Decision number: TPE-D-0000001949-59-05/F

Helsinki, 28 June 2012

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

For 1-ethylpyrrolidin-2-one, CAS No 2687-91-4 (EC No 220-250-6), 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 testing proposals set out in the registration dossier for 1-ethylpyrrolidin-2-one, CAS No 2687-91-4 (EC No 220-250-6), submitted by [redacted] (Registrant), latest submission number [redacted]

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 X:

Annex IX, 8.6.2: Sub-chronic toxicity study by inhalation (90-day) (OECD Guideline 413);

Annex X, 8.7.3: Two-generation reproductive toxicity study (OECD Guideline 416).

The present decision relates solely to the examination of the testing proposal for a Sub-chronic toxicity study by inhalation (90-day). The testing proposal for the Two-generation reproductive toxicity study is addressed in a separate decision although all testing proposals were initially addressed together in the same draft decision.

The examination of the testing proposals was initiated on 3 September 2010.

ECHA opened a third party consultation for the testing proposals including testing on vertebrate animals that was held from 26 January 2011 until 14 March 2011. ECHA received the following comments from third parties:

- [redacted] comments on the use of data on Repeated Dose 90-Day Oral Toxicity in Rodents (OECD 408) before the sub-chronic toxicity study via the inhalatory route (OECD Guideline 413) is performed;

On 21 November 2011 ECHA notified the Registrant of its draft decision and invited it pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

On 21 December 2011 the Registrant provided to ECHA comments agreeing to the draft decision.

On 20 January 2012 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 of the receipt of the notification. Subsequently, Competent Authorities of the Member States submitted proposals for amendment to the draft decision.

On 23 February 2012 ECHA notified the Registrant of proposals for amendment to the draft decision and invited it 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 decided to amend the draft decision accordingly.

On 5 March 2012 ECHA referred the draft decision to the Member State Committee.

On 23 March 2012 the Registrant provided comments on the proposals for amendment. The Member State Committee took the comments of the Registrant into account.

The draft decision was split into two draft decision documents: one relating to the testing proposal for a two-generation reproductive toxicity study and one relating to the testing proposal for a sub-chronic toxicity study.

The Member State Committee reached unanimous agreement on the draft decision relating to the testing proposal for a sub-chronic toxicity study in a written procedure launched on 28 March and closed on 11 April 2012.

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 study in accordance with the indicated test method:

- Sub-chronic toxicity study by inhalation (90-day) (Annex IX, 8.6.2, EU Method B 29 or OECD Guideline 413) in rat by the inhalation route. The study protocol shall be modified with additional urinalysis to characterise kidney toxicity, and additional kidney pathology to evaluate whether there is an alpha-2u mode of action; specifically as provided for in OECD 413, paragraphs 38 and the summary. Additionally, the study protocol shall be modified with additional sperm analysis to characterise toxicity seen in target organs, i.e. on the testis and on spermatogenesis; specifically as provided for in OECD 413, the summary, and paragraphs 42 and 45.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **2 January 2014** an update of the registration dossier containing the information required by this decision.

At any time, the Registrant shall take into account that there may be an obligation to make every effort to agree on sharing of information and costs with other registrants.

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.

Sub-chronic toxicity study by inhalation (90-day)

a) Examination of the testing proposal

The Registrant has submitted a testing proposal for repeated dose toxicity by inhalation route (OECD 413 guideline) to meet the information requirement of Section 8.6.2 of Annex IX of the REACH Regulation.

The wide dispersive consumer and worker exposure via inhalation, combined with the uncertainties in route-to-route extrapolation and the possibility of seeing enhanced potency of toxicity through the inhalation route, gives rise to concern for human health. In addition, according to the results of the Registrant's range-finding inhalation study, the inhalation route may be a sensitive route of exposure, with a local effect (nasal irritation) at 389 mg/m^3. Therefore, it is necessary to do the inhalation study to characterise the toxicity of the registered substance by the inhalatory route after a prolonged exposure period.

Uncertainty arises from the paucity of the description of the kidney pathology in the repeated dose toxicity study (90-days) via the oral route, and whether it does in fact arise from an alpha-2u effect. ECHA considers that this toxicity is an indication of an effect for which the available evidence is inadequate for toxicological and/or risk characterisation, and that consequently, as per the column 2 provision of Annex IX, 8.6.2, ECHA may require further studies. The Registrant should therefore address this concern in the OECD 413 study design. As per paragraph 38 of OECD 413, the Registrant is requested to perform urinalysis to characterise kidney toxicity, and as per the summary of OECD 413, the Registrant is requested to characterise kidney lesions in rat, in order to determine if there are elevated levels of alpha-2u globulin and whether this is causing pathogenesis in the kidney. The OECD 413 study should be performed before the two-generation study.

There is evidence that spermatogenesis is affected, with effects seen on sperm (in the 90-day oral study) and on testis (inhalation range-finding study). ECHA considers that this toxicity is an indication of an effect for which the available evidence is inadequate for toxicological and/or risk characterisation, and that consequently, as per the column 2 provision of Annex IX, 8.6.2, ECHA may require further studies. In order to characterise effects on the relevant target organs, the Registrant is requested to modify the study protocol with additional sperm analysis (as described in OECD 416, paragraphs 29-32 or in OECD 443, paragraphs 56-59) to characterise toxicity seen in target organs, i.e. on the testis and on spermatogenesis; specifically as provided for in OECD 413, the summary, and paragraphs 42 and 45.

b) Consideration of the information received during third party consultation

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 submitted in the context of the third party consultation suggests considering the following:

1. Use of data on Repeated Dose 90-Day Oral Toxicity in Rodents (OECD 408) before the sub-chronic toxicity study via the inhalatory route (OECD Guideline 413) is performed;

ECHA has examined the scientific information submitted in the context of the third party consultation as follows:

1. The third party proposes to use the available oral NOAEL for the chemical to derive a 90 days inhalation NOAEL.

ECHA understands that the third-party argues implicitly that when one test has been performed that meets the information requirements for an endpoint (repeated-dose toxicity in this case), then no further tests are necessary. However, Article 12(1) states, "The technical dossier referred to in Article 10(a) shall include under points (vi) and (vii) of that provision all physicochemical, toxicological and ecotoxicological information that is relevant and available to the registrant and as a minimum the following:", followed by the listing of information requirements per tonnage band. Thus, the information requirements of the Annexes are a minimum level of information to be provided, not a maximum level. ECHA notes that the ECHA Guidance R8 makes clear that there is considerable uncertainty associated with route-to-route extrapolation. In conjunction with widespread worker and consumer exposure arising from the intended use of the substances, the possibility of seeing enhanced potency of toxicity through the inhalation route gives rise to concern for human health. Therefore, ECHA concludes that the third party proposal does not provide a sufficient basis for rejecting the proposed test.

Based on the above, ECHA is of the opinion that the third party comments do not provide a sufficient basis for rejecting the testing proposal.

c) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: Sub-chronic toxicity study (90-day) in rats, inhalation route (test method: EU B.29/OECD 413) using the registered substance.

IV. Deadline for submitting the information

In the draft decision communicated to the Registrant the time indicated to provide the requested information was 30 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested a 2-generation reproductive toxicity study. As the testing proposal for this study is not addressed in the present draft decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated IUCLID5 dossier is 18 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

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.

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.

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