Helsinki, 5 June 2020

Addressees
Registrants of Triamine_C16-18_C18-unsat. listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of a decision
20/12/2013

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: N-(3-aminopropyl)-N'-C16-18 (evennumbered), C18 unsaturated alkyl - propane-1,3-diamine
EC number: 628-863-4
CAS number: 1219458-14-6

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

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***14 March 2022***.

A. Requirements applicable to all the Registrants subject to Annex IX of REACH[1]

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.

Conditions to comply with the requests

Each addressee of this decision is bound by the requests for information corresponding to the REACH Annexes applicable to their own registered tonnage of the Substance at the time of evaluation of the jointly submitted dossier.
To identify your legal obligations, please refer to the following:

- 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 they are required to submit to fulfil the information requirements for their registration.

The testing material used to perform the required studies shall be selected and reported in accordance with the specifications prescribed in Appendix C Observations and technical guidance.

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.

[1] Testing required under this Annex can only be started or performed after the decision has been adopted according to Article 51.

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.

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

[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 A: Reasons for the requirements applicable to all the Registrants subject to Annex IX of REACH

This decision is based on the examination of the testing proposal you submitted.

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 information on PNDT on one species (rat; Wil Research, 2013). You have not provided an OECD TG 414 on a second species.

You have submitted a testing proposal for a PNDT study in rats according to OECD TG 414 by the oral route.

In your testing proposal you propose to repeat the available PNDT study. Your testing proposal is based on the findings in a study according to TG 414 in rat ([redacted] 2013), in which polydactyly and malpositioned metatarsals were noted among the foetuses of treated dams. You state that in this study the interpretation of skeletal evaluations is disputable, and for that reason you propose to perform a new study according to OECD TG 414 in rat via the oral route.

In your comments to the draft decision, you explain that the deviating views related to the interpretation of the findings of the initial study between the foetal pathologist(s) of the testing laboratory and the external expert who re-evaluated the findings are not related to the findings *per se*, but whether or not they are artefacts. You present that there was only one case for which the external expert concluded that polydactyly could not be discounted (and one case that could not be re-evaluated).

You provide various reason to support your view that the observed skeletal findings are artefacts and not developmental toxicity, e.g., the external expert has seen such skeletal lesions before resulting from handling during colouring procedures, there did not seem to be superfluous bone structures present, the lesions were not observed at external examinations, there was no dose-response relationship, other substances in this group of chemicals do not show such malformations, the low incidence of polydactyly, and only unilateral findings. Furthermore, you consider that a mechanistic basis is difficult to understand as these substances have a MoA of general cytotoxicity at contact.

In addition, you consider that a limited study design should be used to partially repeat the rat study in view of animal welfare and no study in a second species is needed.

The skeletal evaluation should allow determination of total number and percent of foetuses and litters with any skeletal alteration, as well as the types and incidences of the anomalies and alterations according to OECD TG 414.

ECHA considers that the study by [redacted] (2013) provides this information and fulfils these criteria, irrespective whether or not the cause of the skeletal findings is established, i.e. if they are artefacts or exposure-related. You have accepted the study as reliable with restrictions and with a statement that "*However, interpretation of skeletal evaluations is disputable*". ECHA agrees that the study is acceptable although there is uncertainty in certain

skeletal findings. Although you have provided with your comments to the draft decision some theoretical explanations how such skeletal findings could have been formed if the foetuses and/or the skeletal specimens have been handled inappropriately, you have not shown evidence that unexperienced or non-trained persons have been handling the foetuses, processed and evaluated the skeletons.

The expert(s) evaluating the study in the performing laboratory did not conclude that the findings were artefacts. Therefore, the handling of the foetuses, skeletons and interpretation of the findings by the performing laboratory are considered appropriate.

ECHA finds that the reasons you present in your comments to support your interpretation that the findings are artefacts do not negate the interpretations of the performing laboratory.

Therefore, ECHA concludes that in spite of the interpretation challenges of the skeletal findings in the rat PNDT study, the study meets the information requirements for the one (first) species (Annex IX, Section 8.7.2, column 1) and it would not be justified to partially repeat it, even with a limited study design.

A PNDT study on second species has to be performed depending on the outcome of the PNDT study on a first species and all other relevant and available data according to Annex IX, Section 8.7.2., column 2 of the REACH Regulation.

You have submitted a study according to OECD TG 414 in rat ([redacted] 2013), in which polydactyly and malpositioned metatarsals were noted among the foetuses of treated dams. ECHA has assessed the descriptions of the disputable findings (polydactyly and malpositioned metatarsals) based on the data provided (original evaluation and evaluation from an external expert) and agrees with the external expert's statement that "*it is probably not possible to reach a definitive conclusion on this issue*". This means that the external expert could not definitively conclude whether the findings are true skeletal malformations or artefacts. However, both malformations are localized in the same region and result from patterning errors during limb development, which increases the concern, and supports the interpretation that they are true malformations. Your comments to the draft decision, which aim to support your interpretation that the findings are artefacts, do not abolish the concern. Therefore, the results from the rat study, polydactyly and malpositioned metatarsals, indicate a concern for skeletal malformations and variations which need to be addressed, and consequently a PNDT study should be carried out in a second species in accordance with Annex IX, 8.7.2., Column 2 of the REACH Regulation. The rabbit is a suitable species to address the concern as the type of skeletal malformations observed in the rat can be also observed in the rabbit, and the rabbit is a preferred second species for a PNDT study.

You proposed testing by the oral route. The oral route is the most relevant route of administration to investigate reproductive toxicity[3].

According to Article 40(3)(d) and (c) of the REACH Regulation, your proposed test is rejected and you are requested to carry out additional test(s).

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

Appendix B: Procedural history

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 24 October 2018.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (pre-natal developmental toxicity). ECHA notes that you provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

ECHA held a third party consultation for the testing proposal from 24 January 2019 until 11 March 2019. ECHA did not receive information from third parties.

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 the REACH.

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 of the notification.

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 C: Observations and technical guidance

1. This testing proposal examination decision does not prevent ECHA from initiating 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 your Member State(s).

3. Test guidelines, GLP requirements and reporting

   According to 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.

   According to 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.

   According to 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[4]'

4. Selection of the test material(s) for UVCB substances

   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. Any constituents that have harmonised classification and labelling according to the CLP Regulation (Regulation (EC) No 1272/2008) must be identified and quantified using the appropriate analytical methods.

   The OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 11 [ENV/MC/CHEM(98)16] requires a careful identification of the test material and description of its characteristics. In addition, the Test Methods Regulation (EU) 440/2008, as amended by Regulation (EU) 2016/266, requires that "if the test method is used for the testing of a [...] UVCB [...] sufficient information on its composition should be made available, as far as possible, e.g. by the chemical identity of its constituents, their quantitative occurrence, and relevant properties of the constituents".

   In order to meet this requirement, all the constituents of the test material used for each test must be identified as far as possible. For each constituent the concentration value in the test material must be reported in the Test material section of the endpoint study record.

[4] https://echa.europa.eu/practical-guides

Technical Reporting of the test material for UVCB substances
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" on the ECHA website[5].

5. List of references of the ECHA Guidance and other guidance/ reference documents[6]

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)[7]

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.

[5] https://echa.europa.eu/manuals
[6] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[7] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

OECD Guidance documents[8]

Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD23.

Guidance Document supporting the OECD TG 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD151.

[8] 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 fulfilled
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]