EUROPEAN CHEMICALS AGENCY

Helsinki, 30 June 2020

Addressees
Registrants of JS_266-587-2 listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
05/09/2019

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: 1-[bis[3-(dimethylamino)propyl]amino]propan-2-ol
EC number: 266-587-2
CAS number: 67151-63-7

Decision number: [Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/D)]

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***7 January 2022***.

A. Requirements applicable to all the Registrants subject to Annex IX of REACH

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 Substance.

You must report the study performed according to the above specifications. Any expansion of the study must be scientifically justified.

Conditions to comply with the requests

You are bound by the requests for information corresponding to the REACH Annexes applicable to your own registered tonnage of the Substance at the time of evaluation.

Therefore you have to comply with the requirements of Annexes VII, VIII and IX of REACH, if you have registered a substance at 100-1000 tpa.

Registrants are only required to share the costs of information that they must submit to fulfil the information requirements for their registration.

The Appendices state the reasons for the requests for information to fulfil the requirements set out in the respective Annexes of REACH.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference documents.

You must submit the information requested in this decision by the deadline indicated above in an updated registration dossier and also update the chemical safety report, where relevant,

including any changes to classification and labelling, based on the newly generated information. The timeline has been set to allow for sequential testing where relevant.

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.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Approved[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[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 A: Reasons for the requests to comply with Annex IX of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier registered at 100 to 1000 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII to IX to REACH.

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

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX to REACH. Annex IX, Section 8.7.2., column 2 provides that the decision on the need to perform a PNDT study on a second species at a tonnage level of 100 to 1000 tonnes per year should be based on the outcome of the PNDT study on a first species and all other relevant and available data.

You have provided a study according to OECD TG 414 in one species (rat) with the Substance [redacted] 2018), but you have not provided an OECD TG 414 on a second species.

We have assessed the information in your registration dossier and identified the following issue:

ECHA considers that a PNDT study on a second species is needed, if there is a concern for developmental toxicity based on the results from the PNDT study on a first species and other relevant data.

You consider that no developmental toxicity was observed in the available OECD TG 414 study (OECD TG 414 in rats; [redacted] 2018) and that the isolated affected skeletal structures are unlikely to be true developmental abnormalities.

However, ECHA disagrees with your conclusion on isolated findings and considers that there is a concern for developmental toxicity based on the information from the study on the first species. Developmental toxicity was observed in one species in the available study (OECD TG 414 in rats[redacted] 2018) at dose levels which were not markedly toxic to dams. More specifically, significantly increased incidences of foetuses/litters showing incomplete ossification of several bone structures observed in the OECD TG 414 study in rats [redacted] 2018) indicates a concern for prenatal developmental toxicity:

- Statistically significantly increased incidence of foetuses/litters with incomplete ossification of femur, interparietal, and sacral arch was reported at the highest dose. These incidences were outside of historical control range.

In your comments you refer to literature (e.g. Nitzsche 2017[2]) and consider that these type of anomalies are reflecting a delay in completion of ossification which may be attributed to limited maternal food intake at the highest dose. Furthermore, you consider that even though the effects were statistically significant, the biological relevance is not fully proven.

ECHA notes that in the OECD TG 414 study in rats ([redacted] 2018), the maternal food intake was reported for six time ranges (3-4 days each, covering gestation days (GD) 3-20). Compared to controls, the food intake in the high dose group was reduced between 8% (GD 14-17) and 28% (GD 5-8). The range of food consumption during the whole study (GD 3-20) was 17.4-25.8 g/rat/day in the high dose group, and 24.2-28.1 g/rat/day in controls. At the end of the

[2] Nitzsche D (2017) Effect of maternal feed restriction on prenatal development in rats and rabbits - A review of publisheddata. Regulatory Toxicology and Pharmacology, 90: 95-103

study on GD 20, the corrected body weight of the dams at the high dose was slightly lower (6.4%) than controls. The high-dose foetal body weight was also slightly lower (3.9%) compared to controls.

The publication of Nitzsche (2017) analyses and reviews feed restriction studies in pregnant rats. Within this review, for example the study by Fleeman *et al.* (2005[3]) has a study design which is comparable to [redacted] 2018 (i.e. OECD TG 414 in rats with the Substance): ca. 15% feed restriction (20 g/rat/day), corrected maternal body weight was 8% and foetal body weight 5% lower compared to controls. Delays in ossification were reported in this study only at the lowest feed level (7.5 g/rat/day, i.e. 70% feed restriction). No evidence of delayed skeletal ossification was observed with any other in any other study group. In other words, a 15% feed restriction only, i.e. without any chemical exposure, did not cause delayed ossification.

ECHA considers that the reduced food intake in the OECD TG 414 study in rats ([redacted] 2018) did not lead to such marked maternal toxicity and/or delays in foetal development which would result in incomplete ossification of femur, interparietal, and sacral arch with incidences outside of the historical control range, and therefore considers that that these effects are biologically relevant and show a concern for developmental toxicity.

- Dose-related increases in incidences of incomplete ossification of sternebra and sacral arch were reported at all dose levels when compared to control. These changes were statistically significant at all dose levels for sternebra and at the highest dose for sacral arch.

In your comments you consider that the incidences for incomplete ossification of sternebra were "*generally within the historical control ranges*", and are therefore less likely to be treatment-related.

According to the data you provided with your comments, the historical control range (group mean % fetuses affected per litter) is 0.0-5.0%. In the OECD TG 414 study in rats ([redacted] 2018), the incidences of incomplete ossification in sternebra are 3.0% (low dose), 3.1% (mid dose) and 5.4% (high dose). ECHA notes that the incidences were statistically significantly increased at all dose levels compared to the concurrent control with incidence of 0%. Furthermore, the indicence at high dose, 5.4%, is outside of the historical control range. Therefore, ECHA considers that there is a concern for developmental toxicity.

- Increased incidence of incomplete ossification of hyoid was statistically significant at mid and high dose foetuses.

In your comments you consider that the incidences for incomplete ossification of hyoid were "*generally within the historical control ranges*", and are therefore less likely to be treatment-related.

According to the data you provided with your comments, the historical control range (group mean % fetuses affected per litter) is 4.0-15.2%. In the OECD TG 414 study in rats ([redacted] 2018), the incidences of incomplete ossification of hyoid are 9.7% (low dose), 15.7% (mid dose) and 11.1% (high dose). ECHA notes that the incidences were increased at all dose levels compared to the concurrent control with incidence of 5.6%. Furthermore, the incidence at mid dose, 15.7%, is outside of the historical control range of 4.0-15.2%. Therefore, ECHA considers that there is a concern for developmental toxicity.

3 Fleeman, T.L., et al., 2005. The effects of feed restriction during organogenesis on embryo-fetal development in the rat. Birth Defects Res. B Dev. Reprod. Toxicol. 74, 442-449.

- The incomplete ossification of bones occurred without a significant delay in foetal growth as evidenced by only slightly increased incidence of small foetuses (5.6% compared to 1.5% in controls) and reduced foetal weights (3.9% lower mean weights compared to control) reported at high dose only.

In your comments you speculate that even though the incomplete ossification of bones occurred without a significant delay in foetal growth, it could not be excluded that the incomplete ossification of bones may be attributed to limited maternal food intake at the highest dose.

As explained above, the lower food intake at the high dose resulted in only slight effects in maternal and foetal body weights, which would not explain the observed incomplete ossification. Furthermore, ECHA notes that incomplete ossification was also observed at low and mid doses where food intake, corrected maternal body weight and foetal body weights were comparable to controls. Therefore, ECHA considers that there is a concern for developmental toxicity.

In your comments you also consider that "*All of the anomalies seen were also found in the historical control data albeit at lower levels*". ECHA considers that the historical control data helps to interpret study results with reference to normal biological variation in certain, defined setting. Therefore, when changes in development are observed at incidences which are above the historical control data, like in the OECD TG 414 study in rats ([redacted] 2018), it raises a concern for developmental toxicity.

Finally, you consider that in the absence of other changes to foetuses (fetal/placental weight or visceral/external anomalies), the changes observed are not likely to be adverse. ECHA notes that irrespective whether or not the findings are considered as adverse, they indicate a change in development which raises a concern for developmental toxicity.

As the condition of Annex IX, section 8.7.2., column 2 is fulfilled, i.e. that there is a concern for developmental toxicity, a pre-natal developmental toxicity study in two species is an information requirement for your registration.

The specifications for the study design

The test in the first species was carried out by using a rodent species (rat). ECHA therefore considers that the most relevant species for a second test should be a non-rodent species. Under OECD TG 414 the preferred non-rodent species is the rabbit.

The study shall be performed with oral[4] administration of the Substance.

[4] ECHA Guidance R.7a, Section R.7.6.2.3.2.

Appendix B: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of REACH.

The compliance check was initiated on 29 August 2019.

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 requests by removing the request for an extended one-generation reproductive toxicity study. Your comments included detailed additional information on the systemic toxicity observed in the OECD TG 422 study, which led to the re-assessment of the concern related to reproductive toxicity. The information provided in your comments shall be provided in the updated registration dossier. As a consequence of removing a request, also the deadline was amended.

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 C: Observations and technical guidance

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

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 the Member States.

3. Test guidelines, GLP requirements and reporting

   Under Article 13(3) of REACH, all new data generated as a result of this decision needs to be conducted according to the test methods laid down in a European Commission Regulation or according to international test methods recognised by the Commission or ECHA as being appropriate.

   Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses shall be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

   Under Article 10 (a) (vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide: 'How to report robust study summaries'[5].

4. Test material

   Selection of the test material(s)

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   While selecting the test material you must take into account the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected test material must contain that constituent/ impurity.

   Technical reporting of the test material

   The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

   Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[6].

.3.2.
PERLINK "https://echa.europa.eu/practical-guides" https://echa.europa.eu/practical-guides
[6] https://echa.europa.eu/manuals

5. List of references of the ECHA Guidance and other guidance/ reference documents[7]

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 in this decision.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[8]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

OECD Guidance documents[9]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.
Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment – No 43, referred to as OECD GD 43.

[7] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[8] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[9] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix D: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fufilled
[redacted]	[redacted]	[redacted]

Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas the decision is sent to the actual registrant.