EUROPEAN CHEMICALS AGENCY

Helsinki, 7 February 2020

Addressees
Registrants of JS_25155-25-3 listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of a decision
16/11/2018

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: [1,3(or 1,4)-phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide
EC number: 246-678-3
CAS number: 25155-25-3

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 ***16 May 2022***.

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

1. The Extended one-generation reproductive toxicity study also requested, and specified, at B.1 below (triggered by Annex IX, Section 8.7.3.).

B. Requirements applicable to all the Registrants subject to Annex X of REACH

1. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route, 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; and
    - Cohorts 2A and 2B (Developmental neurotoxicity).

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

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 to IX of REACH, if you have

registered a substance at 100-1000 tpa;

- you have to comply with the requirements of Annexes VII to X of REACH, if you have registered a substance at above 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 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.

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 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 requirements applicable to all the Registrants subject to Annex IX of REACH

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

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

The basic test design of an extended one-generation reproductive toxicity study (EOGRTS) is a standard information requirement under Annex IX to the REACH Regulation, if the available repeated dose toxicity studies indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. Furthermore, column 2 defines when the study design needs to be expanded.

You have submitted a testing proposal for an EOGRTS according to OECD TG 443 by the oral route in rats with 10-week premating exposure duration.

ECHA considers that concerns in relation with reproductive toxicity are observed in available studies:

- Changes in thyroid histopathology, i.e. hypertrophy of the follicular cells, were observed in both sexes in the OECD TG 408 and 422 studies.
- Reduced fertility index, lower number of corpora lutea and implantation rate, increased postnatal loss, lower litter sizes and lower live birth index were reported in the OECD TG 422 study.

As the condition of Annex IX, Section 8.7.3. column 1 is fulfilled, an EOGRTS study is an information requirement for your registration.

For the legal basis and the specifications of the study design see Appendix B.1.

Appendix B: Reasons for the requirement applicable to all the Registrants subject to Annex X of REACH

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

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

The basic test design of an extended one-generation reproductive toxicity study (EOGRTS) is a standard information requirement under Annex X to the REACH Regulation. Furthermore, column 2 of Section 8.7.3. defines when the study design needs to be expanded.

You have submitted a testing proposal for an EOGRTS according to OECD TG 443 by the oral route in rats with 10-week premating exposure duration. You have provided the following justification and specification of the study design according to the criteria described in Column 2 of Section 8.7.3, Annex IX/X, and detailed in ECHA Guidance R.7a:
"- *Premating exposure duration for parental (P0) animals: 10 weeks*
- *Basis for dose level selection: OCDE 408, 422 and 414 studies in rats (data summarized in the table below)*
- *Exclusion of extension of Cohort 1B to produce F2 generation: the substance has no uses leading to significant exposure of consumers or professionals.*
- *Termination time for F2: not concerned*
- *Exclusion of developmental neurotoxicity Cohorts 2A and 2B: no effects reported on CNS in the OECD 408 study*
- *Exclusion of developmental immunotoxicity Cohort 3: no effects reported on the lymphoid tissues in the OECD 422 and 408 studies*
- *Route of administration: oral"*

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.

The proposed study design requires modification to fulfil the information requirement.

The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

You proposed 10 weeks premating period. ECHA agrees with your proposal.

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 R.7a Ten weeks exposure duration is supported also by the lipophilicity of the Substance to ensure that the steady state in parental animals has been reached before mating (Log Pow 7.3).

You proposed dose levels based on OECD TG 408, 414 and 422 studies in rats. ECHA notes that in order to be compliant and not to be rejected due to too low dose levels, the highest dose level must 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. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

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.

You must provide a justification with your study report that demonstrates that the dose level selection meets the conditions described above.

Cohorts 1A and 1B

Cohorts 1A and 1B belong to the basic study design and must be included.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity.

You proposed not to include Cohorts 2A and 2B.

ECHA notes that existing information on the Substance derived from the available OECD TG 408 and 422 studies shows evidence of thyroid toxicity. Specifically, histopathological changes, i.e. hypertrophy of the follicular cells, was observed in both sexes. Signs of thyroid toxicity rise a particular concern on developmental neurotoxicity (ECHA Guidance R.7a).

The developmental neurotoxicity cohorts 2A and 2B must be conducted because there is a particular concern on (developmental) neurotoxicity.

Species and route selection

You proposed testing by oral (gavage) route in rats. ECHA agrees with your proposal.

Outcome

Under Article 40(3)(b) of the REACH Regulation, you are requested to carry out the proposed test under modified conditions, as explained above, with the Substance.

Further expansion of the study design

The conditions to include the extension of Cohort 1B are currently not met. 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 relevant information becomes available from other studies or during conduct of this study. Inclusion is justified if the available information meets the criteria and conditions, which are described in Column 2, Section 8.7.3., Annex IX/X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance[2].

[2] ECHA Guidance R.7a, Section R.7.6.

Appendix C: Procedural history

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 19 November 2018.

ECHA held a third party consultation for the testing proposal from 27 May 2019 until 11 July 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 REACH.

ECHA notified you of the draft decision and invited you to provide comments within 30 days of the notification.

ECHA did not receive any comments within the 30-day notification period.

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: Observations and technical guidance

1. The substance subject to the present decision was listed in the Community rolling action plan (CoRAP) for the start of substance evaluation in 2015 and decision was adopted in 2017.

2. This testing proposal examination decision does not prevent ECHA from initiating compliance checks at a later stage on the registrations present.

3. 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).

4. 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 must 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'[3].

5. 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 is known to have or could have 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.

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

Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[4].

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

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)[6]

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

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.

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

Appendix E: 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]
[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.