EUROPEAN CHEMICALS AGENCY

Helsinki, 22 August 2018

Addressee: [redacted]

Decision number: TPE-D-2114440664-49-01/F
Substance name: 1,1,3,3-tetramethylbutyl peroxyneodecanoate
EC number: 257-077-0
CAS number: 51240-95-0
Registration number: [redacted]
Submission number: [redacted]
Submission date: 31/05/2017
Registered tonnage band: 100-1000

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation ((EC) No 1907/2006) (the REACH Regulation), ECHA examined your testing proposal(s) and decided as follows.

Your testing proposal is modified and you are requested to carry out:

1. **Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral (gavage) 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 some 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;**
   - **Cohorts 2A and 2B (Developmental neurotoxicity)**

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 an adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by ***31 August 2020***. You also have to update the chemical safety report, where relevant.

The reasons for 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 Kevin Pollard, Head of Unit, Evaluation E1

[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

The decision of ECHA is based on the examination of the testing proposals submitted by you.

1. Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.)

Pursuant to Article 40(3)(b) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test under modified conditions.

The basic test design of an extended one-generation reproductive toxicity study (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 IX of the REACH Regulation if the available repeated dose toxicity studies (e.g. 28-day or 90-day studies, OECD TGs 421 or 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. If the conditions described in column 2 of Annex IX 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 in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

ECHA considers that adverse effects on reproductive organs or tissues or other concerns in relation with reproductive toxicity are observed in the 90-day repeated dose toxicity study conducted according to OECD TG 408 ([redacted], 2016). More specifically, toxicologically significant changes in sperm concentration and motility and an associated increase in sperm abnormalities, and hypertrophy of thyroid follicular epithelium at 100 and 300 mg/kg bw/day were observed. As the condition of Annex IX, Section 8.7.3. is fulfilled, an extended one-generation reproductive toxicity study is an information requirement for the registered substance pursuant to Annex IX, Section 8.7.3.

The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for an extended one-generation reproductive toxicity study according to EU B.56./OECD TG 443 by the oral route and to be performed with the registered substance.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (extended one-generation reproductive toxicity study). 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.

However, ECHA notes that you have not provided any justification and specification of the study design. ECHA therefore concludes that you have submitted a testing proposal for the basic study design according to column 1 of Section 8.7.3., Annex IX. Furthermore, ECHA considers that this basic study design is not appropriate to fulfil the information requirement of Annex IX, Section 8.7.3. of the REACH Regulation and ECHA has further specified the study design.

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

registered substance to meet this information requirement. Thus, an extended one-generation reproductive toxicity study according to column 1 of Section 8.7.3., Annex IX is required. The following refers to the specifications of this required study.

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 *on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017), 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). Ten weeks exposure duration is supported also by the lipophilicity of the substance (Log Kow value of 6.9) to ensure that the steady state in parental animals has been reached before mating.

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of 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 existing 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.

Extension of Cohort 1B

If the column 2 conditions of Section 8.7.3., Annex IX are met, Cohort 1B must be extended, which means that the F2 generation is produced by mating the Cohort 1B animals. This extension provides information also on the sexual function and fertility of the F1 animals.

Although you have not specified whether to include an extension of Cohort 1B, ECHA notes that currently available information in the dossier do not meet the criteria described in column 2 of Section 8.7.3. of Annex IX and detailed in ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

Therefore, ECHA concludes that Cohort 1B must not be extended to include mating of the animals and production of the F2 generation.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity as described in column 2 of Section 8.7.3., Annex IX . When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information.

Although you have not specified whether to include an extension of Cohorts 2A and 2B, ECHA notes that currently available information in the dossier meets the criteria described in column 2 of Section 8.7.3. of Annex IX and detailed in ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.7a, Section R.7.6 (version 6.0, July 2017). More specifically, the existing information on the registered substance itself derived from available *in vivo* study (90-day repeated dose toxicity study by [redacted], (2016)) show evidence of dose related toxicity in thyroid (hypertrophy of the follicular epithelium in both sexes at 100 and 300 mg/kg bw/day). Consequently, such effects raises concern for the developing brain. ECHA notes your argument in the registration dossier that the effects in thyroid are secondary to the adaptive effect in the liver. However, you have not demonstrated that (1) the effects in thyroid are secondary to increased thyroid hormone metabolism in the liver, and (2) the specific mechanism that cause effects in thyroid will be irrelevant during development.

ECHA concludes that the developmental neurotoxicity cohorts 2A and 2B need to be conducted because there is a particular concern on (developmental) neurotoxicity based on the results from the above-identified *in vivo* study on the registered substance itself.

Cohort 3

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity as described in column 2 of Section 8.7.3., Annex IX.

Although you have not specified whether to include an extension of Cohort 3, ECHA notes that currently available information in the dossier do not meet the criteria described in column 2 of Section 8.7.3. of Annex IX and detailed in ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

Therefore, ECHA cocludes that Cohort 3 needs not to be conducted.

Species and route selection

You proposed testing in rats.According to the test method EU B.56./OECD TG 443, the rat is the preferred species. On the basis of this default consideration, ECHA considers that testing should be performed in rats.

You proposed testing by the oral route. ECHA agrees 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 proposal, you specified the oral application to be via gavage without justification.

In your comments on the draft decision according to REACH Article 50(1) you state that you agree with the draft decision. ECHA Secretariat (ECHA-S) acknowledges your agreement. Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, you are requested to carry out the proposed study with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method EU B.56./ OECD TG 443), in rats, oral (gavage) 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 some 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;
- Cohorts 2A and 2B (Developmental neurotoxicity)

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 include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, and/or Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the new information shows triggers which are described in column 2 of Section 8.7.3., Annex IX 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

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 31 May 2017.

ECHA held a third party consultation for the testing proposals from 1 September 2017 until 16 October 2017. ECHA did not receive information from third parties.

This decision does not take into account any updates after **21 May 2018**, 30 calendar days after the end of the commenting period.

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.

In your comments you agreed to the draft decision. ECHA took your comments into account 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 took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided in your registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the 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 the Member States.

3. In carrying out the tests required by the present decision, it is important to ensure that the particular sample of substance tested 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. If the registration of the substance covers different grades, the sample used for the new tests must be suitable to assess these.

   Furthermore, 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.