ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 24 April 2018

Addressee: [redacted]

Decision number: CCH-D-2114401218-61-01/F
Substance name: [1,3-PHENYLENEBIS(1-METHYLETHYLIDENE)]BIS[TERT-BUTYL] PEROXIDE
EC number: 218-664-7
CAS number: 2212-81-9
Registration number: [redacted]
Submission number: [redacted]
Submission date: 02.06.2017
Registered tonnage band: 100-1000T

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. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats with the registered substance;**

2. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD 421/422) in rats, oral route with the registered substance;**

3. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

4. **Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: Alga, growth inhibition test, EU C.3./OECD TG 201) with the registered substance;**

5. **Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: Daphnia magna reproduction test, EU C.20./OECD TG 211) with the registered substance;**

6. **Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210) with the registered substance;**

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 of the REACH Regulation. In order 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 are required to submit the requested information in an updated registration dossier by ***2 November 2020*** except for the information requested under point *[2]* for a screening for reproductive/developmental toxicity study, which, together with an update of the read-across justification, shall be submitted in an updated registration dossier by **31 October 2019**.

If you consider that the outcome of the screening for reproductive/developmental toxicity is sufficient to allow you to adapt the information requirements in Annex IX, section 8.6.2. and Annex IX section 8.7.2. in accordance with Annex XI, section 1.5., then the studies requested under point 1, sub-chronic toxicity study (90 day), and point 3, pre-natal developmental toxicity study, are not required. In this case the deadline **2 November 2020** shall not apply and all requested information (i.e., requests 2, 4,5 and 6), including a read-across adaptation addressing the information requirements in Annex IX, section 8.6.2. and Annex IX section 8.7.2, shall be submitted in the updated registration dossier by **31 October 2019**.

You shall also update the chemical safety report, where relevant.
The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. 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, shall 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

PROPERTIES OF THE SUBSTANCE

0. Grouping of substances and read-across approach

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "provided that the conditions set out in Annex XI are met".

In the registration, you have adapted the standard information requirements for

- Repeated dose toxicity (Annex IX, Section 8.6.2)
- Reproductive toxicity (Annex VIII, Section 8.7.1)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2)
- Long-term toxicity testing on invertebrates (Annex IX, Section 9.1.5)

by applying a read-across adaptation following REACH Annex XI, Section 1.5.

Annex XI, Section 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation. The following analysis presents your justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and an property-specific context.

0.1 Description of the grouping and read-across approach proposed by the Registrant

The technical dossier provides that:

> *"The analogue approach is based on read-across to substance with similar chemical structure and similar physicochemical properties."*
>
> *"The following substance has been identified as a suitable analogue based on structural similarities.*
>
> *[1,3(or1,4)-phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide (CAS 25155-25-3,* ***Meta/para-bisperoxide****).*
>
> *The analogous substance is, in fact, a multi-constituent substance that is a mixture of structural isomers, the* ***Meta-bisperoxide*** *(major, 1,3-isomer) and the Para-bisperoxide (minor, 1,4-isomer)."*

ECHA understands this as the hypothesis under which you make predictions for the properties listed above.

0.2 Support of the grouping and read-across approach

You have provided a read-across justification ([redacted]) as a separate attachment in the technical dossier in IUCLID, Section 13. In summary you provide the following arguments to support the read-across approach:

- Structural similarity between the target substance and the source substance.
- The source substance is a multi-constituent substance that is a mixture of structural isomers, the meta-bisperoxide (major, 1,3-isomer; the target substance) and the para-bisperoxide (minor, 1,4-isomer).
- Impurities are not expected to have any impact on the read-across approach.
- The target substance and the source substance share common physical-chemical characteristics.
- In the event of a bond cleavage in the body, the expected breakdown products would be tert-butanol for both source and target substances, and 1,3-bis[hydroxyl methylethyl]benzene or 1,3(or 1,4) -bis[hydroxyl methylethyl]benzene.
- The toxicological data that exists for the target substance is in agreement with the existing data for the source substance.

In addition, ECHA observes that in the technical dossier of the target substance you have provided studies for the source substance [1,3(or1,4)-phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide (Meta/para-bisperoxide) (CAS no. 25155-25-3) including the following:

- *"Repeated dose 90-day oral toxicity in rodents"* (OECD TG 408; GLP, [redacted] 2015) in Section 7.5.1 as key study.
- *"Combined repeated dose toxicity study with the reproduction/developmental toxicity screening study"* (OECD TG 422; GLP, oral, rat, [redacted] 2008) in Section 7.8.1 as key study.
- *"Pre-natal developmental toxicity study"* (OECD TG 414; GLP, oral, rat, [redacted] 2015a) in Section 7.8.2 as key study.
- *"Long-term toxicity testing on invertebrates"* (OECD TG 211; GLP; *Daphnia*, [redacted] 2016) in Section 6.1.4 as key study.
- *"Growth inhibition study aquatic plants"* (OECD TG 201; GLP; *Pseudokirchneriella subcapitata*, [redacted] 2010) in Section 6.1.5 as key study.

0.3 ECHA analysis of the grouping and read-across approach in light of the requirements of Annex XI, 1.5.

With regard to the proposed predictions ECHA has the following observations:

(i) Substance characterisation of source and target substances

The substance characterisation of the source substance needs to be sufficiently detailed in order to assess whether the attempted prediction is not compromised by the composition and/or impurities. In the ECHA practical guide 6 *"How to report on Read-Across"* it is recommended to follow the ECHA *Guidance for identification and naming of substances under REACH and CLP* (version 1.3, February 2014) also for the source substances. This ensures that the identity of the source substance and its impurity profile allows an assessment of the suitability of the substances for read-across purposes.

In your read-across justification you state the following on the composition of the target and source substances:

"The purity of ***Meta-bisperoxide*** *is ca. 90 %, whereas the purity of the* ***Meta/para-bisperoxide*** *is ca. 80 % (meta + para content).* ***Meta/para-bisperoxide*** *typically contains ca. 65* ***Meta-bisperoxide*** *and ca. 15 % Para-bisperoxide (****Meta-bisperoxide*** *contains ca. 0.1 % Para-bisperoxide)."*

You have also provided impurity profiles of the source and target substances. However, this information on impurity profiles has not been included in the technical dossier of the registered substance. For instance, according to the impurity profile provided in the read-across justification document, source and target substances have the same six impurities in common, present at higher concentrations for the source substance. However, according to the composition provided in the technical dossier, the target substance has only two of these impurities, i.e. [redacted] and [redacted] peroxide (CAS no 96319-55-0). You state that *"The typical impurities of the substances are not expected to have any impact on the read across approach."*

Regarding information on the substance tested in the source studies, this information does not provide clarity on the composition on the test substance. In particular the ratio of the p- and m-isomers in the source tests are not specified. Only the purity for the two isomers combined and not the composition of the substance is given in the respective robust study summaries.

ECHA considers that currently the impurity profile of the target substance as presented in the read-across justification document is not consistent with the information provided in the technical dossier. Furthermore, it remains unclear whether the information given on the source substance in the read-across justification is representative for the testing material used in the source studies. For these reasons it is not possible to compare the structural similarities and differences between source and target substances as a basis for the read-across.

(ii) Explanation on why and how the structural similarities allow predictions

In order to meet the provisions in Annex XI, Section 1.5. to predict human health and environmental effects from data for a reference substance within the group by interpolation to other substances in the group, ECHA considers that structural similarity alone is not sufficient. It has to be justified why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. In particular, the structural similarities must be linked to a scientific explanation of how and why a prediction is possible.

You state the following:

*"The molecular formula for **Meta-bisperoxide** and **Meta/para-bisperoxide** are identical, they differ specifically in the meta/para isomer ratio (typically ca. [redacted] for **Meta-bisperoxide** and ca. [redacted] for **Meta/para-bisperoxide**). The meta and para isomers differ structurally only in the positioning of the substituents on the aryl ring (ie. 1,3-substitution vs. 1,4-substitution).*

As there are no atoms with available electron lone pair, there is no mesomeric possibilities between the phenyl group and the functional groups –C(CH3)2O-O-tBu. Therefore the meta or para position is not suspected to change the reactivity of the molecule. In addition, there are no hydrogen bond possibilities for either of the configurations, and the steric effect is minimally changed by the position of the substitution from meta to para."

ECHA notes that the source substance and the target substance are similar in structure, and that you do not expect the meta-bis-peroxide and the para-bis-peroxide to have different reactivity. You also expect the steric effects due to the structural differences between the meta-bis-peroxide and the para-bis-peroxid to be minimal. However, no evidence has been submitted to substantiate these assumptions. The claim that m- and p- isomers have similar effects is based on considerations of generic chemical reactivity but there are no considerations with regard to interactions with biological systems and for the individual properties you attempted to predict.

Furthermore, no mechanistic explanation is provided why the steric differences would not matter in interactions with biological systems, nor are there explanations provided on how the concentration variations of the source substance constituents may impact this prediction. This would mainly be of concern if the presence of the p-isomer influences the (eco)toxicity of the m-isomer by reducing its (eco)toxicity via toxicodynamic and/or toxicokinetic interactions, thereby causing an underestimation of the m-isomer's (eco)toxicity in the proposed prediction. Currently, such considerations are not provided in your read-across justification.

ECHA concludes that it has not been sufficiently demonstrated that the source substance could be used to predict the (eco)toxicological properties of the target substance.

(iii) Support of a similar or regular pattern as a result of structural similarity

Annex XI, Section 1.5. provides that "*substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances.* One prerequisite for a prediction based on read-across therefore is that the substances involved are structurally similar and are likely to have similar properties. One important aspect in this regard is the analysis of the data matrix to compare the properties of source and target substances and to establish whether indeed they are similar or follow a regular pattern.

ECHA notes the following regarding physico-chemical properties:

You have not provided a data matrix on physico-chemical properties for the source and target substances that would allow comparison of the properties of the target and source substances. However, in your read-across justification you consider that physico-chemical parameters/properties of the target and source substances are similar. You state that "*extremely close or identical physico-chemical properties are reported for Meta-bisperoxide and Meta/para-bisperoxide (Modeling calculates the same physic-chemical properties for*

both the meta and para isomers).". You have proposed that the similar physico-chemical properties of the target and source substances enable the read-across between the substances. You further state that "*Water solubility (< 0.1 mg/L), log Kow (> 7) and other physico-chemical properties should be extremely close or identical, thus supporting the read across rationale.*". Considering the high structural similarity, ECHA agrees that, although supporting evidence is missing, it is apparent that the source and target substances are likely to have similar physical-chemical properties.

ECHA notes the following regarding toxicokinetics:

One important aspect in establishing that substances have similar effects or follow a regular pattern is the comparison of absorption, distribution, metabolism and elimination of source and target substances. This allows assessing the qualitative and quantitative internal systemic exposure of the test organism when exposed to source and target, respectively.

You state that:

"The most remarkable functional group present for both substances is the organic peroxide group. In the event of a bond cleavage in the body, the expected breakdown products would be tert-butanol for both substances, and [redacted]*. For the same reasons as reported in 4.1, the meta or para position is not expected to change the toxicological profiles, thus supporting the read across rationale."*

ECHA takes note of these statements but concludes that you have not submitted any data that could support your statement and support your read-across approach. For instance, it has not been demonstrated which metabolites are formed from p- and m-isomers and whether possible formation of metabolites might occur at different rates or may influence each other when present in combined exposure situation (*i.e.* when the source substance is tested).

Furthermore, no attempt was made to clarify why and how such possibilities would not have a major impact on the prediction of the toxicological profile of the target substance based on the source substance.

ECHA concludes that the lack of information on toxicokinetics prevents proper understanding of the systemic exposure profile following exposure to the target and source substance, respectively, and hence gives no support to the hypothesis that studies with the the source substance could be used to predict the toxicological profile of the target substance.

ECHA notes the following regarding prediction of (eco)toxicity:

You have not provided any study on repeated dose toxicity or reproductive toxicity with your registered substance. For that reason the toxicity profiles for the substances proposed for your read-across cannot be compared between the source and the target substances. Furthermore, the link of the structures with your prediction is not properly specific. There are, for instance, no arguments why for pre-natal developmental toxicity the steric change from m- to p-isomer would not matter, and why a mixture of m- and p-isomer is regarded to have the same toxicity for the developing foetus as the m-isomer alone.

Regarding the environmental hazards, you claim that "*the meta or para position is not expected to change the ecotoxicological profiles*". However, you provide no anchor studies to support this claim, since aquatic toxicity tests are available only for the source substance. For this reason, the aquatic toxicity of source and target substances cannot be compared. Furthermore, you do not provide an explanation on why the different position of the substituents would not change the ecotoxicity of the substances.

ECHA concludes that the presented evidence does not support a similar or regular pattern of (eco)toxicity as a result of structural similarity, nor has it been demonstrated that the (eco)toxicological profile of the target substance would not be affected by the presence of the para-bis peroxide isomer. Therefore it cannot be verified that the proposed analogue substances can be used to predict properties of the registered substance.

0.4 Conclusion on the read-across approach

ECHA considers that structural similarity alone is not sufficient for predicting (eco)toxicological properties. It has to be justified why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. ECHA notes that in view of the issues listed above it has not been demonstrated that the source and read-across substances have the same properties or follow a similar pattern with regard to studies on repeated dose toxicity (Annex IX, Section 8.6.2), reproductive toxicity (Annex VIII, Section 8.7.1.), pre-natal developmental toxicity study in a first species (Annex IX, Section 8.7.2.), growth inhibition study aquatic plants (Annex VII, Section 9.1.2) and long-term toxicity testing on invertebrates (Annex IX, Section 9.1.5). ECHA concludes that you have failed to meet the requirement of Annex XI, Section 1.5. that human health effects may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach).

In your comments to the draft decision according to Article 50(1) of the REACH Regulation and/or in your updated registration dossier you explain/provide the following information:

- You point out that the read-across justification document contains information on all six noted impurities present in both the source and target substances. However, in the IUCLID file of the target substance only two of these impurities are included, due to the fact that only those two are present at > 1 % and therefore included explicitly in IUCLID.
- With regard to the identity of the source substance used in the studies used for read-across you explain in particular related to the ratio of p- and m- isomers that the ratio is known internally based on the ratio in the raw material(s), and has not nominally changed from the time of source substance testing to the time of source substance REACH analytics. Hence, the composition as noted in the read-across justification is indicative of the substance used for source testing. You also offer to provide additional proof of source substance identity for tests which were not conducted with your product.
- A profile of the source and target substances has been run in the OECD Applicability Toolbox (v1.1) (OECD 2010) and shows no major differences in the expected reactivity. Additionally, the substances were also previously run in DEREK NEXUS 3.0.1, ACD ToxSuite 2.9.5 and TOPKAT and showed no differences between the profiles. These summaries were not included in the last dossier update but can be added to the read-across justification.
- A data matrix of existing phys-chem, tox and ecotox/fate data for the source and target substance has been added to the read-across justification.

- With regard to physico-chemical properties, you have conducted in-house non-GLP water solubility and partition coefficient studies with the target substance to further substantiate the read-across (non-GLP to be supporting studies to the GLP studies of the source substance as well as calculated partition coefficient results (and updated read-across justification accordingly.

ECHA acknowledges the provided clarification related to the contamination profiles of the source and target substances as well as on the composition of the source substance used for the read-across studies. The provided QSAR information on reactivity profiles is noted, as well as the data matrix. With regard to the water solubility and partitioning properties of the source substance, ECHA acknowledges the results you provided. Overall the proposed improvements to the read-across justifications seem to make it plausible that the read-across could be sufficiently justified when bridging studies are available. ECHA considers that experimental evidence of the similarity is needed in order to further justify read-across approach for (eco)toxicological endpoints. Furthermore, some endpoint specific issues still remain as indicated under the respective sections below.

Pursuant to Article 41(1) of the REACH Regulation, ECHA concludes that the adaptation of the standard information requirements for the endpoints repeated dose toxicity, reproductive toxicity, pre-natal developmental toxicity, growth inhibition study aquatic plants, and long-term toxicity testing on invertebrates in the technical dossier based on the proposed read-across approach does not at present comply with the general rules of adaptation as set out in Annex XI, Section 1.5. Therefore, ECHA rejects all adaptations in the technical dossier that are based on Annex XI, 1.5.

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing (a) study record(s) for a sub-chronic toxicity study (90-day) (OECD TG 408) with the analogue substance [1,3(or1,4)-phenylenebis(1-ethylethylidene)]bis[tert-butyl] peroxide (CAS no 25155-25-3). However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

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.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA

considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. More specifically, based on the information provided, human inhalation exposure cannot be excluded. However, since the substance is a powder of moderate water solubility without reported local reactivity, there is no high concern for local effects in the respiratory tract following inhalation exposure that would require generation of information by the inhalation route. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

According to the test method EU B.26./OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

In your comments to the draft decision according to Article 50(1) of the REACH Regulation as well as in your updated dossier you state that you find it appropriate to commission an OECD 422 screening study on the target substance in rats by the oral route in order to strengthen the read-across justification to enable read-across of the source substance's OECD 408 data. You further propose ECHA to amend the the draft decision to reflect that the OECD 408 on the target substance is conditionally dependent upon the results of the OECD 422 study on the target substance. ECHA Secretariat agrees with this approach.

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 unless read-across to an acceptable study with a source substance can be sufficiently justified: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD TG 408) in rats.

Note for your consideration

ECHA notes that a revised version of OECD TG 408 may be adopted later on this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. After the adoption of the revised version of the OECD TG 408 you should test in accordance with that version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788.

Even if you start testing before the guideline is published, it is appropriate to consider including these endocrine-sensitive parameters in your testing protocol in accordance with the proposed revised version of the draft guideline (see http://www.oecd.org/env/ehs/testing/section4-health-effects.htm).

2. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH

Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. No such evidence is presented in the dossier. Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have not provided any study record of a screening for reproductive/developmental toxicity in the dossier that would meet the information requirement of Annex VIII, Section 8.7.1.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing (a) study record(s) for a screening study for reproductive/developmental toxicity (OECD TG 422) with the analogous substance [1,3(or1,4)-phenylenebis(1-ethylethylidene)]bis[tert-butyl] peroxide (CAS no 25155-25-3). However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

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.

According to the test methods OECD TG 421/422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with 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 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

In your comments to the draft decision according to Article 50(1) of the REACH Regulation as well as in your updated dossier you agree to perform this study. ECHA acknowledges your agreement.

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: Reproductive/developmental toxicity screening test (test method: OECD TG 421) *or* Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

Notes for your considerations

For the selection of the appropriate test, please consult ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, section R.7.5 and 7.6 (version 4.1, October 2015).

3. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in

Annexes VII to IX of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing (a) study record(s) for a pre-natal developmental toxicity study according to OECD 414 with the analogous substance [1,3(or1,4)-phenylenebis(1-ethylethylidene)]bis[tert-butyl] peroxide (CAS no 25155-25-3). However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

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.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.
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 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

In your comments to the draft decision according to Article 50(1) of the REACH Regulation as well as in your updated dossier you state that you find it appropriate to commission an OECD 422 screening study on the target substance in rats by the oral route in order to strengthen the read-across justification to enable read-across of the source substance's OECD 414 data.

You further propose ECHA to amend the the draft decision to reflect that the OECD 414 on the target substance is conditionally dependent upon the results of the OECD 422 study on the target substance. ECHA Secretariat agrees on this approach.

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 unless read-across to an acceptable study with a source substance can be sufficiently justified: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a first species (rat or rabbit) by the oral route.

Note for your consideration
ECHA notes that a revised version of OECD TG 414 may be adopted later on this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. After the adoption of the revised version of the OECD TG 408 you should test in accordance with that version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788.

Even if you start testing before the guideline is published, it is appropriate to consider including these endocrine-sensitive parameters in your testing protocol in accordance with the proposed revised version of the draft guideline (see http://www.oecd.org/env/ehs/testing/section4-health-effects.htm).

4. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Growth inhibition study aquatic plants" is a standard information requirement as laid down in Annex VII, Section 9.1.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

Column 2 of Annex VII, Section 9.1.2 specifies that the study does not need to be conducted if there are mitigating factors indicating that aquatic toxicity is unlikely to occur for instance if the substance is highly insoluble in water or the substance is unlikely to cross biological membranes.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for an Growth inhibition study aquatic plants (OECD TG 201/EU method C.3) with the analogue substance 1,4-bis[1-(tert-butylperoxy)-1-methylethyl]benzene (CAS no 25155-25-3), referred to as [1,3(or1,4)-phenylenebis(1-ethylethylidene)]bis[tert-butyl] peroxide in the Section 0 of the present decision. However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement cannot be accepted.

Furthermore, ECHA considers that the source study itself is not appropriate to cover the standard information requirement. The reporting of the study has several major flaws and thus does not meet the requirements of Annex XI, Section 1.5 of the REACH (adequate and reliable documentation of the applied method shall be provided):

- You report that the concentration of the substance is not maintained stable in solution. You claim that the disappearance was due to complete degradation of the parent compound. ECHA notes that this is in contrast with evidence provided in the registration dossier of the source substance: a) the source substance is slowly hydrolysed (half-life 74.7d at pH 7 and 25°C); b) the source substance is not readily biodegradable (0%, read-across with target substance); c) the source substance was shown to be highly adsorptive in the long-term invertebrate toxicity study, described in IUCLID Section 6.1.4.
- Growth rates of control samples is not reported, thus it is not possible to verify whether the validity criteria of OECD TG 201 were met.
- The composition of the test material is not provided in the technical dossier. The test material should be clearly defined in order to verify if it represents the source substance, the composition of which is not clarified either in the read-across

hypothesis (see Appendix 1, Section 0 of this decision).

Therefore 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.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 3.0, February 2016) Algae growth inhibition test (test method EU C.3. / OECD TG 201) is the preferred test to cover the standard information requirement of Annex VII, Section 9.1.2.

ECHA acknowledges that in your comments on the draft decision according to Article 50(1) of the REACH Regulation you agreed to perform the requested test with the registered substance.

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: Algae growth inhibition test, EU C.3./OECD TG 201).

Notes for your consideration

Due to the low solubility of the substance in water you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

5. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.
"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a *Daphnia Magna* reproduction test (OECD TG 211) with the analogue substance 1,4-bis[1-(tert-butylperoxy)-1-methylethyl]benzene (CAS no 25155-25-3), regarded as [1,3(or1,4)-phenylenebis(1-ethylethylidene)]bis[tert-butyl] peroxide in Appendix 1, Section 0 of the present decision. However, as explained above, your adaptation of the information requirement cannot be accepted.

In addition to the reasons given in Section 0 above, ECHA notes that the source study is not valid to cover the respective standard information requirement. The reporting of the study

does not meet the requirements of Annex XI, Section 1.5 of the REACH (adequate and reliable documentation of the applied method shall be provided):

- The composition of the test material in this study is not provided in the technical dossier. The test material should be clearly defined in order to verify if it represents the source substance, the composition of which is not clarified either in the read-across hypothesis (see Appendix 1, Section 0 of this decision).

Therefore, 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.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) *Daphnia magna* reproduction test (test method EU C.20. / OECD TG 211) is the preferred test to cover the standard information requirement of Annex IX, Section 9.1.5.

ECHA acknowledges that in your comments on ECHA's draft decision according to Article 50(1) of the REACH Regulation you agreed to perform the requested test with the registered substance. ECHA also acknowledges that you intend to update the study record for the study with the source substance (CAS 25155-25-3) in order to address the noted deficiency of the source study.

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: Daphnia magna reproduction test (test method: EU C.20./OECD TG 211).

Notes for your consideration

Due to the low solubility of the substance in water you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

6. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1. / 9.1.6.2. / 9.1.6.3)

"Long-term toxicity testing on fish" is a standard information requirement as laid down in Annex IX, Section 9.1.6. of the REACH Regulation. Adequate information on Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.), or Fish, short-term toxicity test on embryo and sac-fry stages (Annex IX, 9.1.6.2.), or Fish, juvenile growth test (Annex IX, 9.1.6.3.) needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex IX, Section 9.1.6., column 2. You provided the following justification for the adaptation: "*In accordance with column 2 of REACH Annex IX column II, long-term toxicity testing (as listed below) doesn't need to be proposed by the registrant as the chemical safety assessment according to Annex I indicates there is no need to investigate further the effects on aquatic organisms.*

- Long-term toxicity testing on fish (required in section 9.1.6., column 2 of REACH Annex IX),

- Fish early-life stage (FELS) toxicity test (required in section 9.1.6.1., column 2 of REACH Annex IX),

- Fish short-term toxicity test on embryo and sac-fry stages (required in section 9.1.6.2., column 2 of REACH Annex IX), - Fish, juvenile growth test (required in section 9.1.6.3., column 2 of REACH Annex IX)

According to claimed uses of [1,3-phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide, aquatic compartment exposure is likely. At the moment no data is available for characterizing [1,3-phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide long-term effects on organisms inhabiting aquatic compartment. Risk assessment demonstrated that there is no risk for those organisms using the PNEC derived based upon acute data, however a test on aquatic invertebrates is proposed in order to refine the PNEC value. For these reason, no long-term test on fish is proposed."

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.6., column 2. ECHA notes that the registered substance is poorly water soluble (WS=0.04 mg/L), no toxicity was observed in short-term tests up to the water solubility level and no valid data on invertebrate aquatic toxicity for the registered substance is available. Poorly soluble substances require longer time to be significantly taken up by the test organisms and so steady state conditions are likely not to be reached within the duration of a short-term toxicity test. For this reason, short-term tests may not give a true measure of toxicity for poorly soluble substances and toxicity may actually not even occur at the water solubility limit of the substance if the test duration is too short. Thus, long-term toxicity to aquatic organisms cannot be excluded and should be investigated. Annex VIII 9.1.3. and Annex VII 9.1.1. of the REACH Regulation explicitly recommend that long-term aquatic toxicity tests shall be considered if the substance is poorly water soluble.

You further suggest to test the effects on aquatic invertebrates, but such suggestion does not support an adaptation under Annex IX, Section 9.1.6., column 2 (see also section above on long-term testing on aquatic invertebrates).

ECHA considers that the information available in your chemical safety assessment and technical dossier does not rule out the possibility of the long-term effects to aquatic organisms and that further investigation is needed. Consequently, ECHA concludes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.6., column 2 and cannot be accepted.

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.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 3.0, February 2016) fish early-life stage toxicity test (test method OECD TG 210), fish short-term toxicity test on embryo and sac-fry stages (test method EU C.15. / OECD TG 212) and fish juvenile growth test (test method EU C.14. / OECD TG 215)

are the preferred tests to cover the standard information requirement of Annex IX, Section 9.1.6.

However, the FELS toxicity test according to OECD TG 210 is more sensitive than the fish, short-term toxicity test on embryo and sac-fry stages (test method EU C.15 / OECD TG 212), or the fish, juvenile growth test (test method EU C.14. / OECD TG 215), as it covers several life stages of the fish from the newly fertilized egg, through hatch to early stages of growth (see ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), *Chapter R7b, Figure R.7.8-4)*.

Moreover, the FELS toxicity test is preferable for examining the potential toxic effects of substances which are expected to cause effects over a longer exposure period, or which require a longer exposure period of time to reach steady state (ECHA *Guidance Chapter R7b,* version 4.0, June 2017).

In your comments on the draft decision according to Article 50(1) of the REACH Regulation you propose "*to use a tiered approach. First, the Long-term toxicity testing on aquatic invertebrates (under 5) needs to be conducted, followed by an update of the risk assessment. If the updated risk assessment shows safe use, then no long-term fish study should be required. Furthermore, the source substance is to have an OECD 210, and if the aquatic testing of the target substance under 4 and 5 above supports ecotox read-across between the source substance and target substance, then the OECD 210 endpoint for the target substance could be fulfilled via read-across of the source substance data.*".

As explained above, ECHA considers the registered substance to be poorly soluble and for this reason that information on long-term toxicity to fish is necessary irrespective of the result of the long-term aquatic study on invertebrates. For poorly soluble substances, no proper PNECs can indeed be derived from short-term information. Therefore, for poorly soluble substances, a valid risk assessment requires long-term/chronic toxicity information to be available on three trophic levels: i.e. fish, aquatic invertebrates and algae/aquatic plants. Only then will it be possible to conclude whether safe use of the substance is shown or not. However, ECHA also notes that you also indicated in your comments on the draft decision and in an attachment to your dossier that a long-term fish study (OECD 210) was ongoing for the source substance (CAS: 25155-25-3). You have proposed to use the outcome of the requested tests on algae (issue 4 of the present decision) and on *Daphnia* (issue 5 of the present decision), which you agreed to conduct both with the registered substance, as bridging studies to support the read-across for the long-term toxicity study on fish. ECHA agrees that if the results are consistent between the source and target substances for both the *Daphnia* and algae studies, then they can be used as bridging studies to support your read-across approach. The result of the ongoing OECD 210 test with the source substance (CAS: 25155-25-3) would then constitute an acceptable adaptation for the requested information on long-term toxicity to fish.

A Member State Competent Authority (MSCA) submitted a Proposal for Amendment (PfA) to further align the present Compliance Check (CCH) decision with the ongoing Testing Proposal (TP) decision whereby ECHA has agreed that you may test either the registered substance or the proposed analogue substance. Following the PfA, ECHA did not amend this CCH decision as it considers that while the analogue approach is acceptable for environmental fate endpoints, addressed in the TP decision, the read across approach is however not acceptable for the relevant (eco)toxicity endpoints due to the lack of bridging studies, as discussed above.

In your comments submitted in response to the MSCA PfA, you indicate that you agree with the PfA. Furthermore, in your comments submitted under the endpoint of long-term fish, you refer to the Substance Evaluation (SEv) decision on the substance, CAS: 25155-25-3 whereby it is given that the chronic aquatic studies are to be only conducted if the substance, CAS: 25155-25-3 is shown to fulfil the criteria for P and B. Furthermore, the chronic fish study is only to be conducted, if it is not possible to conclude on T based on the chronic daphnia study. As the performance of the chronic fish study is conditional upon the outcome of P and B and the result of chronic daphnia study under the SEv decision, it is uncertain if a chronic fish study will be performed. You propose to follow the same SEv tiered testing strategy under this Dossier Evaluation (DEv) decision.

You also wish ECHA to align the timeline of this decision with that of the SEv decision (deadline of 14 February 2022) to allow potential read-across for the present endpoint. You also indicate that you have performed two OECD 236 studies (OECD 236 - Fish Embryo Acute Toxicity (FET)) on both the registered substance and the substance, CAS: 25155-25-3. These studies have not been submitted to ECHA and are also not available in the current technical dossier.

ECHA notes that the scope of both Dossier Evaluation (DEv) and SEv processes differ. While SEv addresses a specific concern, such as PBT as in the decision for the source substance, DEv aims at the fulfilment of the standard information requirements set in REACH annexes and the subsequent risk characterisation for the registered substance. In the SEV decision, a tiered testing strategy is proposed to assess the PBT properties of the substance, CAS: 25155-25-3. ECHA notes that under DEv for this decision for the registered substance, the chronic test on fish is required due to the data gap in the standard information requirement at this tonnage level. ECHA also notes that as already discussed above, the aquatic ITS given in ECHA Guidance on information requirements and chemical safety assessment, v.4.0, June 2017, Chapter R7b, Section R.7.8.5.3) is not applicable, due to the substance having a low water solubility, data on three trophic levels, (aquatic invertebrates, fish and aquatic plants) is required for the derivation of the $PNEC_{aquatic}$ and subsequent risk assessment. ECHA considers that it is necessary to provide data for the present endpoint also for other purposes other than the PBT assesment.

Regarding your comments on the MSCAs's PfA on the timelines, ECHA notes that if the timelines for both DEv and SEv decisions woud be aligned, the timeline of the DEv decision would need to be extended significantly. In addition, ECHA does not consider that this extension is justified, as the SEv decision is addressing the substance, CAS: 25155-25-3 for this endpoint whilst the DEv decision is addressing the registered substance for this endpoint. Under DEv, there is currently no read-across approach justification available for this endpoint in the technical dossier. And also, there is a standard information requirement to provide chronic aquatic data on both aquatic invertebrates and fish to accurately assess the risks of the registered substance to the aquatic environment. In addition, regarding your comments on the MSCAs's PfA and on the initial draft decision, no read-across justification for this endpoint was submitted by you. It is the responsibility of you to develop any such adaptation.

Regarding your comments on the MSCAs's PfA on the available two OECD 236 - Fish Embryo Acute Toxicity (FET), whilst these acute studies have not been submitted to ECHA or are not in the current technical dossier, ECHA notes due to the physical chemical properties of the registered substance, notably low water solubility, the validity of these studies may be of

concern. However, as stated in the start of this draft decision, it is the responsibility of the registrant to develop any adaptation.

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: Fish, early-life stage (FELS) toxicity test (test method: OECD TG 210).

Notes for your consideration

Due to the low solubility of the substance in water you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

Deadline to submit the requested information in this decision

In the draft decision communicated to you, the time indicated to provide the requested studies and submit the study results to ECHA in a dossier update was 24 months from the date of adoption of the decision. In your comments on the draft decision, you requested an extension of this timeline to 36 months if the studies requested for endpoints 1, 2 and 3 have to be performed. However, you did not provide a detailed justification for this extension. However, ECHA Secretariat understands that evaluating the results of the OECD TG 422 screening study to determine whether it supports the proposed read-across justifies an extension of the originally proposed deadline. Hence, ECHA Secretariat agrees to extend the deadline by 6 months to 30 months.

In your comments you propose a deadline of 18 months in case only the study requested for endpoint 2 will be performed. ECHA agrees to this request. In that case all the information requested in the decision, including the read-across adaptations for requests 1 and 3, as well as the information for requests 4, 5 and 6 should be provided within 18 months.

Appendix 2: Procedural history

In parallel to the present draft decision ECHA notified you of a draft decision on a testing proposal for your registration (communication number TPE-D-2114351606-49-01/D) on 21 December 2016. You updated your registration with submission number [redacted] on 14 March 2017. However, due to technical reasons this submission failed. You made a second update on 6 June 2017 with submission number [redacted]. Due to the technical issues, ECHA exceptionally took this update into account.

The compliance check was initiated on 18 November 2016.

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. Furthermore, due to the testing proposal being evaluated in parallel, the technical issues and the consideration of the update in that case, ECHA exceptionally took the update with submission number [redacted] into account also for this compliance check. As a consequence, ECHA however did not amend the requests, but it agreed to amend the deadline for providing the information requested.

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

ECHA received a proposal for amendment and did not modify the draft decision.

ECHA invited you to comment on the proposed amendment.

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

In addition, you provided comments on the draft decision. These comments were not taken into account by the Member State Committee as they were considered to be outside of the scope of Article 51(5).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-58 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

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 request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In carrying out the test(s) 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 test(s) must be suitable to assess these. Furthermore, there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.