EUROPEAN CHEMICALS AGENCY

Helsinki, 23 November 2018

as consolidated following decision ED/33/2019

Addressee: [redacted]

Decision number: CCH-D-2114448631-50-01/F
Substance name: 3,7-dimethyloct-6-enenitrile
EC number: 257-288-8
CAS number: 51566-62-2
Registration number: [redacted]
Submission number: [redacted]
Submission date: 29/02/2016
Registered tonnage band: Over 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 X, Section 8.7.2.; test method: OECD TG 414) in a second species, oral route with the registered substance;**

2. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route with the registered substance specified as follows:**

   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce systemic toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;**

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 ***31 May 2021***. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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 **Claudio Carlon**, Head of Unit, Hazard Assessment, C3

[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

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

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

Pre-natal developmental toxicity studies (test method OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The technical dossier contains information on a pre-natal developmental toxicity study in rats by the oral route using the registered substance as test material.

However, there is no information provided for a pre-natal developmental toxicity study in a second species.

The technical dossier does not contain an adaptation in accordance with column 2 of Annex X, Section 8.7.2. or with the general rules of Annex XI for this standard information requirement.

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 method OECD TG 414 and ECHA Guidance on information requirements and chemical safety assessment (version 6.0, July 2017), Chapter R.7a, section R.7.6.2.3.2, Stage 4.5 indicates that the rat and the rabbit are the preferred species. However, ECHA Guidance further indicates that "*The selection of the species for the prenatal developmental toxicity study should be made taking into account substance-specific aspects. If a species other than the rat and the rabbit is selected as the first or second species, the selection should be justified.*"

There are indications in your registration dossier that the registered substance might have some antibacterial activity (low concentrations tested in an OECD 471 study due to bacterial toxicity, long lag-phase in the reported ready biodegradability study). This may influence the species selection as species sensitive to gastrointestinal disturbance may not provide relevant information on prenatal developmental toxicity of substances with potential antimicrobial activity.

In your comments on the draft decision, you argue that a pre-natal developmental toxicity study in rabbit is not deemed justified by referring to the antimicrobial activity of the registered substance. You indicate that "*in the Salmonella/microsome mutagenicity test with Citronellyl nitrile a maximum concentration of 0.06 µg test liquid/0.1 ml methanol/plate was tested because higher concentrations appeared to be toxic by a less dense background lawn of bacteria growth*". You further argue that "*species sensitive to gastrointestinal disturbance, e.g. the rabbit, will not provide relevant information on pre-natal developmental toxicity as the predominant effect at even low concentrations will be the*

disturbance of the gastrointestinal tract". Finally, you indicate that "*there were no toxicologically relevant adverse foetal findings evident*" in a pre-natal developmental toxicity study conducted according to OECD TG 414 with the registered substance. You conclude that you "*do not see a sufficient rationale to provide information* [...] *on a second species*" and specify that you "*will submit an update of the technical dossier including an adaptation in accordance with column 2 of Annex X, Section 8.7.2. for a pre-natal developmental toxicity study in the second species*".

ECHA notes that the original technical dossier and your comments on the draft decision provide information on effects of the registered substance on bacteria and generic considerations on the effects of antibacterial substances on the gastro-instestinal tract of rabbits. As already explained above in the draft decision, the rat and the rabbit are the preferred species. However, another species than the rabbit (non-rodent or rodent) may be selected if you provide factual evidence (e.g., results from a dose-range finding study in rabbits with the registered substance) or other relevant information showing that the registered substance is causing severe effects in rabbits that are not relevant for hazard assessment in humans.

ECHA further emphasizes that a justification that the rabbit may not be appropriate to conduct a pre-natal development toxicity study is not regarded as an appropriate to adapt the information requirement for this endpoint according to Annex X, Section 8.7.2., column 2. As already explained, for dossiers registered at Annex X level, the REACH Regulation requires testing for pre-natal developmental toxicity in a second species. ECHA agrees that the argued species-specific toxicity of the registered substance in rabbit, if demonstrated, may disturb assessment of developmental toxicity. However, it is not a justification to adapt the standard information requirement of a pre-natal developmental toxicity study in a second species, but it may indicate that another species than the rabbit should be used.

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.

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 by the oral route.

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

The basic test design of an extended one-generation reproductive toxicity study (test method OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

Adequate information on this endpoint needs to be present in the technical dossier for the

registered substance to meet this information requirement.

a) *The information provided*

You have not provided any study record of an extended one-generation reproductive toxicity study in the dossier that would meet the information requirement of Annex X, Section 8.7.3.

The technical dossier does not contain an adaptation in accordance with column 2 of Annex X, Section 8.7.3. or with the general rules of Annex XI for this standard information requirement.

In the technical dossier you have provided a study record for a "one-generation reproductive toxicity study" (test method: EU B.34/OECD TG 415). However, this study does not provide the information required by Annex X, Section 8.7.3. because it does not cover key parameters, exposure duration, and life stages of an extended one-generation reproductive toxicity study. The main missing key aspects/element is an extensive postnatal evaluation of the F1 generation. Therefore, your adaptation of the information requirement is rejected.

In your comments on the draft decision, you indicate that "*no observed adverse effect levels (NOAEL) for reproductive toxicity and maternal systemic toxicity already exist and that sufficient regulatory measures are already in place to ensure the protection of human health*". You also specify that "*the derived no-effect levels (DNEL) for reproductive toxicity derived from available studies are higher than the DNEL derived for systemic toxicity. As a result, the DNEL based on systemic toxicity will also be sufficient to protect against reproductive effects. It is very unlikely that performing an EOGRTS would lead to a lower NOAEL (and therefore a lower DNEL and consequently further risk management measures)*". Finally, you acknowledge that you do not consider that further testing is necessary and that you plan to adapt the information requirement for this endpoint according to Annex X, Section 8.7.3, column 2.

As already explained above, a "one-generation reproductive toxicity study" (test method: EU B.34/OECD TG 415) does not provide the information required by Annex X, Section 8.7.3. because it does not cover key parameters, exposure duration, and life stages of an extended one-generation reproductive toxicity study. Accordingly, ECHA considers that available information does not convincingly demonstrate that further testing would not lead to lower NOAELs.

Hence, 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. Thus, an extended one-generation reproductive toxicity study according Annex X, Section 8.7.3. is required. The following refers to the specifications of this required study.

b) *The specifications for the study design*

Premating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should be ten weeks to cover the full spermatogenesis and

folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

The highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no relevant data to be used for dose level setting, it is recommended that results from a range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Species and route selection

According to the test method OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in rats.

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.

c) Outcome

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: Extended one-generation reproductive toxicity study (test method EU OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce systemic toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;

While the specifications for the study design are given above, you shall also submit with the new endpoint study record a scientific justification on each of the following aspects: 1) length of the premating exposure duration and dose level selection, 2) reasons for why or why not Cohort 1B was extended, 3) termination time for F2 generation, and 4) reasons for why or why not Cohorts 2A/2B and/or Cohort 3 were included.

Notes for your consideration

The conditions to trigger the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by

including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the available information, together with the new information shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented.

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 14 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 did not amend the requests.

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Following an appeal registered as Case A-002-2019, on 20 March 2019 the Executive Director of ECHA rectified the decision in accordance with Article 93(1) of the REACH Regulation (decision ED/33/2019), by withdrawing from the decision the following information requests:

(3) *Long-term toxicity testing on aquatic invertebrates (EU C.20./OECD TG 211);*
(4) Long-term toxicity testing on fish (OECD TG 210);
(5) Activated sludge respiration inhibition testing (OECD TG 209);
(6) Robust study summary (RSS) for "Ready biodegradability of CITRONELLYL NITRILE according to OECD Guideline No. 301 F", OR Ready biodegradability (OECD TG 301C) or Ready biodegradability (OECD TG 301D) or Ready biodegradability (OECD TG 301F).

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.