European Chemicals Agency

Decision number: TPE-D-0000001273-82-05/F Helsinki, 21 June 2011

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

For 11-AMINOUNDECANOIC ACID, CAS 2432-99-7 (EC Nr. 219-417-6), registration numbe[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 (the REACH Regulation).

I. Procedure

Pursuant to Article 40(1) of the REACH Regulation, ECHA has examined the testing proposal set out in the registration dossier for **11-aminoundecanoic acid**, CAS 2432-99-7 (EC Nr. 219-417-6), by [redacted] ("Registrant"), latest submission number [redacted] for the tonnage band of [redacted] per year.

In accordance with Article 12(1) (e) of the REACH Regulation, the Registrant submitted the following testing proposal as part of the registration dossier to fulfil information requirements:

- prenatal developmental toxicity (OECD 414 guideline) in a second species in order to fulfil the information requirement of section 8.7.2. of Annex X (prenatal developmental toxicity)

The examination of the testing proposal was initiated on 6 November 2009.

ECHA held a public consultation for the testing proposal from 8 April 2010 until 24 May 2010. ECHA received two comments.

ECHA examined the testing proposal and the information received from third parties and drafted a decision in accordance with Article 40(3) of the REACH Regulation.

On 5 January 2011 ECHA sent a draft decision to the Registrant and invited him to provide comments.

On 2 February 2011 ECHA received comments from the Registrant, agreeing to the ECHA's draft decision.

On 18 February 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 amendments to the draft decision.

On 23 March 2011 ECHA notified the Registrant of the proposals for amendments to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments within 30 days of the receipt of the notification.

ECHA reviewed the proposals for amendments received and decided to amend its draft decision accordingly.

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

On 21 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, a unanimous agreement of the Member State Committee on the draft decision as amended by ECHA was reached on 26 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. Testing required

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

- Prenatal developmental toxicity study in rabbits, oral route (method B.31 of Regulation (EC) No 440/2008; OECD test guideline 414)

Pursuant to Articles 40(4) and 22 of the REACH Regulation the Registrant shall submit to ECHA by 21 June 2012 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 scientific information submitted by the third parties.

Information requirement of section 8.7.2. of Annex X of the REACH Regulation

A pre-natal developmental toxicity study for a first species is required under Annex IX, 8.7.2. According to section 8.7.2 of Annex X of the REACH Regulation a second pre-natal developmental toxicity study conducted in a second species is required to fulfil the standard information requirements. Annex IX, 8.7.2. column 2 provides that the decision on the need to perform a study at a tonnage level of [redacted]

[redacted] per annum or more level should be based on the outcome of the first test and all other relevant available data.

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.

Information provided by third parties:

1. Results from a QSAR model "Nonlinear classification ANN QSAR Model for Combined 28-Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test" and QMRF.

2. Weight of evidence comments by one third party on testing proposal for a developmental toxicity study of 11-aminoundecanoic acid on rabbits as second species.

Comment 1 reports the predictions on developmental toxicity of the registered substance generated by a QSAR model and provides additional information on the model in a QSAR Model Reporting Format (QMRF).

QSAR results can be used instead of testing when the conditions set under Annex XI section 1.3 of the REACH Regulation are met. These conditions require that the scientific validity of the model used to derive the results is established, that the registered substance falls within the applicability domain of the model, that the results provided by the model are adequate for the purpose of classification and labelling and/or risk assessment and that the method applied is adequately and reliably documented.

ECHA has identified several shortcomings in the data set provided by the third party with regard to the fulfilment of the above-mentioned conditions. The level of detail of the documentation describing the algorithm used in the model is not considered sufficient to transparently describe the model and to assess its validity. Detailed information would have been 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. 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. The QSAR prediction is not reported in a QSAR Prediction Reporting Format (QPRF) and is presented in the form "toxic/non-toxic". In the absence of additional information on the meaning of these terms and of a QPRF, the results obtained from this model cannot be used for the purpose of classification and labelling and/or risk assessment. Furthermore, the model is established using the combined 28-day repeated dose study/ reproductive/developmental toxicity screening test as the reference endpoint. This study does not provide an adequate coverage of key parameters, such as examination for skeletal and soft tissues alterations, addressed in the pre-natal developmental toxicity study and is not considered sufficient to fulfil the information requirements for developmental toxicity laid down in Annex IX or the REACH Regulation. Besides, results from a reliable reproductive/developmental toxicity screening study and of a reliable prenatal developmental toxicity study conducted in rats with the registered substance have been submitted in the registration dossier.

Therefore, ECHA concludes that predictions obtained from this QSAR model do not constitute reliable additional information on the developmental toxicity of 11-aminoundecanoic acid.

Comment 2 consists in an argumentation recommending that consideration is given to a series of points before conducting further animal testing.

The first point raised by a third party relates to the outcome of the pre-natal developmental toxicity study conducted in the rat and submitted in the registration dossier. The third party notes that no embryotoxicity or foetotoxicity were observed in this study, with the exception of a slight retardation in growth/skeletal development observed in the mid and high dose groups. Besides, no effects on mating, fertility, gestation or delivery were observed in a screening test for reproductive/developmental toxicity conducted with the registered substance. Considering all this information, the third party concludes that it appears unlikely that the registered substance may present reproductive toxicity and underlines that a request for further pre-natal developmental toxicity test should be appropriately justified. ECHA considers that the pre-natal developmental toxicity study conducted in the rat and submitted in the registration dossier fulfils the information requirement of Annex IX, 8.7.2 of the REACH Regulation. Since the registration dossier was submitted for the tonnage band of [redacted] per year the information requirements specified in Annexes VII to X apply. According to section 8.7.2 of Annex X of the REACH Regulation a second pre-natal developmental toxicity study conducted in a second species, as proposed by the Registrant, is required to fulfil the standard information requirements.

Secondly, the third party makes reference to the conclusions on the developmental toxicity characteristics of an expert group that assessed the registered substance in the context of the OECD High Production Volume Chemical programme (OECD HPV). The experts evaluated the same data on reproductive and developmental toxicity as that included in the registration dossier and concluded that the registered substance is unlikely to present reproductive toxicity and that no additional study is necessary. ECHA has taken note of the conclusions of the assessment performed in the framework of the OECD HPV programme. However, the objectives of the REACH Regulation, which are to ensure the safe use of chemicals in the European Union through standardised information requirements, are significantly different from those of the OECD HPV programme, which focuses on the establishment of initial hazard assessments and on the expression of recommendations on the priority for further work agreed among the OECD member countries. Therefore the conclusions of the OECD HPV assessment cannot directly be extrapolated to dossier evaluation as conducted under the REACH Regulation.

The third party claims that based on Annex IX, 8.7. column 2 no further reproductive toxicity studies are needed since other data included in the registration dossier indicate that the registered substance has a low toxicological activity, is not genotoxic and is rapidly and almost completely metabolised and excreted. Annex IX and X, 8.7. column 2 indicate that reproductive toxicity studies do not need to be conducted if "*the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure*". ECHA notes that, in the repeated dose toxicity tests and in the screening test for reproductive/developmental toxicity included in the registration dossier, the

kidney has been identified as the target organ and other evidence of toxicity was observed. Therefore, the substance cannot be considered as of low toxicological activity as defined in Annex IX and X, 8.7 column 2. Furthermore, toxicokinetic studies performed in the rat have demonstrated that the substance is extensively absorbed after oral administration and that it is rapidly and largely excreted mainly via urine. ECHA concludes that, in the present case, the standard information requirements on reproductive toxicity specified in Annex IX and X, 8.7 cannot be adapted according to the rules for adaptations provided in Annex IX and X, 8.7, column 2, third indent.

In addition the selection of the rabbit as the second species for developmental toxicity is questioned by the third party. It outlines that information on the kinetics and systemic toxicity in the rabbit is lacking and makes reference to the outcome of a retrospective analysis of developmental toxicity studies conducted in the rat and in the rabbit indicating that both species were similarly sensitive. ECHA agrees with the statement of the third party that whether or not the rabbit is the most adequate second species to complement the data set obtained in the rat is an unresolved issue. However, there is evidence in the scientific literature (Janer et al., *Regulatory Toxicology and Pharmacology 50 (2008) 206-217*) indicating that pre-natal developmental toxicity tests conducted in the rabbit provide additional useful information in addition to that obtained from pre-natal developmental toxicity tests performed in rats. At the moment, considering the variability related to pre-natal developmental toxicity testing, it remains unwarranted to omit an additional developmental toxicity study in a second species when negative results have been obtained in a pre-natal developmental toxicity study performed in the rat in the absence of additional specific data or evidence constituting robust scientific justifications for not conducting the test in a second species.

Since the outcome of the *in vivo* tests did not provide definitive indications on developmental toxicity characteristics of the registered substance, the third party recommends using the *in vitro* methods validated by the European Centre for the Validation of Alternative Methods (ECVAM) and mentioned in the Guidance on information requirements and chemical safety assessment R.7, chapter R.7.6. Reproductive and developmental toxicity, to generate the necessary information to complement the existing *in vivo* data. ECHA notes that scientifically validated *in vitro* methods such as the embryonic stem cell text, the limb bud micromas culture and the whole embryo culture may provide additional information which can be assessed together with existing *in vivo* data in a weight of evidence approach. However, ECHA notes that the mentioned *in vitro* tests only cover some of the reproductive toxicity endpoints, modes of action and mechanisms covered by the *in vivo* pre-natal developmental toxicity tests and therefore cannot be used as stand alone replacement tests. Furthermore, these alternative methods are not part of the information requirements laid down in Annex VII to X of REACH and can therefore not be requested by ECHA in the context of a testing proposal examination. ECHA outlines that it is the Registrants responsibility to establish the weight of evidence justification demonstrating that the data set provided by the use of the proposed tests is sufficient to meet the information requirements when submitting and/or updating its registration dossier.

Pursuant to Article 40(3) (a) of the REACH Regulation, the Registrant is thus requested to carry out the following test: Pre-natal developmental toxicity study in rabbits, oral route (method B.31 of Regulation (EC) No 440/2008; OECD test guideline 414).

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 as adapted to the technical progress 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 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]

Director of Regulatory Affairs