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European Chemicals Agency

For final decision: TPE-D-0000001472-80-04/F Helsinki, 02/09/2011

DECISION ON TESTING PROPOSAL PURSUANT TO ARTICLE 40(3) OF REGULATION (EC) NO 1907/2006

For 3-amino-4-octanol, EC No 482-070-6, 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-amino-4-octanol, EC No 482-070-6, Registration Number: [redacted] submitted by [redacted] (the "Registrant"), latest submission number [redacted], for 100 - 1000 tonnes per year.

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

- Viscosity (OECD Guideline 114)
- Pre-natal developmental toxicity (EU test method B.31)

The examination of testing proposal was initiated on 11 January 2011.

ECHA held a public consultation for the testing proposals involving tests on vertebrate animals from 19 November 2010 until 3 January 2011 and received information that addresses the endpoint of pre-natal developmental toxicity. Comment 1 included a reference to 90-day reproductive toxicity study, dermal toxicity, and results of the QSAR Toolbox. Comment 2 included a proposal to evaluate the existing reproduction/developmental toxicity screening study, to analyse exposure, and to use *in vitro* studies and QSAR modelling before testing. More information is provided in the section III, statement of reasons below.

On 21 March 2011 ECHA notified the Registrant of its draft decision and invited him pursuant to Article 50(1) of the REACH Regulation to provide comment on the draft decision.

On 6 April 2011 the Registrant provided to ECHA comments on the draft decision. The registrant expressed agreement to the content of the draft decision and asked for an extension of the deadline for submitting the updated dossier to 18 months.

ECHA reviewed the further information received and amended the draft decision accordingly.

On 17 June 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. By 18 July 2011 ECHA did not receive any proposals for amendments from the Competent Authorities of the Member States.

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 from initiating 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 tests:

- Viscosity (OECD test guideline 114 as a requirement of Annex IX, 7.17)
- Pre-natal developmental toxicity study (EU test method B.31 according to Commission Regulation (EC) No 440/2008 as a requirement of Annex IX, 8.7.2)

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA **by 2 March 2013 – 18 months from the date of decision** an update of the registration dossier 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 scientific information submitted by the third parties. The third party information received during the public consultation was evaluated 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 pre-natal developmental toxicity study needs to be requested, as explained below.

Comment 1: Based on the information described below, it was presented that the no observed effect level (NOEL) for systemic, reproductive and developmental toxicity would not be much higher than the experimentally found NOEL 150 mg/kg bw/day and therefore testing would not be necessary.

90-day reproductive toxicity study: The study the third party refers to is a reproduction/developmental toxicity screening study (OECD 421), which is already present in the dossier for the registered substance. It is neither an alternative to the developmental toxicity test proposed nor does it replace the information requirements for this test. Due to test design (e.g. small number of animals, selectivity of the endpoints, and different dosing regime) of the screening test, negative results do not provide sufficient level of certainty with respect to developmental toxicity. In addition, skeletal and soft tissue alterations are not examined in the screening test. Moreover, the study is requested under Annex VIII, 8.7.1. to the REACH Regulation, and it cannot be used to adapt the standard information requirement for developmental toxicity even though *vice versa* the screening test can be omitted pursuant to column 2 of Annex VIII, 8.7.1. if a pre-natal developmental toxicity study is available.

Dermal toxicity: The reference of the third party is incomplete as it refers only to dermal toxicity in animals at dose level of 170 mg, and to an oral LD50 of 550 mg/kg. No information on the symptoms of dermal toxicity data or any data on developmental toxicity was presented in this information. Thus, the information does not give any data on developmental toxicity of the registered substance.

Results of the OECD Toolbox: A third party suggested read-across for reproductive and developmental toxicity using the latest publicly available version of the QSAR Toolbox 2.0.4/1.0.0.

(Q)SAR Prediction Reporting Format (QPRFs) for reproductive toxicity, developmental toxicity and repeated dose toxicity (as produced by the QSAR Toolbox software) were provided but were not completed manually as necessary to justify adequate data gap filling. Such completion is necessary to provide justification for read-across.

In order to establish the scientific validity of the results derived from read-across from category members to the registered substance as required by Annex XI, 1.5. of the REACH Regulation, adequate information on the validity of the adaptation has to be provided. A group or category of substances can only be established for substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity. The similarity may be based inter alia on common functional groups, common precursors or a constant pattern in the changing of the potency of the properties across the category. For the assessment of validity of a category approach, a transparent description of the category hypothesis and category justification is required. Moreover, the applicability domain needs to be described comprehensively, including information not only on common functional groups but also on those that differ between the group members. Information on how structural fragments (functional groups) may alter the biological mechanism of action of the analogues should be provided especially if there is indication for multiple/different mechanisms for the analogues. Considerations on kinetic properties for the analogues should also be taken into account, if relevant. Additional justification should be provided if the analogues are markedly different from the target substance. Some similarity measure, if not driving the grouping, could be used to indicate the rate of similarity between the target substance and the proposed analogues. None of these scientifically necessary elements in establishing a category are addressed in the third party comment in

such a way that the category could be properly assessed and accepted. Therefore, the criteria for similarity as provided for in Annex XI, 1.5 of the REACH Regulation, are not considered sufficiently met in the third party proposal.

Moreover, the submitted third party data is not able to establish relevance regarding the endpoint in question, which is important to judge on the adequacy of the prediction made by application of Annex XI, 1.5. of the REACH Regulation. The relevance is given by the relationship between the predicted endpoint and the regulatory endpoint of interest. In cases where the predicted endpoint is not the endpoint of regulatory interest, the relevance of the former to the latter should be described as indicated in the REACH Guidance, Chapter R.6: QSARs and grouping of chemicals. However, the third party did not provide such description. The Annex XI, 1.5 requirement for adequate and reliable coverage of the key parameters that need to be addressed by the testing proposal for pre-natal developmental toxicity is not met and therefore, the estimates can not be considered suitable for the fulfilment of the information requirements for this endpoint.

Comment 2: Weight of evidence approach and testing preference comments to adapt the developmental toxicity endpoint was presented. In addition, before testing, the following was proposed to be taken into account: (i) evaluation of reproduction/ developmental toxicity screening study, (ii) *in vitro* testing, (iii) use of QSAR model for ANN classification of reproduction toxicity, and (iv) evaluation of exposure.

(i) Evaluation of existing reproduction/developmental toxicity screening study: the third party comment proposed that no testing is needed since firstly "no specific alerts for an impairment of fertility or prenatal developmental have been identified" in the 90-day and reproductive screening study, and secondly there is no evidence that results of the OECD 414 study with higher number of animals could modify the classification and risk assessment of the registered substance.

ECHA is of the opinion that the repeated dose toxicity study (90-day) does not address the developmental toxicity and therefore it cannot be used to adapt the standard information requirement for developmental toxicity. Regarding the reproduction/developmental toxicity screening study (OECD 421), the same justification as indicated under Comment 1 above applies.

Therefore, the results of the reproduction/developmental toxicity screening and 90-day studies cannot be used to adapt the standard information requirements for developmental toxicity.

(ii) The use of *in-vitro* testing methods which are validated or at the pre-validation stage: before conducting the developmental toxicity study, a third party proposed to conduct *in vitro* studies (Embryonic Stem Cell Test, Limb Bud Micromass Culture, and Whole Embryo Culture tests), and combine these results with the results of existing studies and QSAR prediction (weight of evidence approach).

According to Article 13(1) and Annex XI, 1.4 of the REACH Regulation, confirmation of negative results, i.e. not indicating certain dangerous properties, obtained using *in vitro* methods is required at the appropriate tonnage level.

However, such confirmation may be waived if the following conditions of Annex XI, 1.4 are met: 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 European Centre for the Validation of Alternative Methods (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 substance tested, and absence of a biotransformation system, which have lead to the conclusion that the tests currently have limited value in a regulatory context. Regarding the adequacy of the data for the purpose of classification and labelling and/or risk assessment (point b) above), it is stated 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. Hence, the comment does 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.

(iii) Proposed use of QSAR: the third party proposes to use the nonlinear QSAR based on artificial neural network (ANN) for classification or reproductive toxicity from MolCode. It is stated that the numerical descriptor values for the registered substance should be directly asked form MolCode Ltd. in order to assure that descriptor values fall within the range covered by the model.

The third party suggested the use of a qualitative or quantitative structure-activity relationship model ((Q)SAR) regarding the testing proposal for reproductive toxicity (developmental toxicity). The third party indicated that a model is under development and will be submitted in a QSAR Model Reporting Format (QMRF) to the JRC QSAR Model Inventory. However, it goes beyond ECHA's mandate regarding the examination of testing proposals, as described in Article 40 of the REACH Regulation, to impose on registrants to seek approval from a private legal entity doing business with QSAR to use its proprietary models in order to meet a data requirement. Therefore, it would be expected that the Registrant himself will take the necessary steps, if interested in the provided third party information.

Since the proposed model is under development, ECHA is not able to access it at this stage to examine the validity of the third party proposal for adapting the standard information requirements.

Exposure considerations: the third party states that since testing can be exempted based on the negligible exposure, exposure should be thoroughly analysed before conducting the test. In addition, the third party suggests that the Threshold of Toxicological Concern (TTC) concept should be adopted and cut-off values (human exposure threshold values below which there is no significant risk to human health) for oral (1.0 µg/kg bw/day) and inhalation (0.5 µg/kg bw/day) exposure should be used.

According to Annex XI, Section 3 of the REACH Regulation, the testing can be omitted if it can be demonstrated that there is no or no significant exposure. The Registrant did not use substance-tailored exposure-driven testing according to Annex XI, Section 3 but indicated that when working with the metal working fluid some inhalation and dermal exposure will occur. The exposure values are not considered to be non-significant.

Therefore, ECHA concludes that testing cannot be omitted based on negligible exposure.

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. Thus the Registrant shall refer to Commission Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2008 adapted to the technical progress by Commission Regulation (EC) No 761/2009 and use the applicable test methods to generate the information on the endpoints indicated above.

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,

Jukka Malm
Director of Regulatory Affairs