EUROPEAN CHEMICALS AGENCY

Helsinki, 28 April 2021

Addressee: [redacted]

Decision number: TPE-D-2114550880-48-01/F
Substance name: 4-hydroxy-2,2,6,6-tetramethylpiperidinoxyl
EC number: 218-760-9
CAS number: 2226-96-2
Registration number: [redacted]
Submission number subject to follow-up evaluation: [redacted]
Submission date subject to follow-up evaluation: 04/12/2019

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

By decision TPE-D-2114340336-55-01/F of 14 July 2016 ("the original decision") ECHA requested you to submit information by 21 July 2017 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: EU B.31/OECD 414) in rats or rabbits, oral route.

The reasons of 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. They may consider enforcement actions to secure the implementation of the original decision and exercise the powers reserved to them under Article 126 of Regulation No 1907/2006 (penalties for non-compliance) for the period during which the registration dossier was not compliant[1].

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.

Approved[2] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[1] See paragraphs 61 and 114 of the judgment of 8 May of the General Court of the European Court of Justice in Case T-283/15 Esso Raffinage v. ECHA
[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

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

You were requested to submit information derived with the registered substance for Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in rats or rabbit, oral route.

In the updated registration, you have provided a prenatal developmental toxicity study with the registered substance via an oral route in rats and you claimed that the study has been done according to the OECD TG 414.

According to the EU Test Method B.31, OECD TG 414 for pre-natal developmental toxicity study *"the highest dose should be 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".*

Additionally, the ECHA Guidance on Information Requirements and Chemical Safety Assessment (Chapter R.7.6.2.2.2, version 6.0, July 2017) explains that *"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."* (emphasis added)

You explained that the doses for the pre-natal developmental toxicity study were selected based on a 28-day rat gavage study ([redacted]) with doses 8, 4, 200 and 1000 mg/kg bw/day. In the 28-day rat gavage study, you reported no mortality and no abnormalities in body weight development up to 1000 mg/kg bw/day. You reported that there were changes in haematology at 1000 mg/kg bw/day in both sexes, increase in absolute and relative liver and spleen weights in males and females of 1000 mg/kg bw/day dose group and increase in absolute spleen weight 200 mg/kg bw/day females. You have also reported some additional findings in male rats.

The doses used in the pre-natal developmental toxicity study were 40, 125 and 400 mg/kg bw/day. You reported that in the maternal animals, there were no treatment related clinical signs, no adverse effects on bodyweight, and no mortalities. You reported marginally decreased haemoglobin and increased reticulocytes, correlated with statistically significant increase in spleen weight, which you did not consider to be toxicologically significant. However, in your view, this is an indication that the top dose had been chosen adequately.

Further, for the developmental toxicity, you have reported increased incidences of skeletal malformations and variations in the top and medium dose, and also visceral findings. You have not addressed all the reported findings in the robust study summary.

In your comments you state that alternative markers of maternal toxicity are considered necessary for your Substance as the target organ toxicity identified from the 28-day toxicity study is haemolytic anaemia, which was more pronounced in females. This justifies the

inclusion of haematological assessments and spleen weights to identify maternal toxicity in the OECD TG 414 study.

You claim that in the 28-day study haematological changes indicative of haemolytic anaemia (decreased erythrocytes, haemoglobin concentration, mean cell haemoglobin concentrationand haemocrit values,with increased reticulocytes), splenomegaly (58 % relative increase) and microscopic changes of splenic congestion and hemosiderin-laden cells, attendant with hepatocyte swelling, were evident after dosing at 1000 mg/kg bw/day. Splenic microscopic changes were also seen after dosing at 200 mg/kg bw/day, demonstrating a dose-response.

You further explain that whilst you recognise that only a mild non-adverse haemolytic anaemia was induced after dosing at 1000 mg/kg/day in non-pregnant rats in the 28-day repeated dose toxicity study, normal haematological parameters alter significantly in the gravid female, with plasma volume and red cell counts disproportionally increasing to accommodate the foetal demand, frequently leading to decreases in haemoglobin concentrations and so the consequent risk of anaemia increases.

Therefore you find that existing prenatal developmental toxicity study in rats successful and you derived a NOAEL of 125 mg/kg bw/day for maternal toxicity and 400 mg/kg bw/day for the foetal developmental toxicity, with *"no compromise for the data requirement and hence justifying the reliability score of the study to be 1"*.

With respect to the dose selection for the pre-natal developmental toxicity study, ECHA considers that the study has not been conducted in line with the OECD TG 414/EU B.31 test method.

In particular, the study design has not followed the dose selection as quoted above, as there was no maternal toxicity as defined in the OECD TG 414/EU B.31 test method observed in that study. Your expectation that the maternal toxicity effects as defined in the OECD TG 414/EU B.31 would be observed at the high (400 mg/kg bw/day) and intermediate dose (125 mg/kg bw/d) based on the findings from the 28-day rat gavage study is not plausible. This is because there were no effects as defined in the OECD TG 414/EU B.31 observed in the female rats in the 28-day study conducted with doses up to 1000 mg/kg bw/day and with longer exposure duration (28 days compared to 14 days in the pre-natal developmental toxicity study).

In your comments you explained that the dose selection for the OECD TG 414 study was based on the results of the 28-day repeated dose toxicity study, with extra consideration taken for a possible higher severity in gravid females. ECHA is of the opinion that the observed changes in organ weights and histopathology in liver and spleen indicate a level of toxicity that would not likely be achieved in a PNDT study with a shorter exposure duration (15 days), even in gravid dams. Considering the severity of the toxicity observed in the 28-day study, it seems reasonable to consider that dosing up to, or at least near to, 1000 mg/kg bw/day would be possible in a PNDT study. The highest dose of 400 mg/kg bw/day for the OECD TG 414 cannot be regarded as having been selected 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.

With respect to the reported marginal changes in haematology and spleen weight in the maternal animals, the effects are not relevant for the study design and top dose selection to enable *"focused evaluation of potential effects following prenatal exposure"* with the view 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."[3] (emphasis added) Examination of haematology parameters and spleen weights is actually not required according to the OECD TG 414/EU B.31 test method.

Despite your allocation of a NOAEL for maternal toxicity of 125 mg/kg bw/day in the OECD TG 414 study ECHA retains its view that there was a lack of clear toxicity (maternal or developmental) at the highest dose level of 400 mg/kg bw/day.

For the reasons described above, ECHA is of the opinion that the study is not adequate for robust hazard and risk assessment. Due to the too low doses used, it is not possible unambiguously interpret the results, in particular the increased incidences of skeletal malformations and variations in the top and medium dose, and the statistically significant incidences of thymic remnant in the top dose group. Consequently, ECHA considers the deviation from the OECD TG 414/EU B.31 test method not acceptable, and it is not possible to evaluate whether or not the substance is a developmental toxicant.

As detailed above, the request in the original decision was not met, and you are still required to provide results of the prenatal developmental study in rats, oral route (with the registered substance according to the test guideline EU B.31/OECD 414), as requested by the ECHA decision.

[3] ECHA Guidance on Information Requirements and Chemical Safety Assessment (Chapter R.7.6.2.2.2, version 6.0, July 2017)

Appendix 2: Procedural history

In accordance with Article 42(1) of the REACH Regulation, the Agency examined the information submitted by you in consequence of decision TPE-D-2114340336-55-01/F. The Agency considered that this information did not meet one or more of the requests contained in that decision. Therefore, a new decision-making process was initiated under Article 40 of the REACH Regulation.

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(s).

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

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

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.