European Chemicals Agency

Decision number: TPE-D-0000001365-77-05/F Helsinki, 12 July 2011

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

For 1,5-BIS[1,2-BIS(ETHOXYCARBONYL)ETHYLAMINO]-2-METHYLPENTANE, 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 testing proposals set out in the registration dossier for **1,5-bis[1,2-bis(ethoxycarbonyl)ethylamino]-2-methylpentane, EC no. 433-260-2**, submitted by [redacted] (Registrant), latest submission number [redacted] for 10-100 tonnes per year.

The Registrant submitted the following testing proposals as part of the registration dossier to fulfil the information requirements set out in the REACH legislation:

- Reproductive toxicity: pre-natal developmental toxicity study (OECD Guideline 414); and
- Repeated dose toxicity: sub-chronic toxicity study (90 days) by the oral route (OECD Guideline 408)

The examination of the testing proposal was initiated on 11 June 2010.

ECHA held a public consultation for the testing proposals from 6 September 2010 until 20 October 2010. ECHA received the following comments (also see Section III) that address the hazard endpoints concerned:

- Comments referring to a qualitative or quantitative structure-activity relationship model ((Q)SAR) entitled "Non-linear classification ANN QSAR Model for Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test" that could be used to omit the proposed study;

- Comments suggesting the use of three *in vitro* studies: Embryonic Stem Cell Test (EST, Genschow et al. 2004)[1], Limb Bud Micromass Culture (Spielmann et al. 2004)[2], Whole Embryo Culture (WEC, Piersma et al. 2004)[3] before conducting the pre-natal developmental test; and
- Comments regarding the results of the available 28-day study and other toxicological characteristics of the substance, and suggesting the extrapolation of results from the 28-day study to longer exposure durations.

ECHA examined the testing proposals and the information received from third parties and drafted a decision in accordance with Article 40 of the REACH Regulation. On 7 December 2010, ECHA notified the Registrant of its draft decision and invited it to provide comments.

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

On 18 February 2011, ECHA notified the Member State Competent Authorities of its draft decision and invited them to provide proposals for amendment.

After receiving proposals for amendment from Member State Competent Authorities, ECHA forwarded the proposals for amendment to the Registrant on 23 March 2011 and decided not to amend its draft decision.

On 4 April 2011, the draft decision was referred to the Member State Committee.

On 8 April 2011, the Registrant provided comments on the proposed amendments. The Member State Committee took the comments of the Registrant into account.

After discussion in the Member State Committee meeting on 25-27 May 2011, the Member State Committee modified the draft decision and a unanimous agreement of the Member State Committee on the modified draft decision was reached on 27 May 2011.

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. Decision on the testing proposals

Pursuant to Article 40(3)(b) of the REACH Regulation, the Registrant shall carry out the following tests:

[1] Genschow, E., Spielmann, H., Scholz, G., Pohl, I., Seiler, A., Clemann, N., Bremer, S., Becker, K., 2004. Validation of the embryonic stem cell test in the international ECVAM validation study on three in vitro embryotoxicity tests. Altern. Lab. Anim. 32 (3), 209–244.

[2] Spielmann, H., Genschow, E., Brown, N.A., Piersma, A.H., Verhoef, A., Spanjersberg, M.Q., Huuskonen, H., Paillard, F., Seiler, A., 2004. Validation of the rat limb bud micromass test in the international ECVAM validation study on three in vitro embryotoxicity tests. Altern. Lab. Anim. 32 (3), 245–274.

[3] Piersma, A.H., Genschow, E., Verhoef, A., Spanjersberg, M.Q., Brown, N.A., Brady, M., Burns, A., Clemann, N., Seiler, A., Spielmann, H., 2004. Validation of the postimplantation rat whole-embryo culture test in the international ECVAM validation study on three in vitro embryotoxicity tests. Altern. Lab. Anim. 32 (3), 275–307.

a. Pre-natal developmental toxicity, on the rat by the oral route (OECD Guideline 414 or B31 EU); and
b. Sub-chronic toxicity study (90 days), on the rat, by the oral route (OECD Guideline 408 or B26 EU)

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by 14 January 2013 - 18 months from the date of the decision an update of the registration containing the information required by this decision.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposals of the Registrant for the registered substance and comments submitted by third parties during the public consultation.

a. Pre-natal developmental toxicity, on the rat by the oral route (OECD Guideline 414)

According to 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 proposed test is part of the standard information requirements for Annex IX, Section 8.7.2. 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 in the rat by the oral route, using OECD Guideline 414.

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

1. Comments regarding the use of (Q)SAR models:

A third party suggested the use of a qualitative or quantitative structure-activity relationship model ((Q)SAR) entitled "Non-linear classification ANN QSAR Model for Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test". The third party submitted information on the model in a QSAR Model Reporting Format (QMRF).

ECHA assessed the information provided and concludes that it is not sufficient to provide an acceptable adaptation to the standard testing requirement in the present case. ECHA indeed identified and evaluated several deficiencies related to the suggested (Q)SAR.

According to Annex XI, 1.3 of the REACH Regulation, the results of (Q)SARs may be used instead of testing when the following conditions are met: a) the results are derived from a (Q)SAR model whose scientific validity has been established; b) the substance falls within the applicability domain of the (Q)SAR model; c) results are adequate for the purpose of classification and labelling and/or risk assessment, and; d) adequate and reliable documentation of the applied method is provided. The relevance of the model is determined by the relevance of the predicted endpoint to meet a given information requirement, for which a testing proposal has been made.

The evaluation of the submitted information according to the conditions described above showed that:

- The dependent variable of the model is in the form "toxic/non-toxic". In the absence of additional information on the meaning of these terms, the predicted result could not be directly used or extrapolated to fill a data gap according to the information requirements of the REACH Regulation.
- Contrary to point b) above, based on the information provided in the QMRF, the possibility that the registered substance does not fall within the structural applicability domain of the model cannot be ruled out. Information is needed on how the query chemical falls within the applicability domain of the model.
- Contrary to point d) above, the level of detail in the documentation regarding the algorithm used in the model was not considered sufficient to transparently describe the model (and thus, to assess its certainty). Information is needed on how the descriptors were selected, on the algorithm and the method (approach) used to generate each of the descriptors, and on the algorithm as an output of formalised mathematical approach.
- According to the REACH Guidance (Chapter R.6: QSARs and grouping of chemicals), a QSAR Prediction Reporting Format (QPRF) needs to be filled for each prediction. Without a QPRF it is not possible to examine the adequacy of the prediction.

Therefore, ECHA concludes that on this occasion, the information submitted does not meet the conditions for the (Q)SAR adaptation set out in Annex XI, Section 1.3. Therefore, it cannot constitute an acceptable adaptation to the standard test in question.

2. Comments regarding the use of *in vitro* methods:

One comment received in the public consultation argues that *in vitro* methods should be considered before conducting animal tests. The following three methods were suggested:

- Embryonic Stem Cell Test (EST, Genschow et al. 2004)
- Limb Bud Micromass Culture (Spielmann et al. 2004)
- Whole Embryo Culture (WEC, Piersma et al. 2004)

According to Article 13(1) and Annex XI, 1.4 of the REACH Regulation, confirmation of negative results obtained using *in vitro* methods is required. However, such confirmation may be waived if: a) results are derived from an *in vitro* method whose scientific validity has been established by a validation study, according to internationally agreed validation principles, b) results are adequate for the purpose of classification and labelling and/or risk assessment, and c) adequate and reliable documentation of the applied method is provided.

The evaluation of the submitted information shows that:

- The three suggested tests have been declared to be scientifically validated according to ECVAM. This is also stated in the REACH Guidance, Chapter R.7a (R.7.6 Reproductive and developmental toxicity). However, the REACH Guidance R.7a (R.7.6 Reproductive and developmental toxicity) also states that

there are a number of weaknesses in the design of both the validation study and of the *in vitro* tests that have been identified, such as the limited number and range of substances tested, and absence of a biotransformation system, which have lead to the conclusion that the tests currently have limited value in a regulatory context. In line with point b) above, the REACH Guidance also states that while a positive result in an *in vitro* test could provide justification for further testing, such a result in isolation would not be adequate to support hazard classification.

- The comments do not provide information on the registered substance or a prediction of its properties, and cannot be deemed as providing adequate results for its classification and labelling and/or risk assessment, as required by point b) above. As such, they cannot be considered an adaptation of the standard information requirements according to Annex XI, 1.4.

Therefore, ECHA concludes that on this occasion, the information submitted does not meet the conditions for the adaptation on the basis of *in vitro* methods set out in Annex XI, Section 1.4. Therefore, it cannot constitute an acceptable adaptation to standard testing in question.

b. Sub-chronic toxicity study (90 days) (OECD Guideline 408)

According to 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 proposed test is part of the standard information requirements for Annex IX, Section 8.6.2. 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 in the rat by the oral route, using OECD Guideline 408.

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

1. Comments regarding the use of (Q)SAR models:

The same model as that suggested for the pre-natal developmental toxicity study above was suggested. In this instance, the same analysis and conclusions apply. Accordingly, the suggested (Q)SAR model cannot constitute an acceptable adaptation to the standard testing in question.

2. Comments regarding the results of the 28-day study and other toxicological characteristics of the substance:

One comment from third parties suggests that the findings of the available toxicity studies, including the 28-day study, can be extrapolated to longer exposure duration, and suggests the use of different assessment factors.

ECHA generally refers to Annex XI, 3.2 according to which, without prejudice to column 2 of section 8.6 of Annexes IX and X, a DNEL derived from a 28-day repeated dose toxicity study shall not be considered appropriate to omit a 90-day repeated dose toxicity study.

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 reads:

> *"Ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice provided for in Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or the Agency and with the provisions of Directive 86/609/EEC, if applicable."*

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.

National authorities monitoring good laboratory practice (GLP) maintain lists of test facilities indicating the relevant areas of expertise of each facility.

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.

Done at Helsinki,

[redacted]

Jukka Malm
Director of Regulatory Affairs