

Helsinki, 08 June 2022

Addressees

Registrant(s) of JS_78-63-7 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision

07/02/2019

Registered substance subject to this decision ("the Substance")

Substance name: Di-tert-butyl 1,1,4,4-tetramethyltetramethylene diperoxide

EC number: 201-128-1

Decision number: Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/F)**DECISION ON A COMPLIANCE CHECK**

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of **15 September 2025**.

Requested information must be generated using the Substance unless otherwise specified.

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

1. Long-term toxicity testing on fish (triggered by Annex VIII, Section 9.1.3., column 2; test method: OECD TG 210)
2. Simulation testing on ultimate degradation in surface water, as requested below (triggered by Annex VIII, Section 9.2.)
3. Soil simulation testing, as requested below (triggered by Annex VIII, Section 9.2.)
4. Sediment simulation testing, as requested below (triggered by Annex VIII, Section 9.2.)
5. Identification of degradation products, as requested below (triggered by Annex VIII, Section 9.2.)

B. Information required from all the Registrants subject to Annex IX of REACH

1. Extended one-generation reproductive toxicity study (triggered by Annex IX, Section 8.7.3., column 1; test method: OECD TG 443) by oral route, in rats, specified as follows:
 - Ten weeks pre-mating 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;
 - Cohorts 2A and 2B (Developmental neurotoxicity); and
 - Investigations on learning and memory function as described in paragraph 37 of the OECD TG 426.

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

2. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: OECD TG 210)
3. Simulation testing on ultimate degradation in surface water (Annex IX, Section 9.2.1.2.; test method: EU C.25./OECD TG 309) at a temperature of 12°C. Non-extractable residues (NER) must be quantified and a scientific justification of the selected extraction procedures
4. Soil simulation testing (Annex IX, Section 9.2.1.3.; test method: EU C.23./OECD TG 307) at a temperature of 12°C. Non-extractable residues (NER) must be quantified and a scientific justification of the selected extraction procedures and solvents must be provided.
5. Sediment simulation testing (Annex IX, Section 9.2.1.4.; test method: EU C.24./OECD TG 308) at a temperature of 12°C. Non-extractable residues (NER) must be quantified and a scientific justification of the selected extraction procedures and solvents must be provided.
6. Identification of degradation products (Annex IX, 9.2.3.; test method: using an appropriate test method)

Reasons for the request(s) are explained in the following appendices:

- Appendix entitled "Reasons common to several requests";
- Appendices entitled "Reasons to request information required under Annexes VIII to IX of REACH", respectively.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

For certain endpoints, ECHA requests the same study from registrants at different tonnages. In such cases, only the reasoning why the information is required at lower tonnages is provided in the corresponding Appendices. For the tonnage where the study is a standard information requirement, the full reasoning for the request including study design is given. Only one study is to be conducted; the registrants concerned must make every effort to reach an agreement as to who is to carry out the study on behalf of the other registrants under Article 53 of REACH.

How to comply with your information requirements

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

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

The studies relating to biodegradation are necessary for the PBT assessment. However, to determine the testing needed to reach the conclusion on the persistency of the Substance you should consider the sequence in which these tests are performed and other conditions described in Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to <http://echa.europa.eu/regulations/appeals> for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised¹ under the authority of Mike Rasenberg, Director of Hazard Assessment

¹ As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix on Reasons common to several requests

With a view to the comments received from the addressees of this decision, and the tonnage band for which their registrations were submitted (see the last Appendix of this decision), ECHA notes that the following common considerations only relate to the conditions for adaption of the standard information requirements for registrants subject to Annex VIII of REACH (Appendix A). It is pointed out that these considerations are not relevant where the same information is required by the standard information requirements under Annexes IX of REACH (Appendix B).

1. Triggers for further testing to clarify PBT properties of the Substance

Further testing to clarify degradation and bioaccumulation properties is triggered by the chemical safety assessment (CSA) if the substance is a potential PBT/vPvB substance (Annex VIII, Section 9.2., Column 2 as well as Annex I, Section 4; Annex XIII, Section 2.1). This is the case if the Substance itself or any of its constituents or impurities are present in concentration $\geq 0.1\%$ (w/w) or relevant transformation/degradation product meets the following criteria based on screening information:

- it is potentially persistent or very persistent (P/vP) as:
 - it is not readily biodegradable (i.e. $<60\%$ degradation in an OECD 301D),
- it is potentially bioaccumulative or very bioaccumulative (B/vB) as:
 - it has a high potential to partition to lipid storage (e.g. $\log K_{ow} > 4.5$).
 - for some groups of substances (e.g. ionisable substances, surfactants) other partitioning mechanisms may drive bioaccumulation (e.g. binding to protein/cell membranes) and high potential for bioaccumulation cannot be excluded solely based on its potential to partition to lipid;
 - it has a calculated BCF > 2000 .

Your registration dossier provides the following PBT/vPvB information:

- The Substance is not readily biodegradable (0% degradation after 56 days in a modified test equivalent to OECD TG 301D);
- The Substance has a high potential to partition to lipid storage based on the Log Kow of 7.34 (OECD 117; Powley and Snow, 2008);
- BCF QSAR (EPISuite: Arnot-Gobas model) results showing a calculated BCF of 46097 (assuming zero metabolism).
- Metabolism half-life results from *in vitro* trout liver S9 metabolism assay extrapolated to *in vivo* rate constants of metabolism, which were combined with the BCF QSAR results (EPISuite: Arnot-Gobas model) indicating a BCF value for the Substance between 521 and 839 L/Kg (Erhardt, 2008);
- A BCF study, considered by you to be unreliable (Klimisch score 4), showing BCF values of 3690 and 2250 L/Kg (non-guideline equivalent to OECD TG 305, author unknown, 2004).

In your PBT assessment in Section 2.3 of the registration dossier, you conclude that the Substance is not PBT/vPvB since;

- (1) the Substance undergoes rapid hydrolysis and *'using the extrapolated results of hydrolysis, the $\frac{1}{2}$ life of the substance is significantly shorter than that of 40 days'* therefore the P criteria are not met.
- (2) the Substance is not B based on the results of an *in vitro* to *in vivo* extrapolation (IVIVE) study (Erhardt, 2008) and, that while the expected degradation products are unknown, and may be P, they are not expected to be B based on Log Kow values.

The PBT/vPvB screening information above indicates that the Substance is a potential PBT/vPvB substance. Furthermore, we have assessed the information provided in your PBT assessment and identified the following issues.

With regards to the above point (1) on Persistence:

In the PBT assessment of the Substance in Section 2.3 of IUCLID you consider that the Substance is not persistent or very persistent based on the rapid hydrolysis of the Substance.

Annex XIII Section 3.2 lists the information considered in the assessment of P/vP properties when screening information indicates the substance may have PBT/ vPvB properties. Annex XIII Section 3.2.1 (a-c) states that the results (i.e. degradation half-life) from water, soil and sediment simulation studies must be used to compare against the P/vP criteria stipulated in Annex XIII Sections 1.1.1 and 1.2.1 (e.g. substance fulfils the P criteria if degradation half-life >40 days in fresh or estuarine water).

Furthermore, ECHA Guidance R.11.4.1.1.1 states that concern for P/vP cannot be removed by significant and substantial loss of the parent substance by hydrolysis alone, but additional evidence is also needed to demonstrate rapid hydrolysis across all relevant environmental compartments (including marine water, estuarine water, sediment and soil). In addition, as hydrolysis is only primary degradation, careful consideration needs to be given also to the potential formation of stable degradation products with PBT/vPvB properties. In your dossier, you have not provided simulation studies with the Substance under relevant environmental conditions.

In your comments on the draft decision you acknowledge that no simulation studies have been performed and that further testing is needed to conclude on the P/vP properties of the Substance.

In your PBT assessment of the Substance you concluded that: *'using the extrapolated results of hydrolysis, the ½ life of the substance is significantly shorter than that of 40 days required to meet the P criterion and therefore the parent substance...[..] does not meet the P/vP criterion however, the degradation products may be considered potentially P.'*

As explained above, the Substance is potentially P/vP based on screening information, and in the absence of simulation studies under relevant environmental conditions, it is currently not possible to conclude on P/vP criteria.

Your conclusion that the Substance is not P/vP based on hydrolysis half-life is not valid because only half-life values derived from simulation studies can be used to compare against persistence criteria of Annex XIII. Furthermore, in concluding on the P criteria in your PBT assessment, you have focused only on hydrolysis of the parent Substance. However, you have not provided any evidence to demonstrate rapid hydrolysis across all relevant environmental compartments. In addition, you have not adequately addressed the potential formation of stable degradation products with PBT/vPvB properties. You recognise that potentially P/vP degradation products may be formed but you have not provided definitive information identifying all relevant degradation products and assessed their PBT/vPvB properties as explained in B.6.

In your comments on the draft decision you acknowledge that the Substance may potentially be P based on the negative results from the ready biodegradability test, and based on further data on hydrolysis and adsorptive properties of the substance indicating a hydrolysis half-life of more than 21 days (OECD 111 [REDACTED]; 2019; Non-guideline study, [REDACTED], 2019). The hydrolysis studies provided with your comments do not provide any additional information

on the identity of transformation/degradation products or their potential to meet the PBT/vPvB criteria.

In your comments on the draft decision you state that you have revised the PBT assessment, in line with the draft decision, acknowledging that a conclusion on P/vP cannot be based only on available hydrolysis data for the Substance.

In your comments on the draft decision you agree that the Substance may be considered to be potentially P and that further testing is needed to draw a firm conclusion on P.

With regards to the above point (2) on Bioaccumulation:

In the PBT assessment of the Substance in Section 2.3 of IUCLID you consider that the Substance is not bioaccumulative or very bioaccumulative based on the results of an *in vitro* to *in vivo* extrapolation (IVIVE) study [REDACTED], 2008).

When using the approach of combining metabolism data from the *in vitro* liver S9 with the BCF QSAR (the *in vitro* to *in vivo* (IVIVE) extrapolation approach) OECD GD 280 should be followed. OECD GD 280 states that this approach has been validated only for neutral organic compounds with Log Kows within the range 3-8. The Substance is an organic peroxide and not a neutral organic compound and hence is outside the applicability domain of the IVIVE approach. Therefore the IVIVE results are not reliable and cannot be used to conclude on the B properties of the Substance.

In the PBT assessment of the Substance in Section 2.3 of IUCLID you further indicate that the potential degradation products are not expected to be B.

As explained in Appendix B.6., you have not provided definitive information identifying all relevant degradation products. You state that the expected degradation products would not be bioaccumulative based on Log Kow (as Log Kows indicate low potential to partition to lipid storage). However, one of the degradation products you hypothesize is expected to be formed (2,5-dimethyl-2,5-hexanediol) is surface active hence the potential for bioaccumulation cannot be based only on lipid partitioning as uptake may be driven by mechanisms other than lipid partitioning as explained above.

In conclusion, the Substance screens for bioaccumulation based on the Log Kow (7.34) and BCF QSAR results (estimated BCF with zero metabolism >5000 L/Kg). In addition, your dossier provides a BCF study which you consider not reliable showing BCF values of 3690 and 2250 L/Kg indicating the Substance is potentially B (i.e. >2000 L/Kg). In addition, the bioaccumulation potential of expected degradation products has not been adequately assessed.

Hence, available evidence indicates potential for bioaccumulation.

Therefore, your conclusion of the P/vP and B/vB properties is not reliable and the chemical safety assessment (CSA) indicates the need for further investigation of the PBT/vPvB properties.

The examination of the available information or adaptations, as well as the selection of the requested tests and the tests design are addressed respectively in Appendices B.3-B.6.

Appendix A: Reasons to request information required under Annex VIII of REACH

1. Long-term toxicity testing on fish

Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH (Section 9.1.3.). Long-term toxicity testing on fish must be considered (Section 9.1.3., Column 2) if the substance is poorly water soluble.

You have provided a short-term toxicity to fish study according to OECD TG 203 ([REDACTED] 2004) but no information on long-term toxicity on fish for the Substance.

We have assessed this information and identified the following issue:

Poorly water soluble substances require longer time to reach steady-state conditions. As a result, the short-term tests does not give a true measure of toxicity for this type of substances and the long-term test is required. A substance is regarded as poorly water soluble if, for instance, it has a water solubility below 1 mg/L or below the detection limit of the analytical method of the test material (ECHA Guidance R.7.8.5).

You have provided information which indicates that the water solubility of the Substance is 152 µg/L (OECD TG 105)

Therefore, the Substance is poorly water soluble and information on long-term toxicity on fish must be provided.

The examination of the information provided, as well as the selection of the requested test and the test design are addressed under section B.2.

In the comments to the draft decision you agree to perform the requested study.

2. Simulation testing on ultimate degradation in surface water

Further degradation testing must be considered if the chemical safety assessment (CSA) according to Annex I indicates the need to investigate further the degradation of the substance (Annex VIII, Section 9.2., Column 2).

As explained in the Appendix on Reasons common to several requests, the Substance is a potential PBT/vPvB substance and the chemical safety assessment (CSA) indicates the need for further degradation investigation.

In your comments on the draft decision you acknowledge that further testing is needed to conclude on P for the Substance. However, you propose to omit the surface water simulation study, begin with the sediment simulation study, and then perform the soil simulation study, if needed (based on the results of the sediment study). You indicate that the surface water study (OECD TG 309) should be omitted for the following reasons:

1. The surface water study will be technically difficult to conduct as the Substance is adsorptive (Log Kow 7.34, Log Koc 4.72), has a low water solubility (152 µg/L), and may potentially be volatilized from the water phase.
2. You estimate that the Substance will partition primarily to sludge during waste water treatment (>90% adsorption to sludge estimated by EPIWIN) and be highly removed from effluents (>99% removal predicted (CAS study; [REDACTED], 2013)). You indicate that the surface water compartment is therefore the least relevant compartment for the Substance, and that testing in sediment, and soil, is preferred

We have assessed the information provided in your comments to the draft decision and identified the following issue:

The ECHA Guidance R.11.4.1.1.1 states that the OECD TG 309 is the preferred test to start persistency assessment. If another test is selected, or it is proposed to omit the surface water study, this should be justified, based on the following:

- Aquatic testing is not technically feasible i.e. it can be demonstrated that it has been impossible, with allocation of reasonable efforts, to develop suitable analytical methods and other test procedures to accomplish testing in surface water so that reliable results can be generated. Appropriate analytical methods should have a suitable sensitivity and be able to detect relevant changes in concentration (including that of metabolites). Generally, when water solubility of a substance is very low (typically below 1 µg/L), testing on sediment (OECD TG 308) and/or soil (OECD TG 307) may be needed instead of a pelagic test (OECD TG 309);
- The aquatic compartment is not considered relevant at all, and there are compartment specific concerns for the sediment and soil compartments, including indications from available data (e.g. literature) suggesting that persistence is likely to occur in a different environmental compartment (i.e. in soil or sediment).

We have assessed your comments and note the following issues:

- Based on the information in the dossier the water solubility of the Substance is 152 µg/L which indicates that conduct of the surface water simulation study is technically feasible.
- The aquatic compartment is considered to be a relevant environmental compartment since, by default, the water compartment receives significant amount of emissions directly or indirectly, and transports/distributes the substance through e.g. deposition and run-off (unless based on the fate and release(s) of the substance, it is considered that the water compartment is not a relevant environmental compartment at all). Once entering water, a substance may stay there for very long time and be spread over long distances before it reaches other environmental compartments (via environmental transport, partitioning and distribution processes) such as sediments or (via air) the soil compartment. In addition, particularly for lower water solubility substances which tend to be adsorptive, the OECD TG 309 (with a default concentration of suspended solids of 15 mg dw/L) minimizes potential NER formation. If NER is formed at significant levels in the OECD TGs 307 and 308 studies, this can be difficult to interpret and compare with degradation half-lives criteria of Annex XIII to the REACH Regulation (ECHA Guidance R.11.4.1.1.1). Furthermore, the information provided on partitioning to sludge and removal from effluents indicate that releases to the water compartment would be reduced by these processes, but would not be eliminated. Therefore, you have not demonstrated that the water compartment is not a relevant compartment at all. For these reasons, based on the information provided in the dossier and in your comments, the conditions for omitting the surface water study are not fulfilled and the information from the OECD TG 309 is relevant for the Substance.
- As stated in Appendix D of this decision you are advised to consider the intrinsic properties of the Substance, and its identified uses and release patterns, when determining the sequence of simulation degradation testing. You may therefore choose to conduct simulation studies starting with the worst case scenarios for persistence, with appropriate justifications. In cases where the substance is adsorptive, and releases to surface water are expected to be limited, starting with simulation testing in the sediment/soil compartments may be justified. However, based on the information provided in the dossier, and in your comments on the draft decision, the water compartment cannot be considered as not relevant at all and still warrants investigations in an OECD TG 309, as indicated above. The deadline in this decision allows adequate time for sequential testing.

The examination of the available information or adaptations, as well as the selection of the requested test and the test design are addressed respectively in Appendix B.3.

3. Soil simulation testing

Further degradation testing must be considered if the chemical safety assessment (CSA) according to Annex I indicates the need to investigate further the degradation of the substance (Annex VIII, Section 9.2., Column 2).

As already explained in the Appendix on Reasons common to several requests, the Substance is a potential PBT/vPvB substance. Therefore, the chemical safety assessment (CSA) indicates the need for further degradation investigation.

In your comments on the draft decision you acknowledge that further testing is needed to conclude on P/vP for the Substance. You propose to conduct the sediment simulation study first, and then perform the soil simulation study, if needed (based on the results of the sediment study: tiered testing strategy).

As stated in Appendix D of this decision you are advised to consider the intrinsic properties of the Substance, and its identified uses and release patterns, when determining the sequence of simulation degradation testing. You may therefore choose to conduct simulation studies starting with the worst case scenarios for persistence, with appropriate justifications. The deadline in this decision allows adequate time for sequential testing. The sequence of simulation tests must continue unless there is a conclusion of vP in a previous test.

The examination of the available information or adaptations, as well as further information on the selection of the approach to generate this information are addressed in Appendix B.4.

4. Sediment simulation testing

Further degradation testing must be considered if the chemical safety assessment (CSA) according to Annex I indicates the need to investigate further the degradation of the substance (Annex VIII, Section 9.2., Column 2).

As already explained in the Appendix on Reasons common to several requests, the Substance is a potential PBT/vPvB substance. Therefore, the chemical safety assessment (CSA) indicates the need for further degradation investigation.

The examination of the available information or adaptations, as well as further information on the selection of the approach to generate this information are addressed in Appendix B.5.

In the comments to the draft decision you agree to perform the requested study.

5. Identification of degradation products

Further degradation testing must be considered if the chemical safety assessment (CSA) according to Annex I indicates the need to investigate further the degradation of the substance (Annex VIII, Section 9.2., Column 2).

As already explained in the Appendix on Reasons common to several requests, the Substance is a potential PBT/vPvB substance. Therefore, the chemical safety assessment (CSA) indicates the need for further degradation investigation.

The examination of the available information or adaptations, as well as further information on the selection of the approach to generate this information are addressed in Appendix B.6.

In the comments to the draft decision you agree to identify the degradation products in the sediment simulation study.

Appendix B: Reasons to request information required under Annex IX of REACH

1. Extended one-generation reproductive toxicity study

The basic test design of an extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is a standard information requirement under Annex IX to REACH, 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 the conditions under which the study design needs to be expanded.

In your dossier you have provided the following statement: *"No effects on reproductive organs were found in the 90-day OECD 408 study summarized elsewhere. In addition, there were no developmental effects reported in an OECD 414 study. These results suggest a low risk for reproductive toxicity; therefore, we are waiving the requirement for a reproductive toxicity study"*.

We have assessed this information and identified the following issue(s):

As already mentioned above, an EOGRT study is required if the available repeated-dose studies indicate adverse effects or concerns related to reproductive toxicity.

You consider that no adverse effects on reproductive organs or tissues have been observed in the available repeated dose toxicity studies.

However, adverse effects on reproductive organs or tissues or other concerns in relation with reproductive toxicity are observed in the repeated dose toxicity studies provided in the registration dossier. More specifically:

- A significant reduction in epididymal spermatid count in animals from the high dose group (150 mg/kg bw/day) was reported in the OECD TG 408 study [REDACTED], 2014).
- In addition, evidence of testicular tubular degeneration/atrophy is reported at all dose levels (20, 60 and 200 mg/kg bw/day) in the OECD TG 407 study [REDACTED], 2011).

In your comments to the draft decision, you indicate that the finding of a significantly reduced epididymal spermatid count was an isolated finding of no toxicological relevance. You provided tabular data and noted that *"the range in controls was between 238 and 469 with two additional very high values of 604 and 707; in animals of the high dose group the range was between 148 and 567, thus quite some overlap between the two groups."* Furthermore, you specify that *"Without the two outliers in the control group, the mean control value would be 298 versus 250 in the high dose group, and statistical significance would not be reached. Moreover, there were no associated histopathological findings in the epididymides, and in addition, no treatment-related adverse effect on sperm concentration, motility, morphology or homogenisation resistant epididymal (and testicular) spermatid counts was apparent."*

In addition, you indicate that in the OECD TG 407 study, the evidence of testicular atrophy was with similar incidence/severity among the groups and in the absence of a dose-response relationship, you consider that the finding is of no toxicological relevance.

Related to the cauda epididymal spermatid counts, ECHA notes that in the control group there are no males with concentrations reported below 200 million / gram cauda epididymis (CE) whereas in the high dose group, five out of ten males had sperm counts below 200 million / gram CE. Furthermore, while you have considered presence of outliers in the control group (604 and 707 million / gram CE), no considerations were given for the presence of outlier values in the high dose group. As an example, in the control group, the highest sperm count value (707.9 million/gram CE) is 1.88 times the standard deviation (SD; 155.0) above the mean value (417.0) for control group (mean \pm 1.88xSD). Similarly, in the high dose group, the highest value reported (567.6 million/gram CE) is 2.35 times the SD (135.0) above the

mean value (250.0) for the high dose group (mean \pm 2.35xSD). If the outlier in the high dose group is also removed for the analysis, the clear reduction in the mean CE spermatid counts in the high dose remains with the mean spermatid counts being 357.2 for control compared to 214.7 for the high dose group (-40% of control). Furthermore, in the absence of information on the mid dose and low dose groups, the possible dose dependency cannot be ruled out.

While no associated histopathological findings or effects on sperm motility and morphology were reported, the significantly reduced cauda epididymal spermatid counts in the OECD TG 408 study show a concern in relation with reproductive toxicity. As specified in ECHA Guidance R.7.a, effects on sperm parameters analysis are considered a trigger for the EOGRT study at REACH Annex IX level.

Furthermore, while the evidence of testicular tubular degeneration/atrophy does not show dose dependency, and is only observed in limited number of animals, ECHA notes that it is observed in all treated groups but not in control animals. This can be considered a supporting evidence for the reproductive toxicity concern as indicated by the significantly reduced epididymal spermatid counts in the OECD 408 study.

You propose a tiered approach to investigate the male fertility. You propose that a fertility/developmental screening study (OECD TG 421) (including thyroid weight, pathology and hormone measurements) would be conducted first with the Substance to evaluate if the male testis findings are of toxicological relevance and to confirm if an EOGRTS study would be warranted at Annex IX.

However, as explained above, ECHA considers that the existing information on the Substance including effects on spermatid counts supported by findings in testis, is sufficient to conclude that according the Annex IX, section 8.7.3, column 1, the EOGRT study is triggered at Annex IX. This concern cannot be outweighed by findings from a screening study.

Therefore, an EOGRT study according to the OECD TG 443 as specified in this decision is an information requirement for your registration, because Column 1 criteria at Annex IX, section 8.7.3 are met.

The specifications for the study design

Premating exposure duration and dose-level setting

The length of pre-mating exposure period must be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks pre-mating exposure duration is required to obtain results adequate for classification and labelling and /or risk assessment. There is no substance specific information in the dossier supporting shorter pre-mating exposure duration².

Therefore, the requested pre-mating exposure duration is at least ten weeks.

In order to be compliant and not to be rejected due to too low dose levels, the highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

² ECHA Guidance R.7a, Section R.7.6.

If there is no relevant data to be used for dose level setting, it is recommended that range-finding results are reported with the main study.

You have to provide a justification with your study results 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.

Existing information on the Substance itself derived from available *in vivo* studies (OECD TG 408 [REDACTED] 2014], 28-day toxicity study [JECDB report]) shows evidence of toxicity on the thyroid. More specifically, significantly increased absolute and relative thyroid weights and follicular thyroid hyperplasia in 5/5 males and 5/5 females (vs. 0/5 in control animals, respectively) were reported in the high dose males and females (1000 mg/kg bw/day) in a 28-day repeated dose toxicity study (JECDB report). In addition, in a 90-day study ([REDACTED] 2014), diffuse follicular thyroid hypertrophy was reported at all dose levels (15, 50 and 150 mg/kg bw/day), in both male and female rats. The thyroid weights (or the thyroid hormones) were not measured.

In your comments to the draft decision, you indicate that in the 28-day study ([REDACTED] 2011), only relative thyroid weight was increased in females at top dose, without clear dose-response or histopathological changes. In addition, you indicate that in another 28-day study (JECDB report), the effects on thyroid were reported only at top dose of 1000 mg/kg bw/day and that the effects showed reversibility within two weeks. In the 90-day study, the minimal to mild follicular hypertrophy was reported in all dose levels without a dose-response relationship. You state that *"The underlying mechanism for this finding in treated animals was not apparent as it was also seen in controls; an explanation for its development in treated rats could be a perturbation of thyroid hormone synthesis, transport or metabolism."* You consider that *"since the rat thyroid gland has been shown to be markedly more sensitive than humans in its response to xenobiotics (Chandra et al, 2013) it is reasonable to conclude that the minor, nondose related finding seen in this study, and also seen in controls, would not carry a significant risk to humans."*

ECHA notes that in the JECDB 28-day study (JECDB report), significant increases in absolute and relative thyroid weights were reported in the main study, and following the two weeks recovery the thyroid weights remained increased in both males and females. Also, while the incidences of histopathological findings in thyroid after two weeks recovery were reduced, diffuse follicular cell hyperplasia was still reported for both males and females. Therefore, it cannot be concluded that the effects on thyroid were fully reversible within the study. In addition, some recovery observed following cease of exposure in an experimental study does not remove the concern for potential exposure induced thyroid system disruption occurring during development.

The changes in thyroid weights and histopathology reported only at the top dose of 1000 mg/kg bw/day, but not at mid-dose of 200 mg/kg bw/day in the 28-day study (JECDB report), are consistent with the other 28-day study with the Substance ([REDACTED] 2011) where only minor increase in relative thyroid weight was reported in female rats at the top dose of 200 mg/kg bw/day as you indicate in your comments. In addition, thyroid histopathology was

reported at all doses in the 90-day study with most treated males with 9-10 out of 10 males in each dose group showing minimal to mild follicular hypertrophy compared to 5/10 males in the control group. In females the incidence of mild to minimal follicular hypertrophy was dose dependently increased (total incidence of 3/10, 7/10, 8/10 and 10/10 in controls, low dose, mid dose and high dose, respectively). These findings further support that the thyroid system is affected by the Substance. The higher top dose in the JECDB 28-day study and the longer duration of the 90-day study may explain the lack of or minimal thyroid effects observed in another 28-day study (██████████, 2011) conducted only up to 200 mg/kg bw/day.

According to the ECHA Guidance R.7.a., the cohorts 2A/2B can be triggered in case of a particular concern related to the (developmental) neurotoxicity. A particular concern may be focused on specific type of effects or mechanisms of actions based on e.g. existing information on effects from various different data sources and on a combination of two or several indications (e.g. for a mode of action). According to the guidance, the signs of thyroid toxicity indicating potential changes in thyroid hormone levels can be considered a specific mechanism/mode of action closely linked to (developmental) neurotoxic effects.

Furthermore, the ECHA/EFSA Guidance for the identification of endocrine disruptors³ specifies that "In the absence of substance-specific data which provide proof of the contrary, humans and rodents are considered to be equally sensitive to thyroid-disruption (including cases where liver enzyme induction is responsible for increased TH clearance)". You have not provided substance-specific data which would provide proof that the observed thyroid-related effects would not be relevant to humans.

Therefore, based on the thyroid effects including both thyroid weight changes and histopathology, reported in two studies conducted with a Substance, in a 90-day study (██████████, 2014) and in a 28-day study (JECDB), it is concluded that there is a particular concern for thyroid related mechanism/mode of action and the cohorts 2A/2B are triggered.

Based on the above, the developmental neurotoxicity Cohorts 2A and 2B need to be conducted.

Cognitive functions: learning and memory

Paragraph 51 of OECD 443 provides that, "If existing information indicates the need for other functional testing (e.g. sensory, social, cognitive), these should be integrated without compromising the integrity of the other evaluations conducted in the study."

The Substance caused changes in thyroid weight and histopathology in the OECD TG 408 study (██████████, 2014) and in the 28-day toxicity study (JECDB report), and so perturbs thyroid hormone signalling. It is known that perturbation of thyroid hormone signalling in offspring affects spatial cognitive abilities (learning and memory) [1-3].

Therefore, it is necessary to conduct spatial learning and memory tests for F1 animals. The spatial learning and memory tests must be performed in accordance with OECD 426 paragraph 37, i.e. at adolescence (e.g. PND 25±2 days) and young adulthood (PND 60 and older).

In your comments on the Proposal for Amendment, you argue the following:

(a) that the substance does not perturb thyroid signalling, using the same arguments about thyroid signalling you previously raised in your comments on the draft decision in respect of

³ <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5311>

triggering the DNT cohorts. You additionally suggest that the JECDB study should be a Klimisch 4 study.

(b) that there are no signs that would support the need for other functional sensory, social or cognitive testing. Moreover, you argue that there is no information or argumentation provided why this [the hypothesis that the Substance perturbs thyroid signalling] would specifically apply to the Substance and what this existing information would be.

(c) that the three references [1-3] showed negative and inconsistent results, and specifically that [1] showed inconsistent results between the Morris Water Maze and Radial Arm Maze and that [3] cannot be assessed.

Last, (d) you make reference to the decision of ECHA's Board of Appeal in case A-005-2014 and in particular the three cumulative conditions concerning request for information under substance evaluation.

ECHA has addressed your arguments under (a) in its response to your comments on the draft decision with regard to the triggering of DNT cohorts (see above under '*Cohorts 2A and 2B*'). ECHA further notes that there is consistency among the [REDACTED] (28-day), OECD TG 408 (90-day) and JECDB (28-day) studies in respect of the thyroid effects. ECHA does not consider the JECDB study to be unreliable.

In relation to your arguments under (b), ECHA has already explained that the Substance affects thyroid hormone signalling, and that thyroid hormone signalling is a mode of action which affects spatial cognitive abilities (learning and memory).

Further, in relation to your arguments under (c), the three studies all show that interference with thyroid hormone signalling affects spatial cognitive abilities. Specifically with respect to [3], thyroid hormones were measured in dams and pups, and the effect of propylthiourea (PTU) on hippocampal-dependent learning and memory in adult offspring using an object in-location test (OLT) was statistically significant. ECHA agrees that in [1], PTU treatment caused significant effects in the Radial Arm Maze, but not the Morris Water Maze. Nonetheless, ECHA considers that the effects of perturbation of thyroid hormone signalling on spatial cognitive abilities is consistent in the three studies. ECHA has already provided observations on the most appropriate tests for spatial cognitive abilities (see below '*Observations for the spatial learning and memory testing*').

Regarding your arguments under (d), ECHA notes that the DNT cohorts are triggered on account of a particular concern for developmental neurotoxicity caused by the Substance's effects on the thyroid, as already explained above. Further, as also set out above, OECD 443 paragraph 51 provides that other functional studies should be incorporated if there is a need, and ECHA has explained that the Substance's effects on thyroid hormone signalling show a need to investigate these parameters.

Last, note that the cumulative conditions set out in the abovementioned case A-005-2014 concern specifically requests for information under the substance evaluation process and therefore are not relevant for information requests under compliance check.

- [1] Axelstad *et al.* (2008) Developmental neurotoxicity of Propylthiouracil (PTU) in rats: Relationship between transient hypothyroxinemia during development and long-lasting behavioural and functional changes. *Toxicol. Appl. Pharmacol.* 232, 1-13.
- [2] van Wijk *et al.* (2008) Perinatal and chronic hypothyroidism impair behavioural development in male and female rats. *Exp. Physiol.* 93, 1199-1209.
- [3] Amano *et al.* (2018) Effects of Mild Perinatal Hypothyroidism on Cognitive Function of Adult Male Offspring. *Endocrinol.* 159(4), 1910-1921.

Observations for the spatial learning and memory testing

OECD TG 426, paragraph 37 presents examples of test methods for different types of associative learning and memory. Among the tests given in OECD TG 426, paragraph 37, you should conduct the Morris water maze test or Radial arm maze test at one time point, and the Cincinnati water maze test at the other time point to investigate spatial learning and memory, as these appear to be the most sensitive tests [4-7].

Investigations of spatial learning and memory should not compromise the integrity of the study. In OECD TG 443 adverse effects on sexual function and fertility may limit the number of offspring available for developmental investigations. Dosing must be based on the considerations provided above ('Dose-level setting'), and dosing must not be lowered in order to get a sufficient number of offspring. The priority of the OECD TG 443 test is to identify potential effects on sexual function and fertility.

Taking into account the practical aspects of conducting the OECD TG 443 study, as an alternative to Cohort 2A, the investigations on spatial learning and memory may also be conducted in Cohort 1A animals which can be allocated to two sets of animals, 10 males and 10 females in both; the first set of animals to be tested at adolescence and the other set of animals at young adulthood.

- [4] Levin E. (2015) Learning about cognition risk with the radial-arm maze in the developmental neurotoxicology battery. *Neurotoxicol Teratol.* 52, 88-92.
- [5] Vorhees and Williams (2015) Reprint of "Value of water mazes for assessing spatial and egocentric learning and memory in rodent basic research and regulatory studies". *Neurotoxicol Teratol.* 52, 93-108.
- [6] Vorhees and Makris (2015) Assessment of learning, memory, and attention in developmental neurotoxicity regulatory studies: synthesis, commentary, and recommendations. *Neurotoxicol Teratol.* 52, 109-115.
- [7] Vorhees and Williams (2016) Cincinnati water maze: A review of the development, methods, and evidence as a test of egocentric learning and memory. *Neurotoxicol Teratol.* 57, 1-19.

Species and route selection

The study must be performed in rats with oral⁴ administration.

Further expansion of the study design

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, or Cohort 3 if relevant information becomes available from other studies or during the 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. 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 Guidance⁵.

2. Long-term toxicity testing on fish

Long-term toxicity testing on fish is an information requirement under Annex IX to REACH (Section 9.1.6.).

⁴ ECHA Guidance R.7a, Section R.7.6.2.3.2.

⁵ ECHA Guidance R.7a, Section R.7.6.

You have provided the following justification to omit the study:

'Based on the Organic Peroxides consortium's position paper "Adaption of the Assessment Factor for Aquatic PNEC Derivation for Organic Peroxides - Low acute to chronic ratio" (author: CEHTRA, Report no. CFR-12.012), see also attachment in IUCLID section 13) fish are generally considered the least sensitive of the 3 trophic levels, thus the performance of a long term test will have no added value to the risk assessment process.'

We have assessed this information and identified the following issue:

A registrant may only adapt this information requirement based on the general rules set out in Annex XI. It is noted that Column 2 of Annex IX, Section 9.1, does not allow omitting the need to submit information on long-term toxicity to fish under Column 1 (Decision of the Board of Appeal in case A-011-2018).

Your justification to omit this information does not refer to any legal ground for adaptation under Annex XI to REACH.

Therefore, you have not demonstrated that this information can be omitted.

Your adaptation is therefore rejected.

In the comments to the draft decision you agree to perform the requested study.

Study design

To fulfil the information requirement for the Substance, the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is the most appropriate (ECHA Guidance R.7.8.2.).

The Substance is difficult to test due to the low water solubility (152 µg/L, OECD TG 105), adsorptive properties (based on Log Kow 7.34 (OECD TG 117) and Log Koc 4.72 (OECD TG 121)) and potentially rapid hydrolysis (e.g. half-life of <3 hours at 25°C and pH 7; OECD TG 111 (██████, 2011)).

The OECD TG 210 specifies that, for difficult to test substances, you must consider the approach described in the OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Considering that the Substance is rapidly hydrolysable it is important to take into account the relative toxicities of the parent test chemical and degradation products to determine the appropriate test design and test media preparation methods for the Substance.

Taking the potentially rapid hydrolysis, but also low solubility and adsorptivity, of the parent substance into account it may be difficult to achieve and maintain the desired exposure concentrations of the Substance or its hydrolysis products. Therefore, you must monitor the test concentration(s) of the Substance, or its hydrolysis products, throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in the OECD TG 210. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance, or the hydrolysis product(s), in the test solutions.

3. Simulation testing on ultimate degradation in surface water

Simulation testing on ultimate degradation in surface water is an information requirement under Annex IX to REACH (Section 9.2.1.2.).

You have provided the following information:

- A simulation test in aerobic sewage treatment with activated sludge according to OECD TG 303A showing 0% degradation (IUCLID Section 5.2.2).

We have assessed the information and identified the following issues

To fulfil the information requirement and to allow concluding on the P/vP criteria, ultimate biodegradation simulation tests must simulate degradation under relevant environmental conditions, such as those found in surface water (Annex VIII, Section 9.2. and Annex XIII to REACH; ECHA Guidance R.11.4.).

Your registration dossier provides a simulation test in aerobic sewage treatment with activated sludge units (OECD TG 303A) study.

The SCAS test (i.e. OECD TG 303A) cannot be used for this endpoint since it does not simulate degradation under relevant environmental conditions. For this reason, it also cannot be used to conclude that a substance does not fulfil the criteria for P (ECHA Guidance R.11.4.1.1.).

In your comments on the draft decision you acknowledge that this type of SCAS test cannot be used to fulfil this information requirement.

Therefore the information requirement is not met.

In your comments on the draft decision you acknowledge that further testing is needed to conclude on P for the Substance. However, you propose to omit the surface water simulation study, begin with the sediment simulation study, and then perform the soil simulation study, if needed (based on the results of the sediment study). You indicate that the surface water study (OECD TG 309) should be omitted for the following reasons:

1. The surface water study will be technically difficult to conduct as the Substance is adsorptive (Log Kow 7.34, Log Koc 4.72), has a low water solubility 152 µg/L, and may potentially be volatilized from the water phase.
2. You estimate that the Substance will partition primarily to sludge during waste water treatment (>90% adsorption to sludge estimated by EPIWIN) and be highly removed from effluents (>99% removal predicted (CAS study; ██████████, 2013)). You indicate that the surface water compartment is therefore the least relevant compartment for the Substance, and that testing in sediment, and soil, is preferred

We have assessed the information provided in your comments to the draft decision and identified the following issue:

A registrant may only omit this information requirement based on the specific rules set out for such adaptation in Column 2 of Annex IX or the general rules set out in Annex XI. It is noted that Column 2, Section 9.2.1.2 of Annex IX describes that the study does not need to be conducted if the substance is readily biodegradable.

Your justification to omit this information does not refer to any legal ground for adaptation under Annex XI to REACH. In addition, the fact that the Substance is not readily biodegradable

indicates a need for simulation testing, instead of a possibility to omit the information based on column 2 of Annex IX, Section 9.2.1.2.

Therefore, you have not demonstrated that this information can be omitted.

In the comments to the draft decision, you further indicate that the surface water simulation study (OECD TG 309) should be omitted because it is technically difficult to conduct. ECHA understands that you may consider an adaptation of this information requirement under Annex XI Section 2.

However, under Section 2 of Annex XI, a study may be omitted if it is not technically possible to conduct the study as a consequence of the properties of the substance (Annex XI, Section 2). In order to demonstrate that OECD TG 309 is technically unfeasible, you must provide evidence that it has been impossible, with allocation of reasonable efforts, to develop suitable analytical methods and other test procedures to accomplish testing in surface water so that reliable results can be generated (ECHA Guidance R.11.4.1.1.1).

In the comments to the draft decision you simply claim that the surface water simulation test is technically difficult to conduct. You have not provided any justification nor evidence on the unfeasibility to develop suitable analytical methods and other test procedures.

In the absence of justification and evidence, you have not demonstrated that OECD TG 309 is not technically feasible.

Therefore, you have not demonstrated that this information can be omitted based on Annex XI, Section 2.

Finally, you claim in your comments on the draft decision that the surface water compartment is the least relevant compartment for simulation testing. The information requirement of Annex IX, 9.2.1.2 cannot be waived on the basis of considerations on the relevance of the surface water compartment.

You have not demonstrated, neither in your dossier nor in your comments, that this information can be omitted based on column 2 of Annex IX Section 9.2.1.2 or under Annex XI, Section 2.

Therefore, the information requirement is not met.

Study design

Simulation degradation studies must include two types of investigations (ECHA Guidance R.7.9.4.1.):

- 1) a degradation pathway study where transformation/degradation products are quantified and, if relevant, are identified, and
- 2) a kinetic study where the degradation rate constants (and degradation half-lives) of the parent substance and of relevant transformation/degradation products are experimentally determined.

You must perform the test, by following the pelagic test option with natural surface water containing approximately 15 mg dw/L of suspended solids (acceptable concentration between 10 and 20 mg dw/L) (ECHA Guidance R.11.4.1.1.3.).

The required test temperature is 12°C, which corresponds to the average environmental

temperature for the EU (ECHA Guidance R.16, Table R.16-8) and is in line with the applicable test conditions of the OECD TG 309.

As specified in ECHA Guidance R.7.9.4.1., the organic carbon (OC) concentration in surface water simulation tests is typically 2 to 3 orders of magnitude higher than the test substance concentration and the formation of non-extractable residues (NERs) may be significant in surface water tests. Therefore, non-extractable residues (NER) must be quantified. The reporting of results must include a scientific justification of the used extraction procedures and solvents. By default, total NER is regarded as non-degraded Substance. However, if reasonably justified and analytically demonstrated a certain part of NER may be differentiated and quantified as irreversibly bound or as degraded to biogenic NER, such fractions could be regarded as removed when calculating the degradation half-life(s) (ECHA Guidance R.11.4.1.1.3.). Further recommendations may be found in the background note on options to address non-extractable residues in regulatory persistence assessment available on the ECHA website.

Relevant transformation/degradation products are at least those detected at $\geq 10\%$ of the applied dose at any sampling time or those that are continuously increasing during the study even if their concentrations do not exceed 10% of the applied dose, as this may indicate persistence (OECD TG 309; ECHA Guidance R.11.4.1.).

4. Soil simulation testing

Soil simulation testing is an information requirement under Annex IX to REACH (Section 9.2.1.3.) for substances with a high potential for adsorption to soil.

The Substance has a low water solubility (152 $\mu\text{g/L}$), high partition coefficient (log Kow 7.34) and high adsorption coefficient (log Koc 4.72) and therefore has high potential for adsorption to soil.

Your registration dossier provides the following justification to omit testing:

'The potential biodegradability of Trigonox 101 was extensively studied in screening test. This study shows that Trigonox 101 was not degraded in prolonged Closed Bottle tests inoculated with unacclimated and acclimated sludge from the SCAS unit Given the low water solubility of 152 $\mu\text{g/l}$, the Kow of 7.34, rapid hydrolysis and the lack of toxicity observed in both the OECD 301 and 207 tests, further attempts to determine biodegradation of this compound in aqueous systems appear unwarranted. The results of the chemical safety assessment indicate that the risks to STP microorganisms, soil, aquatic and sediment organisms are controlled during manufacture, formulation and uses of the substance. Conducting a test would not be of any added value to the risk assessment process '

ECHA understands that you adapt according to Section 9.2., Column 2. Under Section 9.2., Column 2 of Annex IX to REACH, the study may be omitted if the chemical safety assessment (CSA) does not indicate the need for further biotic degradation testing. The CSA does indicate such need (Annex I, Section 4; Annex XIII, Section 2.1) if, for instance, the substance is a potential PBT/vPvB substance (ECHA Guidance R.11.4). This is the case if the Substance itself or any of its constituent, impurity or transformation/degradation product present in concentration $\geq 0.1\%$ (w/w) meets the criteria already listed in the Appendix on reasons common to several requests.

As already explained in the Appendix on reasons common to several requests, the CSA indicates the need for further biotic degradation testing and your adaptation is therefore rejected.

In your comments on the draft decision you acknowledge that further testing is needed to conclude on P for the Substance. You propose to conduct the sediment simulation study first, and then perform the soil simulation study, if needed (based on the results of the sediment study: tiered testing strategy).

As stated in Appendix D of this decision you are advised to consider the intrinsic properties of the Substance, and its identified uses and release patterns, when determining the sequence of simulation degradation testing. You may therefore choose to conduct simulation studies starting with the worst case scenarios for persistence, with appropriate justifications. The sequence of simulation tests must continue unless there is a conclusion of vP in a previous test. The deadline in this decision allows adequate time for sequential testing.

Therefore, the information requirement is not met and you remain responsible for complying with this decision by the set deadline.

Study Design

Study designs for the soil and sediment simulation tests are provided in B.5. below.

5. Sediment simulation testing

Sediment simulation testing is an information requirement under Annex IX to REACH (Section 9.2.1.4.) for substances with a high potential for adsorption to sediments.

The Substance has a low water solubility (152 µg/L), high partition coefficient (log Kow 7.34) and high adsorption coefficient (log Koc 4.72) and therefore has high potential for adsorption to sediments.

You have provided a simulation test in aerobic sewage treatment with activated sludge according to the OECD TG 303A showing 0% degradation (IUCLID Section 5.2.2).

We have assessed the information and identified the following issues

To fulfil the information requirement and to allow concluding on the P/vP criteria, ultimate biodegradation simulation tests must simulate degradation under relevant environmental conditions, such as those found in surface water (Annex VIII, Section 9.2. and Annex XIII to REACH; ECHA Guidance R.11.4.).

Your registration dossier provides a simulation test in aerobic sewage treatment with activated sludge units (OECD TG 303A) study.

The SCAS test (i.e. OECD TG 303A, or equivalent) cannot be used for this endpoint since it does not simulate degradation under relevant environmental conditions. For this reason, it also cannot be used to conclude that a substance does not fulfil the criteria for P (ECHA Guidance R.11.4.1.1.).

In your comments on the draft decision you acknowledge that this type of SCAS test cannot be used to fulfil this information requirement.

Therefore the information requirement is not met.

In the comments to the draft decision you agree to perform the requested study.

Study design for the soil and sediment simulation studies

Simulation degradation studies must include two types of investigations (ECHA Guidance R.7.9.4.1.):

1) a degradation pathway study where transformation/degradation products are quantified and, if relevant, are identified, and

2) a kinetic study where the degradation rate constants (and degradation half-lives) of the parent substance and of relevant transformation/degradation products are experimentally determined.

The required test temperature is 12°C, which corresponds to the average environmental temperature for the EU (ECHA Guidance R.16, Table R.16-8) and is in line with the applicable test conditions of the OECD TG 307-309.

Relevant transformation/degradation products are at least those detected at $\geq 10\%$ of the applied dose at any sampling time or those that are continuously increasing during the study even if their concentrations do not exceed 10% of the applied dose, as this may indicate persistence (OECD TG 307 and 308; ECHA Guidance R.11.4.1.).

In accordance with the specifications of the OECD TG 307 and 308, non-extractable residues (NER) must be quantified. The reporting of results must include a scientific justification of the used extraction procedures and solvents (ECHA Guidance R.7.9.4.1.). By default, total NER is regarded as non-degraded Substance. However, if reasonably justified and analytically demonstrated a certain part of NER may be differentiated and quantified as irreversibly bound or as degraded to biogenic NER, such fractions could be regarded as removed when calculating the degradation half-life(s) (ECHA Guidance R.11.4.1.1.3.). Further recommendations may be found in the background note on options to address non-extractable residues in regulatory persistence assessment available on the ECHA website.

Further details on the study designs are provided below for simulation tests on ultimate degradation in soil (OECD TG 307) and sediment (OECD TG 308), respectively.

Soil Simulation Study (OECD TG 307)

In accordance with the specifications of the OECD TG 307, you must perform the test using at least four soils representing a range of relevant soils (*i.e.* varying in their organic content, pH, clay content and microbial biomass).

Sediment Simulation Study (OECD TG 308)

In accordance with the specifications of the OECD TG 308, you must perform the test using two sediments. One sediment should have a high organic carbon content (2.5-7.5%) and a fine texture, the other sediment should have a low organic carbon content (0.5-2.5%) and a coarse texture. If the Substance may also reach marine waters, at least one of the water-sediment systems should be of marine origin.

6. Identification of degradation products

Identification of degradation products is an information requirement under Annex IX to REACH (Section 9.2.3.).

You have provided the following information:

In the PBT assessment of the Substance in Section 2.3 of IUCLID, you acknowledge that the degradation products have not been identified and are therefore unknown. However, you

also hypothesize that the expected degradation products will be tertiary-butyl alcohol (TBA) and 2,5-dimethyl-2,5-hexanediol ("or some similar dimethyl hexane derivative").

Information on identity of relevant transformation/degradation products is required for the purpose of the PBT/vPvB assessment (Annex I, Section 4) and the risk assessment (Annex I, Section 6) of the Substance.

In your dossier, you have provided the following studies where transformation/degradation products were investigated:

- Results from a preliminary hydrolysis study (OECD TG 111; ██████████ 2008) identifying one hydrolysis product i.e TBA (t-butyl alcohol, EC No. 200-889-7).
- Results from a second preliminary hydrolysis study with no identification of hydrolysis products (OECD TG 111 ██████████ 2010).
- Results from a definitive hydrolysis study (OECD TG 111; ██████████ 2011) with no identification of hydrolysis products.
- A biodegradation study where modified OECD TG 301D tests were also conducted using "*potential decomposition products*" of the Substance, i.e. tert butanol and 2,5-dimethyl-2,5-hexanediol. In your PBT/vPvB assessment (Section 2.3 of IUCLID), you indicate that "*the degradation products may be considered potentially P*" (as discussed in the Appendix on reasons common to several requests)

As explained in the Appendix on Reasons common to several requests, the Substance is a potential PBT/vPvB substance and you have not adequately addressed the potential formation of stable degradation products with PBT/vPvB properties, hence the chemical safety assessment (CSA) indicates the need for further degradation investigation.

Regarding the identity of the hydrolysis products, you identify only TBA as a hydrolysis product (██████████ 2008), but you provide no information on other hydrolysis products that could be formed. Furthermore, you have provided no justification or evidence that 2,5-dimethyl-2,5-hexanediol would be a degradation product of the Substance, and whether also other degradation products would be formed.

You have not provided definitive information on the identity and PBT/vPvB properties of all degradation products.

Therefore, this information requirement is not met.

In your comments on the draft decision you agree to identify the degradation products in the sediment simulation study.

Study design

Regarding the selection of appropriate and suitable test method(s), the method(s) will have to be substance-specific. Identity, stability, behaviour, and molar quantity of the degradation/transformation products relative to the Substance must be evaluated and reported, when analytically possible. In addition, degradation half-life, log Kow and potential toxicity of the transformation/degradation may need to be investigated. You may obtain this information from the degradation study requested in Appendix C.3 or by some other measure. If any other method is used for the identification of the transformation/degradation products, you must provide a scientifically valid justification for the chosen method.

To determine the degradation rate of the Substance, the requested study according to OECD TG 309 (Appendix C.3) must be conducted at 12°C and at a test concentration < 100 µg/L.

However, to overcome potential analytical limitations with the identification and quantification of major transformation/degradation products, you may consider running a parallel test at higher temperature (but within the frame provided by the test guideline, e.g. 20°C) and at higher application rate (i.e. > 100 µg/L).

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

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.
2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.
3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries⁶.

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

1. Selection of the Test material(s)

The Test Material used to generate the new data must be selected taking into account the following:

- the variation in compositions reported by all members of the joint submission,
 - the boundary composition(s) of the Substance,
 - the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.
2. Information on the Test Material needed in the updated dossier
 - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
 - The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers⁷.

⁶ <https://echa.europa.eu/practical-guides>

⁷ <https://echa.europa.eu/manuals>

Appendix D: General recommendations when conducting and reporting new tests for REACH purposes

A. Strategy for the PBT/vPvB assessment

Under Annex XIII, the information must be based on data obtained under conditions relevant for the PBT/vPvB assessment. You must assess the PBT properties of each relevant constituent of the Substance present in concentrations at or above 0.1% (w/w) and of all relevant transformation/degradation products. Alternatively, you would have to justify why you consider these not relevant for the PBT/vPvB assessment.

You are advised to consult ECHA Guidance R.7b (Section R.7.9.), R.7c (Section R.7.10) and R.11 on PBT assessment to determine the sequence of the tests needed to reach the conclusion on PBT/vPvB. The guidance provides advice on 1) integrated testing strategies (ITS) for the P, B and T assessments and 2) the interpretation of results in concluding whether the Substance fulfils the PBT/vPvB criteria of Annex XIII.

When determining the sequence of simulation degradation testing you are advised to consider the intrinsic properties of the Substance, its identified uses and release patterns as these could significantly influence the environmental fate of the Substance. You must revise your PBT assessment when the new information is available.

Appendix E: Procedure

This decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

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

The compliance check was initiated on 01 February 2021.

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

ECHA took into account your comments and amended the deadline.

In your comments on the draft decision, you requested an extension of the deadline to provide information from 24 to 36 months from the date of adoption of the decision. You have provided evidence on laboratory capacity indicating significant lead in time is expected for the requested study/ies, and that additional time is required for analytical method development at the testing facility.

ECHA has granted the request and extended the deadline to 36 months.

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

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s) and referred the modified draft decision to the Member State Committee.

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

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-78 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix F: List of references - ECHA Guidance⁸ and other supporting documentsEvaluation of available information

Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping

Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)⁹

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)¹⁰

Physical-chemical properties

Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology

Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate

Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment

Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing

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

OECD Guidance documents¹¹

⁸ <https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment>

⁹ <https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across>

¹⁰ https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316

¹¹ <http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm>

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

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

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

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

Appendix G: Addressees of this decision and their corresponding information requirements

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

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

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