ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 16 July 2018

Addressee: [redacted]

Decision number: TPE-D-2114428801-53-01/F
Substance name: 1-methylimidazole
EC number: 210-484-7
CAS number: 616-47-7
Registration number: [redacted]
Submission number subject to follow-up evaluation: [redacted]
Submission date subject to follow-up evaluation: 17 January 2018

DECISION TAKEN UNDER ARTICLE 42(1) OF THE REACH REGULATION

By decision TPE-D-2114292056-48-01/F of 19 December 2014 ("the original decision") ECHA requested you to submit information by 27 June 2016 in an update of your registration dossier.

Based on Article 42(1) of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA examined the information you submitted with the registration update specified in the header above, and concludes that

Your registration still does not comply with the following information requirement:

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

The reasons for this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3.

The respective Member State competent authority (MSCA) and national enforcement authority (NEA) will be informed of this decision. [1] They may consider enforcement actions to secure the implementation of the original decision.

[1] Only the final decision will be sent to the National enforcement authority so they can consider enforcement actions.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals.

Authorised[2] by Kevin Pollard, Head of Unit E1

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

Appendix 1: Reasons

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

You were requested to submit information derived with the registered substance for Pre-natal developmental toxicity endpoint.

In the updated registration subject to follow-up evaluation, you have provided the results of a GLP-compliant prenatal developmental toxicity study according to the OECD test guideline (TG) 414 via oral route in rats with the registered substance. The doses used in the study were 90, 30, 10 mg/kg bw/day. You indicated that the doses were selected based on a 14-day dose range finder study, which is not reported in the registration dossier, and on the reproduction/developmental toxicity screening study (OECD TG 422), which is reported in the registration dossier. In any case, with respect to the 14-day dose range finder study, ECHA considers that the results of the study are less or not relevant for the dose selection compared to the results of the reproduction/developmental toxicity screening study (OECD TG 422), as the 14-day dose range study is of shorter duration, and is not performed in the pregnant animals.

ECHA observes that you have selected 90 mg/kg bw/day as the highest dose for the pre-natal developmental toxicity study based on the increased urea in parental animals at 90 mg/kg bw/day in the reproduction/developmental toxicity screening study (OECD TG 422). In the OECD TG 414 study, you reported that there were no maternal effects on body weight change or clinical signs except salivation, which ceased within 2-hours after treatment. You concluded that NOAELs for both maternal and developmental toxicity is the highest dose of 90 mg/kg bw/day.

ECHA considers that the doses used in the pre-natal developmental toxicity study were not *"chosen with the aim to induce some developmental and/or maternal toxicity (clinical signs or a decrease in body weight) but not death or severe suffering. At least one intermediate dose level should produce minimal observable toxic effects. The lowest dose level should not produce any evidence of either maternal or developmental toxicity. A descending sequence of dose levels should be selected with a view to demonstrating any dosage-related response and no-observed-adverse-effect level (NOAEL) or doses near the limit of detection that would allow the determination of a benchmark dose" (EU Test Method B.31, OECD TG 414).* ECHA considers that changes in a clinical chemistry parameter cannot be considered as relevant signs of maternal toxicity under the OECD 414 TG, as those effects are not investigated in this study. Additionally, according to the ECHA Guidance on Information Requirements and Chemical Safety Assessment (Chapter R.7.6.2.2.2), version 6.0, July 2017 *"The prenatal developmental toxicity study (EU Test Method B.31, OECD TG 414) provides a focused evaluation of potential effects following prenatal exposure, although only effects that are manifested before birth can be detected. More specifically, this study is designed to provide information on substance-induced effects on growth and survival of the foetuses, and increased incidences in external, skeletal and soft tissue malformations and variations in foetuses."*

Consequently, ECHA is of the opinion that the change to clinical chemistry parameter observed in the OECD 422 study is not relevant for the dose-range selection for pre-natal developmental toxicity study to enable focused evaluation of the developmental effects in offspring. ECHA considers that your expectation that the same dose levels as in the reproduction/developmental toxicity screening study (OECD TG 422) would be sufficiently

high is not plausible. In ECHA's view, your expectation cannot be justified, because there were no signs of developmental and/or maternal toxicity that would be relevant for the pre-natal developmental toxicity study (i.e. clinical signs or a decrease in body weight) observed in the screening study (OECD TG 422). ECHA therefore concludes that the prenatal developmental toxicity study provided by you is not adequate to fulfil information requirement due to the too low dose range selection in which it also deviated from the test guideline.

You provided in your comments to the draft decision and updated dossier information on two sequential 14-day dose-range finding studies showing predominantly effects in male rats. ECHA notes that any effects in male rats cannot be considered relevant for dose selection for pre-natal developmental toxicity study as the male animals are not subject to testing. Similarly, as explained earlier, clinical biochemistry parameters (urea and cholesterol) are not relevant for dose setting in pre-natal developmental toxicity study.

With respect to the female rats, you explained that 250 mg/kg bw/d led to 39,4%, 125 mg/kg bw/d to 35,3%, and 90 mg/kg bw/d to 26,8% decrease in food consumption on study day 3 of the dose-range finding studies. You assumed that the decrease in food consumption in 250 mg/kg bw/d and 125 mg/kg bw/d would have led to severe suffering or even death, and reduced the doses to 30 and 15 mg/kg bw/d. ECHA notes that a transient decrease in food consumption with subsequent recovery is frequently observed in the first days of dosing, as also confirmed with 90 mg/kg bw/d.

ECHA is of the opinion that the comments and the updated information in the dossier provided by you only confirms that the dose 90 mg/kg bw/d was too low to be selected as the highest dose for the pre-natal developmental toxicity study. Since there were no relevant signs of toxicity either in the 14-days studies in female rats or the OECD 422 study in rat dams at 90 mg/kg bw/d, that dose should not have been expected by the registrant to elicit *"some developmental and/or maternal toxicity but no death or severe suffering"* as recommended in the OECD TG 414.

As detailed above, ECHA therefore considers that the information requirement addressed by the original decision has not been met and you still have to provide results of the prenatal developmental study in rats or rabbits, oral route using the registered substance, and according to the test guideline EU Test Method B.31/OECD TG 414, as requested in the original decision.

Notes for your consideration

ECHA notes that a revised version of OECD TG 414 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. New tests should be performed in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

Appendix 2: Procedural history

This decision is necessary after the follow-up evaluation according to Article 42(1) of the REACH Regulation, because in your updated registration you have provided new experimental information, which was not available to you or ECHA at the time when your registration was examined for the original decision.

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft of this decision was notified to the Member States Competent Authorities according to Article 51(1) of the REACH Regulation.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and did not amend the request.

You updated your registration on 17 January 2018. ECHA took the information in the updated registration into account, and did not amend the draft decision. The updated information is reflected in the Reasons (Appendix 1).

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

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

ECHA invited you to comment on the proposed amendments.

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-60 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

2. The Article 42(2) notification for the original decision is on hold until all information requested in the original decision has been received.