ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 20 February 2019

Addressee: [redacted]

Decision number: CCH-D-2114460982-41-01/F
Substance name: 1-(N,N-bis(2-hydroxyethyl)amino)propan-2-ol
EC number: 229-764-5
CAS number: 6712-98-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 16/02/2018
Registered tonnage band: 100-1000

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2., column 2; test method: OECD TG 414) in a second species (rabbit), oral route with the registered substance;**

You 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 to the REACH Regulation. To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **27 May 2020**. You also have to update the chemical safety report, where relevant.

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

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, has to 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[1] by **Ofelia Bercaru**, Head of Unit, Hazard Assessment NC4

[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.

Appendix 1: Reasons

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2., column 2) in a second species

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation

A "pre-natal developmental toxicity study" (test method OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Annex IX, Section 8.7.2., column 2 provides that the decision on the need to perform a pre-natal developmental toxicity study on a second species at a tonnage level of 100 to 1000 tonnes per year should be based on the outcome of the first test and all other relevant and available data. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet these information requirements.

The technical dossier contains a pre-natal developmental toxicity study with rats by the oral route. This study fulfils the standard information requirement for a pre-natal developmental toxicity study in a first species (Annex IX, Section 8.7.2.).

According to Annex IX, Section 8.7.2., column 2 of the REACH Regulation, a pre-natal developmental toxicity study shall be initially performed on one species. A decision on the need to perform a study at this tonnage level or the next on a second species should be based on the outcome of the first test and all other relevant available data. The issue is further elaborated in ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a, Section R.7.6.2.3.2. (version 6.0, July 2017).

In the submitted pre-natal developmental toxicity study in rat ([redacted] 2001) submitted for this endpoint, an increase in the incidence of foetuses with reduction in ossification, restricted mainly to skull bones, was reported. These alterations were dose-dependent and reached statistical significance at the mid and high dose (i.e. at 300 and 1000 mg/kg body weight, respectively). At these exposure levels no reductions in foetal body weight were reported, and it is likely that the findings are thus not related to a general developmental delay. ECHA also notes that there seemed not to be any reduced ossification in other parts of the skeleton. The only sign of maternal toxicity reported in the study was a slight increase in kidney weights at the high dose level. Therefore, there is a concern for developmental toxicity which must be clarified in a pre-natal developmental study in a second species.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

The test in the first species was carried out with rats. According to the test method /OECD TG 414, the rat is the preferred rodent species and the rabbit is the preferred non-rodent species. On the basis of this default assumption, ECHA considers that the test should be performed with rabbit as a second species.
ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction

as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

In your comments on the draft decision you indicate that you agree with ECHAs assessment of the pre-natal developmental toxicity and that you intend either to perform the requested test, or to re-classify the substance for developmental toxicity based on already available information.

One of the Member State Competent Authorities (MSCA) submitted a proposal for amendment (PfA) to remove the request for a PNDT study in a second species, because of the following reasons:

(i.) *"an increase in the incidence of fetuses with delayed ossification in a small number of bones does not constitute sufficient concern to trigger testing in a second species"*;
(ii.) *"minor delays in ossification are readily 'fixed' post-natally, and are not mechanistically linked to malformations"*;
(iii.) With reference to the paper from [redacted] (2018) *"it is important to observe the shape of the calvaria"* to determine *"if there is an adverse finding"*; in the rat study there are no reported abnormalities in the shapes of the bones.
(iv.) *"not unreasonable to conclude that the increases in reduced ossification seen in the rat developmental study are secondary to maternal toxicity, even though the maternal toxicity is not severe, and are not a specific developmental effect."*; and
(v.) the effects noted in the first study do not support a Cat. 2 classification.

In your comments on the PfA you expressed your agreement with the proposal made by the MSCA and you used similar text to that provided by the MSCA (in their PfA), as reasoning to remove this request.

With reference to points (i.) to (v.) above, ECHA notes the following:

(i.) As indicated above, in the rat study there was a statistically-significant and dose-dependent increase in the incidence of foetuses with reduced ossification of several skull bones. Notably there was no reduced ossification in other parts of the skeleton as the effects reported are restricted mainly to the skull bones. Hence, ECHA considers that there is not a generalised effect resulting in reduction of ossification in several bones, but rather that the anatomically-specific effects noted, together with the information on maternal toxicity (minimal) and fetal weight (no reduction), provide sufficient concern for developmental toxicity.
(ii.) Accepts that there are circumstances where minor delays in ossification are linked to maternal toxicity, that the delays are soon 'fixed', and are not mechanistically linked to malformations. However, in this case, it is unlikely that the delays are linked to maternal toxicity (see iv. below) and the specific pattern of ossification seen in this case is not necessarily typical for agents with reduced ossification due to toxicity.
(iii.) Indeed there were no malformations observed in the calvarium, which was one of the affected bones in the rat study. In addition, in the paper by [redacted] (2018) there is no information on how these type of findings should be interpreted when they are specific effects, as observed in this case.
(iv.) As regards the maternal toxicity, as already explained above, in the rat PNDT study, the only sign of toxicity is the slight increase in kidney weights at the highest dose level. In the PfA, the MSCA refers to the findings in the 28d RDT study

([redacted], 1999), which is available in the dossier. In the 28d study, there were no mortalities observed at any dose level. There were no significant differences in body weight changes, the histopathological findings were limited to stomach alterations in both males and females of the highest dose group (1000 mg/kg bw/day), and there was a significant increase in the kidney and liver weights (absolute and relative) of both males and females. Considering the findings of the rat PNDT study and the 28d study, it can be concluded that there is only minimal maternal toxicity. Additionally, the toxicity seen with this agent is restricted to the skull, whereas other bones noted to respond to maternal toxicity (e.g. phalanges, sternebrae 5&6, vertebrae) are not affected. There is thus a concern that this a specific response, rather than a generalised delayed ossification response which is secondary to maternal toxicity and hence non-specific. Hence, the reduced ossification noted cannot be considered as secondary to maternal toxicity.

(v.) Classification as a Cat. 2 developmental toxin is not required as a basis for triggering a second species PNDT study, and ECHA does not make the case that the substance should be classified as a Cat. 2 developmental toxin. The triggering of the second species PNDT study is based on the concern for developmental toxicity.

In view of the above, ECHA considers that a second species is necessary as the rat PNDT study shows effects of concern, and this is a trigger to request a prenatal developmental toxicity study in a second species.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: OECD TG 414) in a second species (rabbit) by the oral route.

Deadline to submit the requested Information

In the draft decision communicated to you the deadline indicated to provide the requested information was 12 months from the date of adoption of the decision. In your comments on the draft decision you indicated that you would need an extension of the deadline of 12 months given in the draft decision. You do not specify the length of this extension. To justify your request you explain that you will need time to communicate with your suppliers and co-registrants to decide on the best course of action, i.e. whether to perform the requested study or to re-classify the substance with regard to pre-natal developmental toxicity. ECHA agrees with your request and has extended the deadline to 15 months.

Appendix 2: Procedural history

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 decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 01 March 2018.

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 amended the deadline.

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

ECHA received proposal(s) for amendment and did not modify the draft decision.

ECHA invited you to comment on the proposed amendment(s).

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 during its MSC-63 meeting and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests 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 or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.