSAR model; c) results are adequate for the purposes of classification and labelling and/or risk assessment; and d) adequate and reliable documentation of the applied method is provided.

No adequate and reliable documentation of the applied method is included in the dossier. Therefore, ECHA concludes that from, the submitted QSAR information for genetoxicity does not meet the conditions for the QSAR adaptation set out in Annex XI, Section 1.3. Therefore, it cannot constitute an acceptable adaptation to the standard test in question. Finally, the results of the QSAR predictions provided indicate that substance's metabolites may present a genetoxicity hazard, and are in agreement with the results of the *in vitro* tests, which indicate the need for further investigation.

- Exposure and the TTC concept

The third party states that before conducting *in vivo* genetoxicity testing, the TTC concept shall be adopted as a benchmark to distinguish between relevant and non relevant exposure and external exposure should be compared to the cut-off values.

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) 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 for rejecting the testing proposal.

- Reduced information requirements for an intermediate used under strictly controlled conditions

The third party notes that for transported isolate intermediates, a reduced set of information requirements apply when the substance is used under strictly controlled conditions. Furthermore, he states that the registration dossier describes different exposure conditions during manufacture, including use in batch and other process (synthesis) where opportunity for exposure arises, and states that this should be evaluated in detail before proceeding to an *in vivo* test.

The third party has proposed a strategy for the Registrant to consider before further tests on animals are requested. However, third parties were invited, as specified by Article 40(2) 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 for rejecting the testing proposal. Furthermore, as the dossier describes conditions under which opportunity for exposure arises, this strengthens the need for performing further studies in order to investigate the genetoxicity of this substance.

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 your dossier was sufficient to confirm the identity of the substance for the purpose of assessing the testing proposal. You 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 the joint registrants of the same substance to agree with the tests 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 studies must be shared by the joint registrants concerned.

V. 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.

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