~~Confidential~~

Helsinki, 11 January 2022

Addressees
Registrants of JS_Acetylcaprolactam listed in the last Appendix of this decision

Date of submission of the dossier subject of a decision
18/12/2018

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: N-acetylhexanelactam
EC number: 217-565-6
CAS number: 1888-91-1

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

DECISION ON TESTING PROPOSAL(S)

Based on Article 40 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by ***18 July 2023***.

The requested information must be generated using the Substance unless otherwise specified.

A. Information required from the Registrants subject to Annex VIII of REACH

1. **Pre-natal developmental toxicity study (triggered by Annex VIII, Section 8.7., column 2 and Section 0.5. of Annex I of REACH; test method: EU B.31./OECD TG 414) by oral (gavage) route, in one species (rat), starting dosing from the gestation day 0.**

Reasons for the requests are explained in the following appendix entitled "Reasons to request information required under Annexes VIII of REACH".

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH, the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa.

How to comply with your information requirements

To comply with your information requirements you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

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[1] under the authority of Mike Rasenberg, 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 to request information required under Annex VIII of REACH

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

1. Pre-natal developmental toxicity study

According to Annex VIII, 8.7.1., Column 2, at the tonnage level of 10 to 100 tonnes per annum, the Registrant may propose an extended one-generation reproductive toxicity study (EOGRTS, OECD TG 443) (Annex IX, section 8.7.3) or a pre-natal developmental toxicity study (PNDT, OECD 414) (Annex IX, Section 8.7.2) instead of a screening study (OECD TG 421/422) in cases where there are serious concerns about the potential for adverse effects on fertility or development.

Pursuant to Article 12(1) and Annex VI of the REACH Regulation the standard information requirements listed in Annex VII to X of the REACH Regulation are considered minimum requirements. Annex VI, step 4 of the 'Guidance note on fulfilling the requirements of Annexes VI to XI' provides that the rules set out in Annexes VII to XI may require certain tests to be undertaken earlier than or in addition to the standard requirements. Furthermore, in accordance with Annex I of the REACH Regulation, certain additional information may have to be generated if it is necessary for producing the chemical safety report (CSR). According to the last subparagraph of Section 0.5. of Annex I of REACH, if the manufacturer or importer considers that further information is necessary for producing his CSR and that this information can only be obtained by performing tests in accordance with Annex IX and X, he shall submit a proposal for a testing strategy, explaining why he considers that additional information is necessary and record this in the CSR under the appropriate heading. Further, under Section 1.3.2 of Annex I to REACH, if the information is inadequate to decide whether a substance should be classified for a particular hazard class or category, the registrant shall indicate and justify the action or decision he has taken as a result.

This means that when justified, higher tier/further studies may be conducted for substances where the tonnage level would not normally require this as a standard requirement. In order to understand the toxicological properties of the registered substance in light of the adverse effects observed, it is necessary to investigate further so that appropriate risk management measures can be put in place and safe use of the substance can be ensured.

1.1 Information provided in your dossier

Your dossier contains a screening study ([redacted] 2018; OECD TG 421) with the Substance. This study shows a dose-dependent increase in post-implantation loss (%) at low and mid dose levels, 100 and 300 mg/kg bw/day respectively, as 15.1 and 27.2 %, compared to control group with 9.6 %. There was also a significantly lower survival index on post-natal day 4 at low dose and mid dose levels. Furthermore, the study showed reduced mean number of implantations at high dose level, 1000 mg/kg bw/day, but also severe clinical signs and mortality (5/10 females during treatment days 32-34, i.e. gestation day (GD) 14-18, all remaining females were sacrificed on treatment Day 37 (i.e. GD 17 to 21)). There were no treatment-related adverse effects on the mean pre-coital time, mating and fertility indices of sires and dams at all the doses tested.

Based on these effects, you have identified a serious concern as a reliable no observed adverse effect level (NOAEL) for reproductive toxicity for females could not be determined.

ECHA considers that the adverse effects reported in the screening study (OECD TG 421) raises serious concerns about the potential for adverse effects on development (e.g. significant/severe effects). In addition, PNDT study can provide NOAEL values and reliable

hazard classification having higher statistical power compared to the screening study and detailed investigations on developmental toxicity.

ECHA considers that the Substance shows toxicological properties which need to be further investigated in order to conclude on risk assessment and classification based on a more definitive study design and thus in order to produce the CSR. This is necessary for appropriate risk management measures.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Developmental toxicity. 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 agrees that there is a serious concern on developmental toxicity and a PNDT study in a first species is necessary.

1.2 Specification of the study design

To clarify the toxicity profile of the Substance, you propose to perform an OECD TG 414 study in rats, to investigate the prenatal exposure on the pregnant test animal and on the developing organism.

The reduced number of implantations occurred at high dose level where also mortality was observed from GD 16 onwards in the OECD TG 421 study. Based on the information provided, it is not possible to conclude if the recorded post-implantation loss is indeed reflecting real post-implantation loss that can be observed in an OECD TG 414 study or includes perinatal mortality that cannot be observed in an OECD TG 414 study. However, in the absence of one study design based on recognised test methods to fully investigate all the observed effects, ECHA agrees that the OECD TG 414 is a suitable study to investigate the concern related to *in utero* deaths of offspring (real post-implantation loss).

You proposed testing in the rat as a first species. ECHA agrees that the rat should be used for an OECD TG 414 as the concern was observed in the rat. You shall aim to conduct the study using the same rat strain that was used for the OECD TG 421 study.

You proposed testing by the oral gavage route. ECHA agrees with your proposal because oral route of administration is the most appropriate to investigate reproductive toxicity (ECHA Guidance R.7a, Section R.7.6.2.3.2.). You shall use gavage dosing to replicate the administration route of the OECD TG 421.

Furthermore, in cases where preliminary studies do not indicate a high potential for pre-implantation loss, treatment may be extended to include the entire period of gestation, from mating to the day prior to scheduled humane killing (OECD TG 414, para. 13). In this case, there is no such indication of high potential for pre-implantation loss and the concern being (post)implantation loss, it is necessary to ensure a comprehensive evaluation of potential effects on implantation and the dosing needs to start on GD0.

1.3 Outcome

Your testing proposal is accepted under Article 40(3)(b) and you are requested to conduct the test with the Substance, as specified above.

Appendix B: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

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

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

3. 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 on How to report robust study summaries[2].

B. Test material

1. Selection of the Test material(s)

   The Test material used to generate the new data must be selected taking into account the following:
   - the boundary composition(s) of the Substance,
   - 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.

2. Information on the Test material needed in the updated dossier
   - You must report the composition of the Test material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   - The reported composition must include all constituents of each Test material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test material is relevant for the Substance.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[3].

[2] https://echa.europa.eu/practical-guides
[3] https://echa.europa.eu/manuals

Appendix C: Procedure

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 30 April 2020.

ECHA held a third party consultation for the testing proposal(s) from 17 June 2020 until 3 August 2020. ECHA did not receive information from third parties.

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

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

ECHA took into account your comments and amended the deadline.

> In your comments on the draft decision, you requested an extension of the deadline to provide information from 12 to 18 months from the date of adoption of the decision. You justified the deadline extension with the possible challenges in selecting appropriate dose levels for this requested information.
>
> On this basis, ECHA has granted the request and extended the deadline to 18 months.

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 D: List of references - ECHA Guidance[4] and other supporting documents

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 where relevant.

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 where relevant.

Read-across assessment framework (RAAF, March 2017)[5]

RAAF - considerations on multi-constituent substances and UVCBs (RAAF UVCB, March 2017)[6]

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.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

[4] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[5] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[6] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316

OECD Guidance documents[7]
Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

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

[7] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix E: Addressees of this decision and the corresponding information requirements applicable to them

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.