ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-2114303451-66-01/F Helsinki, 30 September 2015

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

For Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs., CAS No 97925-95-6 (EC No 308-208-6), 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 the following testing proposal submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(e) thereof for Ethanol, 2,2'-iminobis-, N-(C13-15-branched and linear alkyl) derivs., CAS No 97925-95-6 (EC No 308-208-6), submitted by [redacted] (Registrant).

- Developmental toxicity / teratogenicity study (OECD 414) on rabbit by oral route

This decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band of 1000 tonnes or more per year. This decision does not take into account any updates after 5 March 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 updated registration dossier containing the above-mentioned testing proposal for further examination pursuant to Article 40(1) on 6 June 2014.

ECHA held a third party consultation for the testing proposal from 14 August 2014 until 29 September 2014. ECHA received information from third parties (see section III below).

On 3 December 2014 ECHA sent the draft decision to the Registrant and invited him to provide comments within 45 days of the receipt of the draft decision.
That draft decision was based on submission number [redacted].

On 18 December 2014 ECHA received comments from the Registrant agreeing to ECHA's draft decision but asking for an extension of the deadline due to laboratory capacity.

On 28 January 2015 the Registrant updated his registration dossier submission number [redacted].

The ECHA Secretariat considered the Registrant's comments and update.
On basis of this information only the deadline in Section II was amended and the Statement of Reasons (Section III d) was changed accordingly.

On 5 March 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.

Subsequently, a proposal for amendment to the draft decision was submitted, suggesting to reject the testing proposal based on the findings from the first prenatal developmental toxicity study.

On 10 April 2015 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.

The ECHA Secretariat reviewed the proposal for amendment received and did not amend the draft decision.

On 20 April 2015 ECHA referred the draft decision to the Member State Committee.

By 11 May 2015, in accordance to Article 51(5), the Registrant provided comments on the proposal for amendment maintaining the view on the necessity to conduct a second prenatal developmental toxicity study test in another species. The Member State Committee took the comments of the Registrant on the proposal for amendment into account.

After discussion in the Member State Committee meeting on 8-11 June 2015, a unanimous agreement of the Member State Committee on the draft decision, to reject the testing proposal, was reached on 11 June 2015. Sections II and III were amended accordingly.

ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Rejection of the testing proposal

Pursuant to Article 40(3)(d) of the REACH Regulation the proposal for performing a

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

is rejected.

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, scientific information submitted by third parties and the proposal for amendment submitted by one Member State Competent Authority.

Pursuant to Article 40(3)(d) of the REACH Regulation, ECHA may reject a proposed test.

Pre-natal developmental toxicity studies on two species are part of the standard information requirements for substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The dossier contains a pre-natal developmental toxicity study in rats as first species. No information is available for a pre-natal developmental toxicity study in a second species. The Registrant has submitted a testing proposal for a pre-natal developmental toxicity study in a second species (rabbits) according to EU B.31/OECD 414 to be performed with the registered substance with the following justification:

"The test substance led to developmental effects in Han-Wistar rats at administered doses of 30 mg/kg bw/d and above under the experimental conditions of the study. The relevance of the effects observed for man is unclear. The conduct of another prenatal developmental toxicity study in a second species is proposed in order to find out if the effects observed in rats are species-specific findings. For the time being, the conclusion with regards to classification and labelling for toxicity to reproduction (developmental toxicity) will be CLP: Category 2, H361. (...) Since the outcome of the first study provided adverse developmental effects in the rat, the relevance of these findings in another species will be clarified with the conduct of a further developmental toxicity study in a non-rodent species (rabbit)."

ECHA received third party information concerning the testing proposal during the third party consultation indicating that *the proposed study in a second species would not add any relevant information for the purpose of classification and/or risk assessment. On this background further testing may not be required (cf. REACH Guidance R.7.6.6.3).'*

Based on ECHA's initial draft decision that approved the proposed testing, the Registrant expressed its consent with the draft decision while requiring more time for conducting the study. This latter request is no longer relevant as the testing proposal is rejected with the present decision.

During the consultation of the Competent Authorities of the Member States a proposal for amendment indicated that there is no necessity to conduct a prenatal developmental toxicity study.

The developmental effects observed in the first prenatal developmental toxicity study in rats included, but were not limited to, both pre- and post-implantation loss of foetuses, embryonic/foetal deaths and bone and cartilage abnormalities after exposure to 90 mg/kg bw/day. Effects at the LOAEL of 30 mg/kg bw/day included pre-implantation foetal loss and anomalies of the cervical vertebra ventral, arch, body or dorsal arch. Considering the severity and dose-dependency of these effects, there is at this stage no necessity to conduct a second species prenatal developmental toxicity study.

In response to the proposal for amendment, the Registrant stated that a classification of the substance as category 1B for reproductive toxicity would not be justified at this time on the basis of a single animal gavage study for the following reasons.

First, he claims that it does not model human dietary exposures and may result in significant differences in toxicokinetics compared to oral exposure.

However, ECHA notes that prenatal developmental toxicity studies are performed to identify the intrinsic properties of the substance. For that purpose, the dosing method likely to produce the highest systemic exposure should be used. In the first prenatal developmental toxicity study, severe effects were observed after administration by gavage indicating that gavage is the most suitable method to identify the intrinsic property of the substance. In the OECD TG 414, the default route is oral by intubation (gavage) which is considered the most suitable route in majority of cases.

Second, the Registrant claims that gavage administration can be problematic due to associated stress.

The Registrant did not demonstrate that gavage dosing method *per se* would have caused the developmental effects observed.

However, a scientific paper referred by the Registrant deals with alterations of endocrine responses and assessment of endocrine disrupting chemicals and not with severe developmental effects observed. Thus, it does not provide adequate evidence to nullify severe developmental toxicity observed.

Third, the Registrant also states that for corrosive substances, such as the registered substance, the oral administration via gavage is not suitable. The substance is self-classified as Skin Corr. 1 C which indeed may suggest that a high oral dosing could cause irritation in the stomach.

However this effect was not reported in the prenatal developmental toxicity study on the rats and the maternal toxicity reported seem to be only slight. In addition, the dose levels used were quite low. It is not demonstrated by the registrant or evident from the results of the prenatal development toxicity study how the severe developmental toxicity observed (e.g. increased embryonic/foetal deaths and malformations) would be linked to slight maternal toxicity.

Fourth, the Registrant claims that "the relevance of the effects observed from the initially conducted tests is unclear. The conduct of another prenatal developmental toxicity study in a second species; with dietary route of administration, is therefore necessary."

ECHA notes that the Registrant has not provided justification why the results from another species, in this case in the rabbit, would be more relevant and would dismiss the adverse effects observed in the rat study.

Additionally, the Registrant claims in his comment that in light of the potential difficulties in extrapolating meaningful results from the initial testing, he does not consider that the requirements of column 2 of Annex X Section 8.7 would be fulfilled. The Registrant considers that there would be insufficient information in the earlier conducted test that requires a further experimental study.

Based on column 2 of Annex X Section 8.7, a developmental toxicity study in a second species does not need to be conducted if the substance in question is known to cause developmental toxicity, meeting the criteria for classification as toxic for reproduction category 1A or 1B and the available data are adequate to support a robust risk assessment.

ECHA is of the opinion that in this specific case, there appears to be sufficient evidence to allow assessment whether the substance subject to the present decision meets the criteria for classification as toxic for reproduction category 1B and the available data are adequate to support a robust risk assessment. This is without prejudice to any opinion of ECHA's Risk Assessment Committee and a possible decision by the Commission on the harmonisation of the classification of the substance in accordance with the CLP Regulation (EC) No 1272/2008. Furthermore, a Member State Competent Authority has submitted an intention to ECHA to prepare a dossier for harmonised classification on this basis. Due to the above, a further study is currently not tailored to real information needs.

Based on the justification outlined above, ECHA, following the deliberation at the meeting of the Member State Committee, concluded that there is no need at this stage for further testing and rejects the proposed test accordingly.

IV. 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.

Authorised[1] by Guilhem de Seze, Head of Unit, Evaluation

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.