EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-2114296566-33-01/F Helsinki, 9 March 2015

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

For Pyridine, alkyl derivs., CAS RN 68391-11-7 (EC No 269-929-9), 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 the following testing proposal submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(d) thereof for Pyridine, alkyl derivs., CAS RN 68391-11-7 (EC No 269-929-9), submitted by [redacted] (Registrant):

> Developmental toxicity / teratogenicity study (OECD 414) on the analogue substance 5-ethyl-2-methylpyridine (MEP) via oral route.

This decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band [redacted]. This decision does not take into account any updates after 15 January 2015, the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) of the REACH Regulation.

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 registration at a later stage.

ECHA received the registration dossier containing the above-mentioned testing proposal for further examination pursuant to Article 40(1) on 17 April 2013.

ECHA held a third party consultation for the testing proposal from 4 April 2014 until 19 May 2014. ECHA did not receive information from third parties.

On 30 June 2014 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision. That draft decision was based on submission number [redacted].

On 31 July 2014 ECHA received comments from the Registrant on the draft decision.

On 27 August 2014 the Registrant updated his registration dossier (submission number [redacted]).

The ECHA Secretariat considered the Registrant's comments and update. The information is reflected in the Statement of Reasons (Section III) whereas no amendments to the Information Required (Section II) were made.

On 15 January 2015 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 for amendment of the draft decision within 30 days of the receipt of the notification.

As no proposal for amendment was submitted, ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

II. Testing required

A. Tests required pursuant to Article 40(3)

The Registrant shall carry out the following proposed test pursuant to Article 40(3)(c) and 13(4) of the REACH Regulation using the indicated test method and the registered substance subject to the present decision Pyridine, alkyl derivs.:

> Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31/OECD 414) in rats or rabbits, oral route,

while the originally proposed test for a Developmental toxicity / teratogenicity study (OECD 414) proposed to be carried out using the analogue substance 5-ethyl-2-methylpyridine is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

Note for consideration by the Registrant:

The Registrant may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring to and conforming with the appropriate rules in the respective Annex, and an adequate and reliable documentation.

Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, shall result in a notification to the Enforcement Authorities of the Member States.

B. Deadline for submitting the required information

Pursuant to Articles 40(4) and 22(2) of the REACH Regulation, the Registrant shall submit to ECHA by **16 March 2016** an update of the registration dossier containing the information required by this decision, including, where relevant, an update of the Chemical Safety Report.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposal submitted by the Registrant for the registered substance.

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

With respect to the testing proposals subject to the present decision, the Registrant has used a read-across and grouping approach based on Annex XI, Section 1.5. of the REACH Regulation and proposed to perform the tests on the analogue substance 5-ethyl-2-methylpyridine (CAS No. 104-90-5). To the extent that the proposed testing relies upon a read-across hypothesis ECHA has considered the documentation and the scientific validity of the proposed read-across and grouping approach (Section 0, below), before assessing the testing proposed (Sections 1, below).

ECHA notes that the present decision concerns the one-to-one read-across proposal from 5-ethyl-2-methylpyridine (CAS No. 104-90-5, source substance) to Pyridine, alkyl derivs. (target substance), the substance subject to the present decision, as submitted in the registration dossier for Pyridine, alkyl derivs. for the prenatal developmental toxicity endpoint. ECHA did not evaluate the read-across used in any other endpoint for compliance with the REACH information requirements. Such evaluation may be carried out in a compliance check under Article 41 of the REACH Regulation at a later stage.

0. Grouping of substances and read-across approach

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "*provided that the conditions set out in Annex XI are met*". As far as the testing proposals addressed in this decision are concerned, the Registrant has described an analogue approach of a related substance and proposes to use information from this substance to predict the prenatal developmental toxicity for the registered substance using read-across.

ECHA considers that the analogue approach and the read-across proposed by the Registrant, does not convincingly show how the relevant properties of the registered substance can be predicted from the information on properties of the analogue substance. More specifically, Annex XI, Section 1.5. of the REACH Regulation sets out the conditions to be met by grouping and read-across so that information requirements will be considered met. At present, the read across proposed by the Registrant does not fulfil those conditions, both in relation to the documentation provided (see section 0.1) and the scientific rationale of the read-across approach (see section 0.2).

0.1 Documentation of the read-across approach

It is a requirement of Annex XI, Section 1.5., that "*adequate and reliable documentation of the applied method shall be provided.*"

An updated read-across justification was provided on 27 August 2014 (submission [redacted]). ECHA has reviewed and considered the updated read-across information provided by the Registrant.

The Registrant has provided more detailed information on (i) the read-across hypothesis and justification, (ii) the substance identity and structural similarities of both the source (MEP) and the target (registered) substances, (iii) the physico-chemical properties, (iv) the fate and ecotoxicity data, (v) the toxicokinetics assessment, (vi) the comparison of data from human health endpoints and (vii) the classification and labelling. The Registrant has in addition stated that "*the read-across from MEP to [registered substance] can be considered a worst-case approach*".

As further specified below, ECHA considers that the information provided under points (i), (v) and (vi) fails to meet the requirement of Annex XI, Section 1.5. for adequate and reliable documentation of the applied method. Indeed, regarding point (i), the Registrant states that "*the available data on the UVCB substance and selected model constituents reveals similar properties*" and that "*the read-across between the UVCB substance and the model constituent is justified*". However, the Registrant has not provided adequate and reliable documentation of the read-across approach, the justification rationale in the registration dossier and its approval by different regulatory authorities (eg. Environment Canada, 2011). Consequently, this condition for an acceptable adaptation argument of Annex XI, 1.5. has not been met.

Regarding point (v), information is provided on piperidine and pyridine, which are neither the registered substance nor the read-across substance. The Registrant does not provide a justification for why it is possible to read-across from these compounds to the registered substance. This information fails as well to meet the requirement of Annex XI, Section 1.5. for adequate and reliable documentation of the applied method.

Regarding point (vi), there is no justification as to why it is possible to read-across from methyl Pyridines to the registered substance or MEP. To the extent that this information is provided as information about constituents of the registered substance, there is no reasoning provided as to why it supports the proposed read-across, and hence this information fails to meet the requirement of Annex XI, Section 1.5 for adequate and reliable documentation.

0.2 Scientific assessment of the analogue approach

Section 1.5. of Annex XI states: *Substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or 'category' of substances.*

ECHA notes that in the current case, the Registrant did not use a group approach but a one-to-one analogue approach. ECHA also notes that the proposed analogue substance to be tested is in fact a component of the registered substance, representing merely [redacted]% of the total substance composition.

The Registrant states in general that the read-across is justified from MEP to the registered substance subject to the present decision and that the source and target substances have similar properties. This is based on the following arguments:

(i) the read-across hypothesis and justification; the Registrant advances that the *"presented read-across approach was previously used"* by other regulatory programs (US EPA HPV and screening assessment by Canadian EPA).
(ii) The substance identity and structural similarities of both the source (MEP) and the target (registered) substances. Additionally, the Registrant states that "*the side chains of the various constituents are chemically simple structures which have no structural alerts for toxicity*".
(iii) Similar physico-chemical properties.
(iv) Similar environmental fate and ecotoxicity data.
(v) A toxicokinetics assessment of pyridine, piperidine, the source and target substance which is said to be similar.
(vi) Similar local and systemic toxicity profiles for both target and source substance, as well as for the additional Pyridine, alkyl constituents.
(vii) The Classification and Labelling of both substances is similar.

(viii) The Registrant stated that *"the read-across from MEP to [registered substance] can be considered a worst-case approach"*.

ECHA has considered these arguments in light of the requirements of Annex XI, Section 1.5. of the REACH Regulation. ECHA considers that the prediction is that *"source and target substance have similar properties"* and concludes for the arguments listed above as follows:

(i) The fact that a read-across approach has been accepted by a different regulatory authority does not in itself meet the requirements of Annex XI, Section 1.5 as other regulatory authorities may have different requirements and objectives.
(ii) ECHA considers that the information provided on structural similarity and substance identity is not sufficient to demonstrate that the two substances will exert similar toxicity and does not provide an adequate basis for predicting their toxicological properties. ECHA considers that the chemical simplicity of the side-chains, and the lack of structural alerts in the side-chains, does not provide an adequate basis for predicting their toxicological properties in the context of a molecule.
(iii) ECHA considers that similar physicochemical properties is not an adequate basis to predict the (eco)toxicological properties of a substance.
(iv) ECHA considers that there is not an explanation why similar environmental fate and ecotoxicity data allow for the prediction of the human health endpoint(s), and ECHA considers that similar environmental fate and ecotoxicity data is not an adequate basis to predict the toxicological properties of a substance.
(v) ECHA considers that the conclusion of similar metabolism between MEP and the registered substance is speculative. The conclusions on the toxicokinetic behaviour of MEP and the Registered substance is not based on substance-specific *in vivo* toxicokinetic information and cannot be considered sufficient to show similar toxicokinetic properties. Toxicokinetics data on both the source and target substances could allow to demonstrate that their metabolism are similar and lead e.g. to similar degradation products. ECHA considers that the information provided is insufficient to characterise the specific toxicokinetics of the source or target substance, and cannot be used to support a claim of similar toxicokinetic and hence toxicological properties. Consequently the information provided does not provide an adequate basis for predicting their toxicological properties. Further ECHA considers that similar toxicokinetic properties *per se* are not a sufficient basis to predict the toxicological properties of a substance.
(vi) Information is provided on Pyridine alkyl derivative constituents (methyl pyridines). The Registrant has provided existing toxicological data for the source and target substances as a basis to show that the substances are similar. ECHA considers that the limited amount of human health data on both substances, and the absence of repeated-dose or reproductive toxicity data on the registered substance, precludes that the comparison of toxicological properties by itself provides any reliable prediction that the two substances have similar toxicological properties for repeated-dose or reproductive/ developmental toxicity.
(vii) ECHA notes that the classification and labelling of the two substances are different for skin irritation/ corrosion, sensitisation and chronic aquatic toxicity. ECHA considers that the classification and labelling of the substances does not provide a basis for predicting the outcome of toxicological tests on repeated dose toxicity or reproductive/ developmental toxicity.

The registrant claims that *"MEP was shown to be slightly more hazardous than the target substance"*. However, ECHA considers that there is insufficient toxicological information to demonstrate this in repeated-dose or reproductive/ developmental toxicity studies. Accordingly, ECHA considers that there is an insufficient basis to predict that MEP is a worst-case approach.

The predictive power of MEP as far as the pre-natal developmental endpoint is concerned is therefore considered speculative. The Registrant has not demonstrated that the other constituents of this UVCB substance do not contribute to toxicological effects and so prediction of pre-natal developmental toxicity effects by a one to one analogue approach is not possible with the read-across method currently applied. ECHA considers that similarity of effects for other endpoints between "representative model structures" and the registered UVCB substance does not prove an absence of effects exerted by other constituents for the relevant endpoint. Furthermore, none of the arguments presented above has provided by itself a sufficient basis whereby the human health effects may be predicted from data for reference substance(s). The adaptation presented fails to meet the requirements of Annex XI, Section 1.5. and cannot be accepted

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

A pre-natal developmental toxicity study for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. 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. Consequently there is an information gap and it is necessary to provide information for this endpoint.

The Registrant has submitted a testing proposal for a pre-natal developmental toxicity study in rats according to EU B.31/OECD 414 with the following justification "*According to REACH Annex IX section 8.7.2 a pre-natal developmental toxicity study is proposed according to EU Method B.31 and OECD 414 (Prenatal Developmental Toxicity). The study is to be carried out in the rat as the preferred rodent species. The test substance is to be administered orally by intubation. The study is to be carried out with 5-ethyl-2-methylpyridine (MEP).*"

ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation. However ECHA requests that testing is performed on the registered substance Pyridine, alkyl derivs.

As elaborated above in section III. 0 the proposed read-across does not meet the requirements of Annex XI, Section 1.5., and is therefore rejected together with the respective testing proposal as non-compliant with the REACH Regulation (Article 40(3)(d) of the REACH Regulation).

The Registrant proposed testing in rats. He proposed testing by the oral route. According to the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant is requested to carry out the following study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414).

IV. Adequate identification of the composition of the tested material

The process of examination of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the new study meets real information needs. Within this context, the Registrant's dossier was sufficient to confirm the identity of the substance to the extent necessary for examination of the testing proposal. The Registrant must note, however, that this information has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

In addition, it is important to ensure that the particular sample of substance tested in the new study is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured. If the registration of the substance covers different grades, the sample used for the new study must be suitable to assess these.

Finally, there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the study to be assessed.

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://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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