~~Confidential~~

Helsinki, 10 January 2022

Addressees
Registrant(s) of CEM JS 1843-03-4 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
31/01/2013

Registered substance subject to this decision ("the Substance")
Substance name: 4,4',4''-(1-methylpropanyl-3-ylidene)tris[6-tert-butyl-m-cresol]
EC number: 217-420-7

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 ***16 July 2025***.

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

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

1. Long-term toxicity testing on aquatic invertebrates also requested below (triggered by Annex VII, Section 9.1.1., column 2)

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

1. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) by oral route, in rats

2. Long-term toxicity testing on fish also requested below (triggered by Annex VIII, Section 9.1.3., column 2)

3. Simulation testing on ultimate degradation in surface water also requested below (triggered by Annex VIII, Section 9.2.)

4. Soil simulation testing also requested below (triggered by Annex VIII, Section 9.2.)

5. Sediment simulation testing also requested below (triggered by Annex VIII, Section 9.2.)

6. Identification of degradation products also requested below (triggered by Annex VIII, Section 9.2.)

7. Bioaccumulation in aquatic species also requested below (triggered by Annex I, Sections 0.6.1. and 4; Annex XIII, Section 2.1.)

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

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rat or rabbit)

2. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: EU C.20./OECD TG 211)

3. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: OECD TG 210)

4. 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 and solvents must be provided.

5. 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.

6. 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.

7. Identification of degradation products (Annex IX, 9.2.3.; test method: using an appropriate test method)

8. Bioaccumulation in aquatic species (Annex IX, Section 9.3.2; test method: OECD TG 305, aqueous exposure /dietary exposure)

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

- Appendix entitled "Reasons common to several requests";
- Appendix entitled "Reasons to request information required under Annexes VII 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 and bioaccumulation are necessary for the PBT assessment. However, to determine the testing needed to reach the conclusion on the persistency and bioaccumulation 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.

Authorised[1] 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

1. Assessment of your read-across approach under Annex XI, Section 1.5.

You seek to adapt the following standard information requirements by applying (a) read-across approach(es) in accordance with Annex XI, Section 1.5:

- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

ECHA has considered the scientific and regulatory validity of your read-across approach(es) in general before assessing the specific standard information requirements in the following appendices.

Grouping of substances and read-across approach

Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (addressed under 'Assessment of prediction(s)').

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance R.6. and related documents[2,3].

A. Predictions for (eco)toxicological properties

You have provided a read-across justification document in IUCLID sections 6.1.4 and 7.8.1.

You predict the properties of the Substance from the following source substances:

- Reproductive/developmental toxicity: 6,6'-di-tert-butyl-4,4'-butylidenedi-m-cresol, EC No. 201-618-5 (CAS No. 85-60-9) [source substance 1];
- Long-term toxicity testing on aquatic invertebrates: 3,3',3",5,5',5"-hexa-tert-butyl α,α',α"-(mesitylene-2,4,6-triyl) tri-p-cresol; EC No. 216-971-0 (CAS No. 1709-70-2) [source substance 2].

You have provided the following reasoning for the predictions of (eco)toxicological properties:

"The structural similarity and the similarity of chemical endpoints suggest a common mechanism and mode of action and ability to extrapolate worst case scenarios thereby provide further supporting evidence for the read-across between the substances."

You further specify for both source substances that "*The multiple di-tert butyl p-cresol groups are a common factor of both substances suggesting that the ability to bind with proteins and enzymes in vivo would be similar; although in practice such binding may be inhibited due to the steric hindrance of the di tert butyl groups. Data available on both species suggests that neither molecule is metabolised or absorbed in vivo.*"

[2] Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki.
[3] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki.

ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted based on a worst-case approach.

ECHA notes the following shortcomings with regards to predictions of (eco)toxicological properties.

Read-across hypothesis contradicted by existing data

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*". The Guidance on IRs and CSA, Section R.6.2.2.1.f. indicates that "*it is important to provide supporting information to strengthen the rationale for the read-across*". The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substances.

The observation of differences in the properties between the source substance(s) and the Substance would contradict the hypothesis that the properties of the Substance can be predicted from the data on the source substances. An explanation why such differences do not affect the read-across hypothesis must be provided and supported by scientific evidence.

As indicated above, your read-across hypothesis is based on the assumption that the Substance or source substances are not metabolised or absorbed *in vivo* and that the properties of the Substance are predicted from information on the source substances based on worst-case approaches.

In the dossier, you have provided

- A 13-week toxicity study (90-day) in rats, conducted with the Substance showing significantly lower body weights (up to 18%) in high dose males (appr 391.5 mg/kg bw/d) and females (490.2 mg/kg bw/d). This resulted in body weight gains of high dose in males and females of 74% and 65% of the body weight gains of control animals, respectively.
- A reproduction/developmental toxicity screening study in rats, conducted with the source substance [1] showing no signs of toxicity up to the highest dose of 1000 mg/kg bw/d.
- A C^{14}-label bioavailability study in rats, conducted with the source substance [2] indicating that less than 0.2% of the administered doses of source substance 2 were systemically absorbed.

In addition, in the read-across justification documents, you compare the physico-chemical properties of the source substances and the Substance. You provide a logKow value of 8.5 for the Substance and 17.17 for the source substance [2]. Furthermore, for the source substance [1] and for the Substance, you indicate that "*The molecule weight for both molecules is <700 suggesting that the molecules may be prone to absorption across cell membranes*.".

While you have provided information for the source substances suggesting that these substances may not be well absorbed, you have not provided such evidence for the Substance. To the contrary, your statement that the source substance [1] and the Substance "*may be prone to absorption across cell membranes*" contradicts the hypothesis that the Substance and the source substance(s) would not be absorbed.In addition, the information on the Substance i.e. the 13-week study conducted with the Substance (sub-chronic toxicity study, 90-day) demonstrates absorption as the following effects are seen: significant reductions in the terminal body weights and body weight gains at the highest dose tested (appr 390 and

490 mg/kg bw/day of the Substance in males and females, respectively). You also consider the effects observed at the highest dose tested as adverse and set the no observed adverse effects level (NOAEL) at the mid dose (500 ppm) based on "*statistically significant reduction in growth rate associated with reduced food intake, plus reduced relative liver weights and small increases in relative spleen and adrenal weights*".

Therefore, the provided information does not support your hypothesis that the source substances and the Substance would not be absorbed *in vivo* and that the source substances would present worst-cases for the Substance.

Furthermore, the reported logKow of the source substance [2] is much higher than the logKow of the Substance. In general, the logKow above 10 is expected to indicate hindered uptake (ECHA Guidance R.11, Figure R.11-4). Therefore, the reported logKow values actually indicate lower absorption of the source substance [2] than of the Substance. Therefore, the physicochemical properties provide further contradicting evidence to your hypothesis that the source substance [2] would provide a worst-case prediction for the ecotoxicological properties of the Substance.

Adequacy and reliability of source studies

According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across should:

- have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3)

For the reproductive toxicity, you have provided a Reproduction/Developmental Toxicity Screening Test (OECD TG 421), which ECHA understood was also provided to cover the requirement for the pre-natal developmental toxicity. For the specific reasons explained further below under the relevant information requirement under Appendix C, section 1, the study does not meet the necessary conditions.

B. Conclusions on the read-across approach

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the analogue substance. Therefore, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected.

2. 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 constituent or impurity present in concentration ≥ 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 301B), and
- 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).

Your registration dossier provides the following PBT/vPvB screening information:

- The Substance is not readily biodegradable (12% degradation after 28 days in OECD TG 301B study);
- The Substance has a high potential to partition to lipid storage (Log K_{ow} of >6.5 based on OECD TG 117; and log Kow 12.7 based on QSAR).

In your PBT assessment in Section 2.3 of the registration dossier, you conclude that the Substance is not B/vB with the following justifications:

- "QSAR assessment of the substance by the Arnot-Gobas BCF & BAF Methods by structural fragmentation suggests a BCF of 1.064 L/kg wet-wt";

- Hindered uptake arguments indicating low bioaccumulation based on high logKow and toxicokinetic and mammalian toxicity data.

By this justification you have addressed the PBT/vPvB properties of the main constituent but you have not provided explanation how this justification applies to (potential) impurities present in concentration ≥ 0.1% (w/w) or relevant transformation/degradation product.

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

QSAR prediction

As described under request C.8, ECHA cannot establish that your prediction of BCF by the Arnot-Gobas BCF & BAF Methods meets all the conditions of Annex XI, Section 1.3. and therefore the prediction cannot be used to meet the information requirement on Bioaccumulation in aquatic species.

Hindered uptake arguments

ECHA Guidance R.7.8.5. explains that there is no scientific basis to define molecular characteristics that would render a substance unlikely to cross biological membranes. In this context, the indicators used for low likelihood of a high bioaccumulation potential (ECHA Guidance R.11, Figure R.11-4) must be considered, including:

- physico-chemical indicators of hindered uptake due to large molecular size (*e.g.* D_{max} > 17.4 Å and MW > 1100 or MML > 4.3 nm) or high octanol-water partition coefficient (log K_{ow} > 10) or low potential for mass storage (octanol solubility (mg/L) < 0.002 x MW), and
- supporting experimental evidence of hindered uptake (no chronic toxicity for mammals and birds, no chronic ecotoxicity, no uptake in mammalian toxicokinetic studies, very low uptake after chronic exposure).

In your PBT assessment in Section 2.3 of the registration dossier you provide the following arguments to substantiate your claim of the hindered uptake:

- physico-chemical indicators which you consider supportive of hindered uptake (logKow 12.7);
- Toxicokinetic data available on a structural analogue (CAS No 1709-70-2) demonstrates that the substance is not metabolised in a mammalian system and around 0.06% absorbed to blood and tissues;
- Chronic toxicity data on mammals:
    - On the basis of the genetic toxicity data available the substance is considered as not having potential for carcinogenic hazard;
    - The Reproduction/Developmental Toxicity Screening Test (OECD TG 421) on a structural analogue (CAS No. 85-60-9) demonstrates a lack of effects to parent and F1 animals and an absence of toxicity to reproduction; and

- In the sub-chronic mammalian toxicity study with the Substance, a NOAEL at 500 ppm in diet (reported appr 38-45 mg/kg/day) was achieved based on "*statistically significant reduction in growth rate associated with reduced food intake, plus reduced relative liver weights and small increases in ralative spleen and adrenal weights*".

The available information on the Substance does not support that the Substance is unlikely to cross biological membranes for the following reasons:

- You refer to LogKow = 12.7 (QSAR) to support hindered uptake, however there is also a LogKow of 8.5 (OECD TG 117), which you use e.g. in the read-across justification document (see above section 1). Since different LogKow values are available for the Substance, it is not clear if the LogKow is indeed indicating hindered uptake;
- The toxicokinetic study was performed with the source substance [2], and the read-across is rejected for the same reasons as described in section 1 (contradicting evidence on logKow and observed effects indicating absorption of the Substance);
- The *in vitro* genotoxicity studies indicate that the Substance is not genotoxic *in vitro*. However, this does not alone provide evidence that the Substance would not cross biological membranes;
- The Reproduction/Developmental Toxicity Screening Test in mammals was performed with the source substance [1] and the read-across prediction is rejected (see above section 1);
- The dietary study on mammals conducted with the Substance indicates absorption of the Substance (see above section 1).

PBT/vPvB properties of the impurity not addressed

In the context of the PBT/vPvB assessment (Annex I, Section 4) and the risk assessment (Annex I, Section 6) of the Substance, the CSA must address relevant constituents and transformation/degradation products (Annex XIII, 5th paragraph; ECHA Guidance R.11.4.1.).

Your PBT assessment is solely based on the properties of the main constituent of the Substance and does not address the PBT/vPvB properties of all the relevant constituents/impurities present in concentration ≥ 0.1% (w/w) or relevant transformation/degradation products.

Without this information, no conclusion on vPvB and PBT properties of the Substance and its potential degradation products can be made.

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

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 C.4-C.8.

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

1. Long-term toxicity testing on aquatic invertebrates

Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII to REACH (Section 9.1.1.). Long-term toxicity testing on aquatic invertebrates must be considered (Section 9.1.1., Column 2) if the substance is poorly water soluble.

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).

In the provided an OECD TG 105 study (2012), the saturation concentration of the Substance in water was determined to be <0.04 mg/L.

Therefore, the Substance is poorly water soluble and information on long-term toxicity on aquatic invertebrates 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 Appendix C.2.

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

1. Screening for reproductive/developmental toxicity

A Screening for reproductive/developmental toxicity study (test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) is a standard information requirement under Annex VIII to REACH, if there is no evidence from analogue substances, QSAR or in vitro methods that the Substance may be a developmental toxicant. There is no information available in your dossier indicating that your Substance may be a developmental toxicant.

You have adapted this information requirement by using a read-across approach under Annex XI, Section 1.5.

Your dossier contains the following study:

i. Reproduction/Developmental Toxicity Screening Test (OECD TG 421; 2012) conducted with 6,6'-di-tert-butyl-4,4'-butylidenedi-m-cresol (EC No 201-618-5; CAS RN 85-60-9)

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

As explained under Appendix on 'Reasons common to several requests', your adaptation under the Annex XI, section 1.5 is rejected.

Therefore, the information you provided does not fulfil the information requirement.

In the comments to the draft decision, you agree that information to fulfil this information requirement is missing. However you "*question the requirement to conduct this screening test when a further request for the OECD TG 414 is made further below. In accordance with Annex VIII, Section 8.7 on Reproduction Toxicity, tests OECD TG 421 and/or OECD TG 422 do not need to be conducted if a pre-natal toxicity study is available… Whilst an OECD TG 414 test is not specifically available at this time, it will be per the subsequent deadline set by ECHA in any future final decision. Therefore, the co-registrants suggest that this animal test is not required and can be replaced by the OECD 414 test requested below*".
As you correctly indicate in your comment, Annex VIII, Column 2 Section 8.7.1 states that the screening for reproductive/developmental toxicity study does not need to be conducted when a pre-natal developmental toxicity study is available. Since no such study is currently available, the information requirement of Annex VIII, Section 8.7.1 cannot be waived, at this time, on the basis of this column 2 provision. Therefore the data gap identified in this decision remains.

Information on the study design

A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats with oral[4] administration of the Substance.

2. 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.

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

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

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).

As already explained under Section A.1, 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 C.3.

3. 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.

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 C.4.

4. Soil simulation testing

5. 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 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.

The Substance has low water solubility (<0.04 mg/L), high partition coefficient (log Kow >6.5) and high adsorption coefficient (log K_{OC} of 7.53), indicating high potential to adsorb to soil and sediment. Based on the adsorptive properties of the Substance, soil and sediment represent a relevant environmental compartment.

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 C.5-C.6.

6. 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 under 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 C.7.

7. Bioaccumulation in aquatic species

Bioaccumulation in aquatic species is required for the purpose of PBT/vPvB assessment (Annex I, Sections 0.6.1 and 4 to REACH).

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 investigation on bioaccumulation in aquatic species.

The examination of the available information or adaptations, as well as the selection of the requested test and the test design are addressed in Appendix C.8.

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

1. Pre-natal developmental toxicity study in one species

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX to REACH.

You have have provided a justification for data waiving stating that "*Based on the data available by read across to a structurally related substance, the substance presents no concern for reproductive effects and animal testing to allow further assessment is not justifiable*"

In addition, ECHA understands that in the above justification you refer to the Reproduction/Developmental Toxicity Screening Test (OECD TG 421; 2012) conducted with 6,6'-di-tert-butyl-4,4'-butylidenedi-m-cresol (source substance 1; EC No 201-618-5; CAS RN 85-60-9) and provided under the Toxicity to reproduction (IUCLID 7.8.1).

ECHA understands that you intended to adapt according to 'Grouping of substances and read-across approach' (Annex XI, Section 1.5.), and has evaluated the information accordingly.

As explained in the Appendix Reasons common to several requests, section 1, your grouping and read-across approach (Annex XI, Section 1.5) is rejected.

On this basis, the information requirement is not fulfilled.

In addition, the following endpoint-specific deficiencies have been identified in your read-across adaptation:

Adequacy and reliability of source study

According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across should have adequate and reliable coverage of the key parameters foreseen to be investigated.

According to the provisions of Annex IX, Section 8.7.2., information provided has to meet the requirements of OECD TG 414 in one species, e.g external, skeletal and visceral malformations and variations has to be investigated as described in OECD TG 414.

You have not provided information following OECD TG 414. Instead, you have provided a "Screening for reproductive/developmental toxicity" (OECD TG 421). This study does not inform on skeletal and visceral malformations and variations as required by OECD TG 414.

Therefore, the provided study conducted with the source substance (ii) does not have adequate and reliable coverage of the key parameters foreseen to be investigated in the OECD TG 414.

On this basis, the information requirement is not fulfilled.

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

Information on the study design

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit

as preferred species with oral[5] administration of the Substance.

2. Long-term toxicity testing on aquatic invertebrates

Long-term toxicity testing on aquatic invertebrates is an information requirement under Annex IX to REACH (Section 9.1.5.).

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5 and provided the following information:

i. a study according to OECD TG 211 conducted with the substance EC No 216-971-0 (CAS No 1709-70-2), *i.e.* source substance [2] .

As explained in the Appendix Reasons common to several requests, section 1, your grouping and read-across approach (Annex XI, Section 1.5) is rejected.

On this basis, the information requirement is not fulfilled.

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

Study design

The Substance is difficult to test due to the low water solubility (<0.04 mg/L) and adsorptive properties (logKoc 7.53). OECD TG 211 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance 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 OECD TG 211. 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 in the test solution.

3. 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.).

You have provided the following information:

i. a justification to omit the study: "*Acute exposure of the substance to fish resulted in completion of the study with limit values, based on nominal exposure due to the high water insolubility of the substance. Experimental assessment of this endpoint is therefore considered unnecessary*".

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).

[5] ECHA Guidance R.7a, Section R.7.6.2.3.2.

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.

In the comments to the draft decision, you indicate that this study should be omitted according to Column 2 of Annex IX, Section 9.1 because "*the test is not needed to refine hazard and risk*". To support your adaptation, you refer to a publication (M May and S Hahn, 2015, Report No. (UBA-FB) 002221/E) and you propose that for the Substance "*there is unlikely to be effects in a chronic test*" because no effects are observed in the available short-term aquatic toxicity studies.

However, as explained above, the Column 1 information requirement cannot be waived based on Column 2 referring to the Chemical Safety Assessment. In any case, as explained in requests A.1 and B.2 above, the Substance is poorly water soluble and absence of effects in short-term studies does not give a true measure of toxicity (ECHA Guidance R.7b), thus short-term studies cannot be used to conclude on hazards and long-term studies are needed.

On this basis, the information requirement is not fulfilled.

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.).

OECD TG 210 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix C.2.

4. 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:

i. a justification to omit the study: "*The data available are adequate to determine that the substance is not readily biodegradable. Assessment of this endpoint will add no further useful data to the registration*."

We have assessed this information and identified the following issue:

A registrant may only adapt this information requirement based on the specific rules set out in Annex IX, section 9.2 or the general rules set out in Annex XI. It is noted that Column 2 of Annex IX, Section 9.2.1.2, describes that the information requirement can be adapted if the substance is ready 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 you indicate that the surface water simulation study (OECD TG 309) should be omitted because it is technically not feasible. ECHA understands that you adapt this information requirement under Annex XI Section 2.

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

Under Section 2. of Annex XI to REACH, 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 not feasible. 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.

On this basis, the information requirement is not fulfilled.

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 ≥ 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.).

5. Soil simulation testing

6. Sediment 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.

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 sediment.

The Substance has a low water solubility (<0.04 mg/L), high partition coefficient (log K_{ow} 12.7) and high adsorption coefficient (log K_{oc} 7.53) and therefore has high potential for adsorption to soil and sediment.

You have provided the following information:

i. a justification to omit the study: "*The data available are adequate to determine that the substance is not readily biodegradable. Assessment of this endpoint will add no further useful data to the registration.*"

We have assessed this information and identified the following issue:

A registrant may only adapt this information requirement based on the specific rules set out in Annex IX, section 9.2 or the general rules set out in Annex XI. It is noted that Column 2 of Annex IX, Section 9.2.1.3 and 9.2.1.4, describe that the information requirement can be adapted if the substance is ready 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 9.2.1.3 and 9.2.1.4.

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

On this basis, the information requirement is not fulfilled.

In the comments to the draft decision, you agree to perform the requested studies.

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.

In accordance with the specifications of 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).

In accordance with the specifications of 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.

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 307/308.

In accordance with the specifications of OECD TG 307/308, 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.

Relevant transformation/degradation products are at least those detected at ≥ 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 307/308; ECHA Guidance R.11.4.1.).

7. Identification of degradation products

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

You have provided no information on the identity of transformation/degradation products for the Substance.

Therefore, this information requirement is not met.

On this basis, the information requirement is not fulfilled.

In the comments to the draft decision, you agree to perform the requested 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 K_{ow} and potential toxicity of the transformation/degradation may need to be investigated. You may obtain this information from the degradation studies requested in Appendices C.4-C.6 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 307-309 (Appendix C.4-C.6) must be conducted at 12°C and at a test concentration < 100 µg/L (OECD 309) (or at test material application rates reflecting realistic assumptions, OECD 307-308). 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, OECD 309; or 10 times, OECD 307-308).

8. Bioaccumulation in aquatic species

Bioaccumulation in aquatic species is an information requirement under Annex IX to REACH (Section 9.3.2.).

You have provided the following information:

i. an adaptation according to Annex XI, Section 1.3, by providing results from a (Q)SAR prediction: EPIWIN BCFBAF model.

We have assessed this information and identified the following issues:

Lack of or inadequate documentation of the prediction (QPRF)

Under Annex XI, Section 1.3., the following conditions must be fulfilled whenever a (Q)SAR approach is used:

1. the prediction needs to be derived from a scientifically valid model,
2. the substance must fall within the applicability domain of the model,
3. results need to be adequate for the purpose of risk assessment or classification and labelling, and
4. adequate and reliable documentation of the method must be provided.

ECHA Guidance R.6.1.6.3 states that the information specified in or equivalent to the (Q)SAR Prediction Reporting Format document (QPRF) must be provided to have adequate and reliable documentation of the applied method. For a QPRF this includes, among others:

- the model prediction(s), including the endpoint,
- a precise identification of the substance modelled,
- the relationship between the modelled substance and the defined applicability domain,
- the identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

You have not provided documentation for the prediction, in the form of QPRF. In the absence of this information, it cannot be confirmed that

- the Substance is within the applicability domain of the model;
- the prediction covers all relevant constituents and impurities (no information provided on the identity of the substance modelled);
- the prediction is reliable (no information provided on close analogues).

In absence of such information, ECHA cannot establish that all the conditions of Annex XI, Section 1.3. are met and the prediction can be used to meet this information requirement.

On this basis, the information requirement is not fulfilled.

In the comments to the draft decision, you have not provided any new scientific information that could change ECHA's above assessment on the compliance of the information submitted for this endpoint. You rather inform on the step-wise testing strategy you intend to follow. You agree to conduct the requested study if the Substance is P/vP based on the

outcome of the simulation studies (requests C.4-7). If the Subtance is not P/vP, you mention that you intend to adapt this standard information requirement by providing QSAR data and appropriate QPRF.

Regarding any such future adaptation of the standard information requirement, ECHA can only point out that any such adaptation will need to meet either the conditions set-out in the specific rule under Annex IX, Section 9.3.2, Column 2 or one of the general adaptation rules under Annex XI.

Study design

Bioaccumulation in fish: aqueous and dietary exposure (Method EU C.13 / OECD TG 305) is the preferred test to investigate bioaccumulation (ECHA Guidance R.7.10.3.1.). Exposure via the aqueous route (OECD TG 305-I) must be conducted unless it can be demonstrated that:

- a stable and fully dissolved concentration of the test substance in water cannot be maintained within ± 20% of the mean measured value, and/or
- the highest achievable concentration is less than an order of magnitude above the limit of quantification (LoQ) of a sensitive analytical method.

This test set-up is preferred as it allows for a direct comparison with the B and vB criteria of Annex XIII of REACH.

You may only conduct the study using the dietary exposure route (OECD 305-III) if you justify and document that testing through aquatic exposure is not technically possible as indicated above. You must then estimate the corresponding BCF value from the dietary test data according to Annex 8 of the OECD 305 TG and OECD Guidance Document on Aspects of OECD TG 305 on Fish Bioaccumulation (ENV/JM/MONO(2017)16).

Appendix D: 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 summaries[6].

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 dossiers[7].

[6] https://echa.europa.eu/practical-guides
[7] https://echa.europa.eu/manuals

Appendix E: 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.

In particular, you are advised to first conclude whether the Substance fulfils the Annex XIII criteria for P and vP, and then continue with the assessment for bioaccumulation. 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 F: 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 11 December 2020.

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

ECHA took into account your comments and did not amend the request(s).

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

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix G: List of references - ECHA Guidance[8] and other supporting documents

Evaluation 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 documents[11]

[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 H: 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]
[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.