ECHA
EUROPEAN CHEMICALS AGENCY

Decision number TPE-D-0000001597-66-05/F 17 January 2012

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

For [redacted], EC No [redacted], 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 [redacted], EC No [redacted], Registration Number: [redacted] submitted by [redacted], (the "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 X:

Pre-natal developmental toxicity (OECD 414 Guideline).

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

ECHA held a public consultation for the testing proposal involving test on vertebrate animals from 19 November 2010 until 3 January 2011 and received comments from third parties relating to the following items:
- Proposal to evaluate the existing reproductive/developmental toxicity screening study (OECD 421),
- *in vitro*-testing methods which are validated or at the pre-validation stage,
- QSAR model (Artificial Neural Network (ANN) classification model),
- proposal to analyse exposure.
More information is provided in section III.

On 13 July 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.

By 12 August 2011 the Registrant did not provide to ECHA any comments on the draft decision.

On 2 September 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

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proposals to amend the draft decision within 30 days. Subsequently, one Competent Authority of the Member States submitted a proposal for amendment to the draft decision. ECHA reviewed the proposal for amendment received and did not modify the draft decision.

On 5 October 2011 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 the proposal for amendment within 30 days of the receipt of the notification.

On 17 October 2011, the draft decision was referred to the Member State Committee.

On 18 October 2011 the Registrant provided comments on the proposal for 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 18 November 2011 in a written procedure launched on 7 November 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 test:

> Pre-natal developmental toxicity study in rat by oral administration (OECD Guideline 414 or EU test method B.31 according to Commission Regulation (EC) No 440/2008 as a requirement of Annex IX, 8.7.2).
>
> The Registrant shall consider the need for testing the substance in a second species (preferably rabbit) depending on the outcome of the test in rats and include a testing proposal or a justification, why testing is not needed in the updated dossier.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **17/01/2013** 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 proposal of the Registrant for the registered substance and scientific information submitted by the third parties.

Pre-natal developmental toxicity (8.7.2) studies are part of the information requirements as laid down in Annexes IX and X of the REACH Regulation. As the information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements, it follows that there is an information gap and that it is necessary to generate the data for this endpoint.

ECHA received third party information concerning the testing proposal during the public consultation that does not lead to a different conclusion. The third party proposed that

before further animal testing is carried out to meet the information requirements consideration should be given to the following points that would remove the need to conduct vertebrate testing:

OECD 421 reproductive toxicity screening study
The study the third party refers to is a reproductive/developmental toxicity screening study, which is already present in the dossier. It is not an alternative to, and it does not replace, the developmental toxicity test (OECD 414). Due to test design (e.g. small no of animals, selectivity of the endpoints, and different dosing regime) of the screening test, negative data do not indicate sufficient safety with respect to developmental toxicity. In addition, skeletal and soft tissue alterations are not examined in the screening test. Moreover, the study is a requirement under Annex VIII, 8.7.1., and it cannot be used to adapt the standard information requirement for developmental toxicity.

Use of in vitro testing methods which are validated or at the pre-validation stage and Artificial Neural Network (ANN) classification model for reproductive toxicity
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 cannot be regarded as such information or studies, ECHA concludes that this is not a sufficient basis for rejecting the Testing Proposal.

Additionally, ECHA notes the following:

For *in vitro* tests (Embryonic Stem Cell Test, the Limb Bud Micromass culture and the Whole Embryo Culture), the Guidance on information requirements and chemical safety assessment R.7, chapter R.7.6, states that these tests have limited value in a regulatory context. Considering the possibility of establishing a weight of evidence approach on the basis of such tests and existing *in vivo* data, which could fulfil the information requirements of REACH, is the registrant's responsibility and cannot be requested by ECHA.

For QSAR, the third party suggested estimating reproductive and developmental toxicity using nonlinear QSAR based on "ANN Classification Model for Reproductive Toxicity" from MolCode Ltd. The third party states that the model is under revision and a Quality Model Reporting Format is planned to be submitted by MolCode Ltd to Joint Research Centre for approval at a later stage. No QSAR Prediction Reporting Format was provided for developmental toxicity in the registration dossier or by a third party. Therefore, the conditions of Annex XI section 1.3 have not been fulfilled.

ECHA concludes that on this occasion, the information submitted by the third party does not meet the conditions for the adaptation on the basis of *in vitro* or QSAR methods set out in Annex XI, sections 1.3 and 1.4. Therefore, it cannot constitute an acceptable adaptation to standard information requirements.

Exposure considerations
The third party refers to REACH Annexes VIII-XI stating that testing can be omitted based on the negligible exposure, and that therefore 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

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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, the testing can be omitted if it can be demonstrated that there is an absence of or no significant exposure in all exposure scenarios. The Registrant did not use exposure-based adaptations according to Annex XI, section 3 but indicated in its exposure assessment that oral, dermal or inhalation exposure may occur to the general population and worker.

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

IV. Avoidance of unnecessary testing by data and cost sharing

The Registrant is hereby designated already now to perform the above mentioned tests in accordance with Article 53(1) of the REACH Regulation in case the same substance is registered by further registrant(s) at a later stage and subject to evaluation. This is to avoid unnecessary testing and the duplication of tests as a general aim of the REACH Regulation (Article 25). The legal text foresees the sharing of information between registrants.

In case an evaluation decision for another registration of the same substance will request the same elements of information requested from the Registrant of this decision, ECHA will inform the subsequent registrant of this decision. The costs of the test shall be shared equally and the Registrant shall provide each of the other registrant(s) concerned with a copy of the full study report. This is stipulated by Article 53(2) and (3) of the REACH Regulation.

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.

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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.

Done at Helsinki,

[redacted]

Jukka Malm
Director of Regulatory Affairs