European Chemicals Agency

Decision number: TPE-D-0000001417-76-06/F Helsinki, 24/10/2011

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

For [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 testing proposals set out in the registration dossier for [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)(d) 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:

Annex IX, 8.6.2: Sub-chronic toxicity study (90 days) in rats by the oral route;

Annex IX, 8.7.2: Pre-natal developmental toxicity study in rats by the oral route.

The examination of testing proposal was initiated on 22 September 2010.

ECHA opened a third party consultation for testing proposals including testing on vertebrate animals that was held from 13 December 2010 until 27 January 2011 and received some comments (see Section III below).

ECHA examined the testing proposals and the information received from third parties and drafted a decision in accordance with Article 40 of REACH. 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 comments within 30 days of the receipt of the draft decision.

By 20 April 2011 the Registrant did not provide any comments on the draft decision to ECHA.

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. Subsequently, Competent Authorities of the Member States submitted proposals for amendments to the draft decision.

On 20 July 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.

ECHA reviewed the proposals for amendment received and did not modify the draft decision.

On 25 July 2011 the Registrant provided comments on the proposals for amendment.

On 1 August 2011, the draft decision was referred to the Member State Committee.

The Member State Committee took the comments of the Registrant into account.

After discussion in the Member State Committee meeting on 20-23 September 2011, a unanimous agreement of the Member State Committee on the draft decision was reached on 21 September 2011.

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 tests using the indicated test method while taking full account of the obligation to agree on sharing of information and costs with other registrants:

- Sub-chronic toxicity study (90 day) (Annex IX, 8.6.2. EU Method B.26) in rats by the oral route;
- Pre-natal developmental toxicity study (Annex IX, 8.7.2, EU Method B.31) in rats by the oral route.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by 24 April 2013 - 18 months from the date of this 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 proposal of the Registrant for the registered substance and scientific information submitted by third parties.

According to Articles 10(a)(vii), 12(1)(d) and Annex IX of the REACH Regulation, the sub-chronic toxicity (90-day) and the pre-natal developmental study must be included in the technical dossier as part of the standard information requirements for substances manufactured or imported in quantities of 100 tonnes or more. However, test results are not available yet and therefore the tests need to be performed. The information submitted by third parties during the public consultation (comments 1 to 5) are not capable to omit the necessity to fulfil the information requirements by performing test due to the following reasons:

Comment 1: A proposal to evaluate available human data on systemic toxicity from repeated exposure (IUCLID dossier) before a sub-chronic toxicity study is conducted.

Evaluation of available human data: The third party concluded that human data are available in the IUCLID dossier which fulfil the criteria for assessing data adequacy according to Annex XI, 1.1.3, and should be taken into consideration for risk assessment and classification purposes as well as in an integrated approach to derive DNELs.

ECHA also evaluated the "Occupational medical statement" reported in the IUCLID dossier. First, the information provided in the IUCLID dossier does not meet the criteria of a robust study summary according to Article 3(28) since it does not give a detailed summary of the objectives, methods, results and conclusions to make an independent assessment. Second, due to this insufficient information, no judgement can be made if the criteria specified in Annex XI, 1.1.3 of the REACH Regulation are met:
(1) proper selection and characterisation of exposed and control groups;
(2) adequate characterisation of exposure;
(3) sufficient length of follow-up for disease occurrence
(4) valid method for observing an effect;
(5) proper consideration of bias and confounding factors; and
(6) a reasonable statistical reliability to justify the conclusion.

In conclusion, the "Occupational medical statement" reported in the IUCLID dossier does not meet the criteria to be considered for the purposes of risk assessment and classification.

Comment 2: A proposal to reconsider the "no observed adverse effect level" (NOAEL) of the 28-day study, to apply an assessment factor to extrapolate the 28-day NOAEL to derive a 90-day NOAEL, and to take into account low toxicity of the substance.

Reconsider the NOAEL of the 28-day study: The third party indicates that in the 28-day short-term repeated dose toxicity study deviations of hematological and clinical-biochemical parameters and organ weights in the range of historical values were reported at the high dose. The third party therefore proposes that the full study report should be supplied by the registrant and the raw data evaluated if the NOAEL is 1000 or 300 mg/kg bw/day.

Registrants are not obliged to provide full study reports. According to Article 10(a)(vii) of the REACH Regulation only robust study summaries have to be included in a technical dossier. Furthermore, re-evaluation of the NOAEL and the DNEL can only be requested by ECHA following a compliance check of the registration (Article 41).

Apply assessment factors to extrapolate to the 90-day NOAEL: The third party proposes to use an assessment factor of 3 to extrapolate the 28-day NOAEL to derive a 90-day NOAEL.
As there is neither a specific rule for adaptation of the information requirement for a 90-day study under column 2 of Annex 8.6.2 for a substance showing no severe toxic effects nor a general rule under Annex XI of the REACH Regulation, the third party proposal does not allow to omit the proposed test.

Low toxicity of the substance: The third party indicates that no additional effect would be expected with a 90-day study since the substance is not expected to bioaccumulate, is not acute toxic, not skin irritating or sensitizing, not genotoxic and not toxic to fish, daphnia, algae and is readily biodegradable.
According to Annex IX, 8.6.2, Column 2 of the REACH Regulation, the study needs not to be conducted if the substance is unreactive, insoluble and not inhalable and there is no evidence of absorption and no evidence of toxicity in a 28-day "limit test", particularly if such a pattern is coupled with limited human exposure. First, the Registrant has not proposed to adapt the information requirement on this basis. Second, there is no information in the IUCLID dossier which indicates that the substance is not absorbed. Third, the Registrant did not provide data on human exposure.

The argumentation provided by the third party does not allow an adaptation of the information requirement for a 90-day sub-chronic toxicity study using the specific rules under column 2 of Annex IX, 8.6.2.

Comment 3: A proposal to thoroughly analyze exposure during the manufacturing process(es) and downstream users and to consider the application of the TTC concept.

Exposure assessment and TTC: The third party mentioned that the substance is used only in industrial processes and not by consumers or professional workers and that exemption from conducting individual toxicity tests is possible when exposure is negligible. In order to evaluate if exposure is negligible, exposure during the manufacturing process(es) and downstream users should be thoroughly analysed. Furthermore, the Threshold of Toxicological Concern (TTC) concept should be adopted to distinguish between relevant and non relevant exposure regarding a possible risk for repeated dose and reproductive toxicity.
However, the Registrant has not proposed to adapt the information requirement on the basis of Annex XI, Section 3 of the REACH Regulation. Furthermore, the Registrant did not perform an exposure assessment. Therefore, it can not be assessed if exposure is negligible.

The argumentation provided by the third party does not allow an adaptation of the information requirement for a 90-day sub-chronic toxicity study or for a pre-natal developmental toxicity study using the specific rules under column 2 of Annex 8.6.2 or column 2 of Annex 8.7.2 of the REACH Regulation.

Comment 4: A proposal to evaluate toxicological activity, systemic absorption data from occupational exposure and human exposure before a developmental toxicity study is conducted.

Third party indicates that according to Annex IX, 8.7.3, Column 2, a developmental toxicity study may be omitted if "the substance is of low toxicological activity (...), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (...), and there is no or no significant human exposure."
First, the Registrant has not proposed to adapt the information requirement on this basis. Second, there is no information in the IUCLID dossier indicating that the substance is not absorbed. Third, the Registrant did not provide data on human exposure.

The argumentation provided by the third party does not allow an adaptation of the information requirement for a developmental toxicity study using the specific rules under column 2 of Annex IX, 8.7.2

Comment 5: A proposal to perform an *in vitro* validated test for the evaluation of the embryotoxic potential instead of a developmental toxicity study.

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 Proposals.
Additionally, ECHA notes the following. For *in vitro* tests (embryonic stem cell test, the limb bud micromas 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, it is the registrant's responsibility and cannot be requested by ECHA.

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 information requirements.

In conclusion, the argumentation provided by the third party does not allow an adaptation of the information requirement for a 90-day sub-chronic toxicity study or for a pre-natal developmental toxicity study that are proposed by the registrant and are not available in the technical dossier yet.

Therefore, the Registrant shall carry out the sub-chronic toxicity study (90 days) (Annex IX, 8.6.2) and the pre-natal developmental toxicity study (Annex IX, 8.7.2) pursuant to Article 40(3)(a) of the REACH Regulation.

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."*

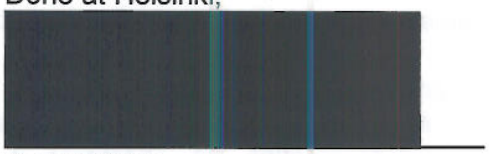
According to Article 13(3) of the REACH Regulation, tests that are required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the 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,



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