~~Confidential~~

Helsinki, 03 February 2022

Addressees
Registrants of JS_5384-21-4_[redacted] as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
28/11/2018

Registered substance subject to this decision ("the Substance")
Substance name: 4,4'-methylenedi-2,6-xylenol
EC number: 226-378-9
CAS number: 5384-21-4

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 in C.1, by the deadline of ***08 November 2022*** and all other information listed below by ***08 August 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. Partition coefficient n-octanol/water (Annex VII, Section 7.8.; using an appropriate test method)

2. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: EU B.13/14. / OECD TG 471)

3. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: EU C.2./OECD TG 202)

4. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: EU C.3./OECD TG 201)

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

1. In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.; test method: OECD TG 473) or In vitro micronucleus study (Annex VIII, Section 8.4.2.; test method: OECD TG 487)

2. If negative results are obtained in tests performed for the information requirement of Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. then: In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490)

3. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: OECD TG 203)

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

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.; test method: OECD TG 408) by oral route, in rats.

   The above requested study (90-day sub-chronic toxicity study, OECD TG 408, 2017) is already available in the opt-out registrant's dossier for the Substance[1]. Under Article 26(3) of REACH, you must not repeat a study involving vertebrate animals conducted on the same substance.

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

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

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

5. 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.

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. 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.

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

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

D. Information required from all the Registrants subject to Annex X of REACH

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

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 VII to X of REACH", respectively.

[1] https://echa.europa.eu/registration-dossier/-/registered-dossier/5565/7/6/2/?documentUUID=fbcce32c-d4d1-40f0-a613-7c05977fcf9b

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 Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

The registrant with registration number 01-2119965148-29-0002 is not requested to provide the study listed under C.1., because they opted out from the joint submission for that specific information requirement.

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

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[2] under the authority of Mike Rasenberg, Director of Hazard Assessment

[2] 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 weight of evidence adaptation under Annex XI, Section 1.2.**

You seek to adapt the following standard information requirements by applying weight of evidence approaches in accordance with Annex XI, Section 1.2:

- *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- Short-term toxicity study on aquatic invertebrates (Annex VII, Section 9.1.1.)
- *In vitro* cytogenicity study in mammalian cells or *In vitro* micronucleus study Annex VIII, Section 8.4.2.)
- *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Short-term toxicity study on fish (Annex VIII, Section 9.1.3.)
- Prenatal developmental toxicity study in a first species *(*Annex IX, Section 8.6.2.)
- Long-term toxicity study on aquatic invertebrates (Annex IX, Section 9.1.5.)
- Bioaccumulation in aquatic species (Annex IX, Section 9.3.2)
- Prenatal developmental toxicity study in second species *(*Annex X, Section 8.6.2.)

In the comments to the draft decision of the lead registrant, you indicate that, in addition to the data on the Substance that is currently reported in your technical dossier, you intend to cover the algae growth inhibition (Annex VII, Section 9.1.2.) standard information requirement by using data of the analogue substance 2,3,5-Trimethylquinol (EC no 211-838-3). You claim in your comments that you intend to do this to "strengthen" the data currently reported in the dossier and you continue that by adding this data you "adapt the weight of evidence approach".

From the above, ECHA understands that you now intend to adapt also the algae growth inhibition (Annex VII, Section 9.1.2.) by applying weight of evidence approach.

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

Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach.

In the technical dossier and in the comments of the lead registrant, you have provided summaries of the studies as separate endpoint study records, and you briefly present each of

the sources of information and describe the results. However, the references provided are secondary references which do not allow an independent assessment of the primary source of information. Without further information the sources of information cannot be considered as reliable, as further explained in section A below.

In addition, you have not submitted any explanation why the sources of information provide sufficient weight-of-evidence leading to the conclusion/assumption that the Substance has or has not a particular dangerous property.

In your comments to the draft decision of the lead registrant, you have summarised the sources of information for ecotoxicological standard information requirements, that you adapt using weight of evidence approaches, in relation to the reliability, coverage of key parameters, consistency and results and conclude that as a weight of evidence based on the available sources of information, no further studies are needed. However, your summary does not provide a sufficient justification for assessing if relevance, reliability, coverage, consistency and results of the sources of information are balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required studies.

In spite of these critical deficiencies, ECHA has nevertheless assessed the validity of your adaptation.

Your weight of evidence approach has deficiencies that are common to all information requirements under consideration and also deficiencies that are specific for these information requirements individually. The common deficiencies are set out below, while the specific ones are set out under the information requirement concerned in the Appendices A, B and C.

A. Reliability of the provided information with analogue substances

ECHA understands that you intend to predict the (eco)toxicological properties of the Substance for the listed above endpoints, from data obtained with source substances in a read-across approach as part of your weight of evidence adaptation. For this information to be considered reliable, it would thus have to meet the requirements for Grouping of substances and read-across approach.

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[3] and related documents[4, 5].

[3] ECHA Guidance R.6
[4] Read-Across Assessment Framework (RAAF)
[5] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs

Predictions for (eco)toxicological properties

For toxicological and ecotoxicological properties you read-across to the Substance from the following source substances:

- 2,3,5-trimethylphenol, EC No. 211-806-9
- 2,2',6,6'-Tetra-tert-butyl-4,4'-methylenediphenol, EC No. 204-279-1
- 6,6'-di-tert-butyl-2,2'-methylenedi-p-cresol, CAS No. 119-47-1
- 2,4,6-trimethylphenol, EC No. 208-419-2
- 2,2'-methylenebis(6-tert-butyl-4-methylphenol), EC No 204-327-1
- tert-dodecanethiol, EC No. 246-619-1
- 2,6-dimethylphenol, EC No 209-400-1
- Hexachlorophene, EC No 200-739-8

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

Absence of read-across justification

Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide a justification for the read-across including a hypothesis, explanation of the rationale for the prediction of properties and robust study summary(ies) of the source study(ies).[6]

You have provided studies conducted with other substances than your Substance in order to comply with the REACH information requirements. You have not provided documentation as to why this information can be used to predict the (eco)toxicological properties of your Substance.

In the absence of such documentation, ECHA cannot verify that the properties of your Substance can be predicted from the data on the source substance(s).

In the comments to the draft decision of the lead registrant, you have provided a justification document entitled "[redacted]" This document however only addresses the predictions for ecotoxicological properties.

For environmental fate and ecotoxicological properties under the weight of evidence for the endpoints listed above, you read-across between the following substances, reported in your dossier and in the comments to the draft decision, as source substances and the Substance as target substance:

Source substance	Environmental information requirements
6,6'-di-tert-butyl-2,2'-methylenedi-p-cresol (EC no 204-327-1; CAS no 119-47-1)	Short-term toxicity to fish Short-term toxicity to aquatic invertebrates Long-term toxicity to aquatic invertebrates Bioaccumulation in aquatic species (added in the comments)
2,3,5-Trimethylquinol (EC no 211-838-3; CAS no 700-13-0)	Short-term toxicity to fish (added in the comments)

[6] ECHA Guidance R.6, Section R.6.2.6.1

	Short-term toxicity to aquatic invertebrates (added in the comments) Growth inhibition study aquatic plants (added in the comments)
6-tert-butyl-2,4-xylenol (EC no 217-533-1; CAS no 1879-09-0)	Long-term toxicity to aquatic invertebrates (added in the comments)

You indicate that the "*read-across of environmental fate and ecotoxicological data from an analogue may be justified based on:*

- *Identifying the read across substances based on common functional groups and further filled with relate mechanistic approaches and finally fine-tuned with Structural similarity using the QSAR Toolbox Version 3.4*
- *Common structural alerts or reactivity*
- *Common physico-chemical properties*
- *Likelihood of common breakdown products via biological/degradation processes"*

You further conclude that "*the descriptors, various alerts and scenario (for analogue approach) which were taken into consideration for environmental fate and ecotoxicological assessment as reported in this RA justification document obtained by using OECD QSAR toolbox v.3.4 of the target substance and read across analogues were evaluated to be similar and therefore justified and appropriate*" and indicate that you have selected the 'Scenario 2'' for the analogue approach to justify the read across analogues.

Therefore, ECHA understands that you read-across between CAS no 119-47-1, CAS no 900-13-0, and CAS no 1879-09-0 as source substances and the Substance as target substance, and 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 to be quantitatively equal to those of the source substance(s) or based on a worst-case approach.

ECHA notes the following shortcoming with regards to predictions of environmental fate and ecotoxicological properties based on analogue approach.

The common deficiencies are set out here, while the specific ones, which also add to the overall conclusion, are set out under Appendix A sections 3 and 4, Appendix B section 3, and Appendix C sections 3 and 9 below.

Missing of supporting information

Annex XI, Section 1.5 of the REACH Regulation states that "*physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)*". For this purpose "*it is important to provide supporting information to strengthen the rationale for the read-across*"[7]. 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 substance(s).

Supporting information must include information to confirm that the Substance and the source substances have similar (eco)toxicological properties and that the structural differences would not affect the predicted properties of the substances.

[7] ECHA Guidance R.6: Section R.6.2.2.1.f

As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and of the source substance(s) is necessary to confirm that both substances cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance(s).

In order to support your read-across hypothesis, you have provided the following information:

- Alert profiles using the QSAR Toolbox

You have provided target and source substances which have xylenol as common structural element. In addition to this, common group shared between the target substance and the source substances include alkyl arenas and phenol group.

You have assessed the impact of potential structural differences using a set of physico-chemical and environmental fate and ecotoxicological properties, structural characteristics and mechanistic alerts obtained from the QSAR Toolbox v3.4 for the Substance and for each of the source substances.

You indicate that "As the target and read-across analogues contain nearly similar functional groups, different structural activity amongst the various read-across substances is not expected. As per the analysis conducted with the OECD (Q)SAR Toolbox v.3.4, it is indicated that the target and the read-across analogues share similar structural alerts."

- Experimental studies

In the read-across justification you argue that the target and source substances have similar ecotoxicity values. In your dossier and/or in your comments to the draft decision, you have provided the following information for aquatic toxicity on the Substance and the analogue substances:

Study	**Target substance (EC 226-378-9 / CAS 5384-21-4)**	**EC 204-327-1 / CAS 119-47-1**	**EC 211-838-3/ CAS 700-13-0**	**EC 217-533-1 / CAS 1879-09-0**
Short-term toxicity to fish		Study (ii), OECD TG 203 . 96-h LC50 >5 mg/L (nominal)	Study (iii), DIN 38412, part L15 . 96-h LC50 <2.2 mg/L (nominal)	
Short-term toxicity to invertebrates		Study (iii), OECD TG 202. 48-h EC50 >0.01 mg/L	Study (iv), EU method C.2. 48-h EC50 0.97 mg/L (nominal)	
Toxicity to algae	Study (i), OECD TG 201, 72h: ErC50 > 48.6 mg/L. (nominal)		Study (ii), DIN 38412, part 9, 72h: ErC50 13 mg/L. (nominal)	

Long-term toxicity to invertebrates		Study (iii), OECD TG 211, 21d: NOEC = 0.34 mg/L (measured)		Study (iv), OECD TG 202 (1984), 21d: NOEC = 0.32 mg/L (nominal)
Bioaccumulation		Study (v), OECD TG 305 C: BCF = 23-125, 490-710		

We have assessed this information and identified the following issues:

- Alerts obtained from the QSAR toolbox

There are structural differences between the target and source substances. While the similarity in presence or absence of structural alerts may indicate that the differences do not influence the reactivity of the substance, e.g. on the protein or DNA, this information does not confirm, on its own, that the Substance and the source substances have similar ecotoxicological properties such as aquatic toxicity (growth inhibition of algae, short-term toxicity to fish and Daphnia, and reproductive toxicity to Daphnia). In fact, the complexity of the aquatic toxicity and the mechanisms associated are not covered by computational tools. Therefore, the structural alerts reported in the justification document do not represent adequate information on the above mentioned properties of the Substance and the source substances, e.g. bridging studies of comparable design and duration.

Similarly regarding the predicted bioaccumulation properties, while this information might be relevant to support similarity in toxicokinetics behaviour in aquatic compartment, this information do not allow the prediction of complex information requirement that you intend to cover with your adaptation, as indicated above.

- Experimental studies

ECHA has identified shortcomings with the reliability of the experimental studies provided as supporting information. All the experimental studies are provided as secondary references which do not allow an independent assessment of the primary source of information. More specifically, insufficient reporting of the results (e.g., only effect values are reported without providing data in the tabular form or data in the control(s)) does not allow to assess independently if the test validity criteria were met. Without this information ECHA cannot consider the studies as reliable and sufficient to be used to support the weight of evidence approach.

Furthermore, we note that for aquatic toxicity (except algae growth inhibition endpoint) and bioaccumulation, you have not provided any experimental information on the Substance (EC 226-378-9 / CAS 5384-21-4). Therefore, no comparison can be made between the Substance and the analogues to support your claim of similarity in ecotoxicological and environmental fate properties.

Conclusion on the reliability of the analogue substances

Therefore, based on the information in the dossier and provided in the comments, the information from the analogue substances submitted under your weight of evidence adaptation is not considered reliable.

B. Reliability of the provided information with QSAR estimations

ECHA understands that you intend to predict the ecotoxicological properties of the Substance for the listed above endpoints, from data obtained with QSAR estimations as part of your weight of evidence adaptation.

For this information to be considered reliable, it would have to meet the requirements for QSAR adaptation approach.

For the same reasons as explained in section 2 below, the criteria specified in Annex XI, Section 1.3. are not fulfilled. The information from the QSAR estimations submitted under your weight of evidence adaptation is therefore not considered reliable.

Additional issues related to weight of evidence are addressed under the corresponding information requirements.

2. Assessment of your Qualitative or Quantitative Structure Activity Relationship ((Q)SAR) adaptation, under the requirements of Annex XI, Section 1.3.

For ecotoxicological and physico-chemical properties you have provided (Q)SAR adaptations in accordance with Annex XI, Section 1.3 for the following standard information requirements:

- Partition coefficient n-octanol/water (Annex VII, Section 7.8.)
- Short-term toxicity study on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Simulation testing on ultimate degradation in surface water (Annex IX, Section 9.2.1.2)
- Sediment simulation testing (Annex IX, Section 9.2.1.4)
- Soil simulation testing (Annex IX, Section 9.2.1.3.)
- Long-term toxicity in fish (Annex IX, Section 9.1.6)
- Bioaccumulation in aquatic species (Annex IX, Section 9.3.2)

Annex XI, Section 1.3. states that results obtained from valid QSAR models may be used instead of testing when the following cumulative conditions are met, in particular:

1. results are derived from a QSAR model whose scientific validity has been established;
2. the substance falls within the applicability domain of the QSAR model;
3. adequate and reliable documentation of the applied method is provided; and
4. the results are adequate for classification and labelling and/or risk assessment.

ECHA notes that with regards to (Q)SAR predictions there are issues that are common to all information requirements listed above and also issues that are specific for these information requirements individually. Altogether, they result in a failure to meet the requirements of Annex XI, 1.3., as all the cumulative conditions of this provision are not fulfilled. The common issues are set out in the below, while the specific issues are set out under the information requirements concerned in the Appendix C, Section 5 to 7.

According to ECHA's Practical guide "How to use and report (Q)SARs", section 3.4, a QSAR Model Reporting Format (QMRF) and a QSAR Prediction Reporting Format (QPRF) are required to establish the scientific validity of the model, to verify that the Substance falls within the applicability domain of the model, and to assess the adequacy of the prediction for the purposes of classification and labelling.

You have not provided any documentation for the QSAR predictions. In particular, you have not included a QMRF and a QPRF in your technical dossier for the relevant endpoints. Therefore, ECHA cannot establish whether the model is scientifically valid, whether the Substance falls within the applicability domain of the model, and whether the results are adequate for classification and labelling and/or risk assessment.

In their comments to the draft decision, the lead registrant claims that as per ECHA's request they have now attached in the technical dossier the QMRF reports of the predictions for the partition coefficient and short-term toxicity in aquatic invertebrates endpoints and the supportive document of the prediction for the bioaccumulation endpoint. However, as the information provided by the lead registrant is currently not available in the registration dossier and since the information provided in the comments is not sufficient for ECHA to make an independent assessment of the adequacy and reliability of this data, the data gap remains.

The adaptations you provided do not fulfil the criteria specified in Annex XI, Section 1.3. and they are therefore rejected.

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

1. Partition coefficient n-octanol/water

Partition coefficient n-octanol/water is a standard information requirement in Annex VII to REACH (Section 7.8).

You have adapted this information requirement by using the following QSAR estimated data under Annex XI, Section 1.3:
(i) QSAR estimation based on OPERA V1.02, 2017, for the Substance.

We have assessed this information and identified the following issue:

As explained under Appendix on Reasons common to several requests, your QSAR adaptation is rejected.

On this basis, the information requirement is not fulfilled.

In their comments to the draft decision, the lead registrant agrees to conduct the requested study by saying that the "*study of partition coefficient n-octanol/water according to the internationally accepted standard test guideline*" will be performed.

Other registrants have indicated in their own comments that a GLP study on the Substance conducted according to OPPTS 830.7560 Partition Coefficient (n-Octanol/Water), Generator Column Method being equivalent or similar to OECD 117 (HPLC Method) is already available. These registrants state that they intend to submit this information either in an update of the jointly submitted dossier or in an opt-out in order to fulfil the information requirement.

However, the information provided in the comments with regard to the exisiting study is not sufficient for ECHA to make an independent assessment of its adequacy and reliability. Therefore, the data gap remains.
Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation").

Study design

Guidance for determining appropriate test methods for the partition coefficient n-octanol/water is available in the ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.1.8 (version 6.0, July 2017).

2. In vitro gene mutation study in bacteria

An *in vitro* gene mutation study in bacteria is an information requirement under Annex VII to REACH (Section 8.4.1.).

You have adapted this information requirement by using Weight of evidence under Annex XI, Section 1.2. based on the experimental data from various chemicals:
(i) bacterial reverse mutation test with the Substance ([redacted] 2018a)
(ii) bacterial reverse mutation test with the analogue substance 2,2'-Methylen-bis(4-methyl-6-tert-butylphenol), EC No. 204-327-1 (J-check 2018a)
(iii) bacterial reverse mutation test with the analogue substance 2,3,5-trimethylphenol, EC No. 211-806-9 (Florin 1980)

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

As explained under Appendix on Reasons common to several requests, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.4.1 at Annex VII include:

- Detection and quantification of gene mutations (base pairs, substitution or frame shift) in cultured bacteria including data on the number of revertant colonies; and
- Data provided on 5 bacterial strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101).

The sources of information provide relevant information for the information requirement.

However, the reliability of these sources of information is significantly affected by the following deficiencies:

The reliability of sources of information (ii) and (iii) is significantly affected by the deficiency identified and explained under Appendix on Reasons common to several requests, Section 1.A.

The reliability of source of information (i) is significantly affected by the following deficiency:

For a study conducted according to OECD TG 471[8] (1997), the following specifications must be met:

a) Triplicate plating must be used at each dose level.
b) One positive control must be included in the study. The positive control substance must produce a statistically significant increase in the number of revertant colonies per plate compared with the concurrent negative control.
c) The number of revertant colonies per plate for the concurrent negative control must be inside the historical control range of the laboratory.
d) The mean number of revertant colonies per plate must be reported for the treated doses and the controls.

In your dossier you have provided very limited information on the study design. In particular, the reported data for the source of information (i) do not include:

a) triplicate plating at each dose level.
b) a positive control that produced a statistically significant increase in the number of revertant colonies per plate compared with the concurrent negative control.
c) a negative control with a number of revertant colonies per plate inside the historical control range of the laboratory.
d) data on the number of revertant colonies per plate for the treated doses and the controls.

In the absence of information on these critical aspects of the specification/conditions of the provided study, ECHA cannot evaluate the reliability of the conclusions on the frequency of gene mutations in bacteria.

In summary, all three sources of information have significant reliability issues and cannot contribute to the conclusion on the potential of the Substance to gene mutations in bacteria.

[8] ECHA Guidance R.7a, Table R.7.7–2, p.557

Finally, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 471 study because there are no reliable sources of infromation.

On this basis, your adaptation is rejected and the information requirement is not fulfilled.

In their comments to the draft decision, the lead registrant agrees with the request. Other registrants have indicated in their own comments that a GLP study on the Substance conducted according to the OECD test guideline 471 and providing negative results exists. These registrants state that they intend on submitting this information either in an update of the jointly submitted dossier or in an opt-out in order to fulfil the information requirement.

The existing information referred to by some registrants in their comments has the potential to address the incompliances identified in this decision for this information requirement however, the level of information provided in your comments is not sufficient for ECHA to make an independent assessment of the adequacy and reliability of this experimental data. Therefore, the data gap remains.

Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation").

Study design

To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471)

3. Short-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.).

You have adapted this information requirement by using Weight of evidence under Annex XI, Section 1.2. Your weight of evidence is based on the following QSAR estimated and experimental data from various chemicals:

(i) QSAR estimation based on ECOSAR Version 1.11 (class neutral organics) for the Substance ([redacted] 2018)

(ii) OECD TG 202 short term toxicity test to aquatic invertebrates for the analogue substance tert-dodecanethiol, EC No. 246-619-1 (J-check 2018a)

(iii) OECD TG 202 short term toxicity test to aquatic invertebrates for the analogue substance 2,2'-methylenebis(6-tert-butyl-4-methylphenol), EC No. 204-327-1 (J-check 2018b)

In their comments to the draft decision, the lead registrant provides also the following additional study (iv):

(iv) EU method C.2 short term toxicity test to aquatic invertebrates for the analogue substance 2,3,5-Trimethylquinol, EC No. 211-838-3. According to the lead registrant, data are taken from different published literature/secondary source & reliable handbook.

We have assessed this information and identified the following issues:

As explained under Appendix on Reasons common to several requests, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of

information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 9.1.1 at Annex VII includes similar information that is produced by the OECD TG 202. This includes that the concentration of the test material leading to the immobilisation of 50% of daphnids at the end of the test is estimated.

The provided sources of information provide relevant information for the information requirement.

However, the reliability of all three sources of information and the reliability of the information regarding the study (iv) provided in your comments is significantly affected by the deficiencies identified and explained under Appendix on Reasons common to several requests (Section 1. A and B).

ECHA concludes that the sources of information as indicated above provide information on immobilisation of daphnids, but the information provided on this key investigation is not reliable.

Accordingly, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 202 study.

On this basis, your adaptation is rejected and the information requirement is not fulfilled.

Other registrants have indicated in their own comments to the draft decision that a study on the Substance conducted according an OPPTS guideline test without analytical monitoring of test concentrations is available for the short-term toxicity to aquatic invertebrates endpoint.

However, these registrants state that they intend to adapt the requested short-term toxicity study based on REACH Annex VII section 9.1.1 column 2, if the long-term toxicity to aquatic invertebrates study (OECD TG 211) requested in Appendix C. Section 3 remains in the final decision. They also conclude that the available OPPTS guideline test can be used as a supporting study for short-term toxicity endpoint and as a range finder for the long-term test, and they intend to submit this information either in an update of the jointly submitted dossier or in an opt-out in order to fulfil the information requirement.

REACH Annex VII section 9.1.1 column 2 specifies that the short-term toxicity study does not need to be conducted if a long-term aquatic toxicity study on invertebrates is available. However, as the information on short-term or long-term toxicity studies on the Substance is currently not available in the registration dossier and since the information provided in your comments is not sufficient for ECHA to make an independent assessment of the adequacy and reliability of the experimental short-term data, the data gap remains. Regarding any 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 VII, Section 9.1.1, Column 2 or one of the general adaptation rules under Annex XI.

Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation").

Study design

The Substance is difficult to test due to the adsorptive properties (Log koc 5.0). OECD TG 202 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 202. 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.

4. Growth inhibition study aquatic plants

Growth inhibition study aquatic plants is an information requirement under Annex VII to REACH (Section 9.1.2.).

You have provided the following information:

(i) OECD TG 201 alga growth inhibition test with the Substance [redacted] 2014)

In their comments to the draft decision, the lead registrant provides also the following additional study (ii):

(ii) The study following the principles of "Scenedesmus cell proliferation inhibition test, DIN 38412 part 9" with the analogue substance 2,3,5-Trimethylquinol, EC No. 211-838-3. According to the lead registrant, data are taken from different published literature/secondary source and the reliable handbook.

We have assessed this information and identified the following issue:

According to Article 13(4) of REACH, ecotoxicological tests and analyses must be carried out in compliance with the principles of good laboratory practice (GLP). According to Article 141(2), Article 13 applies from entry into application of the REACH Regulation on 1 June 2008.

The study you provided was conducted in 2014 but it was not performed in compliance with GLP. Consequently, it cannot be used as key study for the purpose of hazard identification.

In their comments to the draft decision, the lead registrant, while providing a short summary of the study (i), does not provide any additional information regarding the non-GLP status of this study to address the identified incompliance.

In addition, as regards the lead registrants comments related to the study (ii), ECHA understands that you now intend to adapt this standard information requirement by applying weight of evidence approach in accordance with Annex XI, Section 1.2. As explained under Appendix on Reasons common to several requests, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Relevant information that can be used to support weight of evidence adaptation for

information requirement of Section 9.1.2 at Annex VII includes similar information that is produced by the OECD TG 201. This includes that the concentration of the test material leading to the growth inhibition of 50% of the tested algae species at the end of the test is estimated.

The provided sources of information provide relevant information for the information requirement.

However, the reliability of the sources of information is significantly affected by the deficiencies identified and explained under Appendix on Reasons common to several requests (Section 1. A).

ECHA concludes that the sources of information as indicated above provide information on growth inhibion of algae, but the information provided on this key investigation is not reliable.

Accordingly, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 201 study.

Therefore, the information requirement is not fulfilled.
Other registrants have indicated in their own comments to the draft decision that they agree with the request.

Other registrants also state in their comments that a study on the Substance conducted according an OPPTS guideline without analytical monitoring of test concentrations is available for the algae growth inhibition endpoint and they intend to use this as a supporting study and as a range finder for the repeat algae growth inhibition test. They intend to submit this information either in an update of the jointly submitted dossier or in an opt-out in order to fulfil the information requirement.

As the information on the algae growth inhibition study on the Substance is currently not available in the registration dossier and since the information provided in your comments is not sufficient for ECHA to make an independent assessment of the adequacy and reliability of the experimental data, the data gap remains.

Study design

OECD TG 201 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 A, Section 3.

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

1. In vitro cytogenicity study in mammalian cells or In vitro micronucleus study

An *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study is an information requirement under Annex VIII to REACH (Section 8.4.2.).

You have adapted this information requirement by using Weight of evidence under Annex XI, Section 1.2. based on the experimental data from various chemicals:

(i) in vitro mammalian cell chromosome aberriation test test with the Substance ([redacted] 2018b)
(ii) in vitro mammalian cell chromosome aberriation test test with the analogue substance 2,2'-Methylen-bis(4-methyl-6-tert-butylphenol)m EC No. 204-327-1 (J-check 2018b)
(iii) in vitro mammalian cell chromosome aberriation test test with the analogue substance 2,2',6,6'-Tetra-tert-butyl-4,4'-methylenediphenol, EC No. 204-279-1 (J-check 2018c)

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

As explained under Appendix on Reasons common to several requests, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.4.2. at Annex VIII includes:

- Detection and quantification of structural or numerical chromosomal aberrations in cultured mammalian cells including data on the cytotoxicity and the frequency of cells with chromosomal aberrations or micronuclei.

This information is covered by OECD TG 473 or OECD 487.

The sources of information provide relevant information for the information requirement. However, the reliability of these sources of information is significantly affected by the following deficiencies:

The reliability of sources of information (ii) and (iii) is significantly affected by the deficiency identified and explained under Appendix on Reasons common to several requests, Section 1.A.

Insufficient level of reporting for an independent assessment of the information

In order to independently assess the reliability of the information obtained from a study and establish its contribution to a weight of evidence approach, a robust study summary must be provided (Art. 3(28) and 10(a)(vii) and Annex I, Section 1.1.4 of REACH).

Robust study summaries must provide a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study (Article 3(28)).

Information on the following key investigations required from the OECD TG 476 or OECD TG 490[9] are missing from the endpoint study records included in your dossier for studies (i) to (iii):

a) The maximum concentration tested must induce 55+5% of cytotoxicity compared to the

[9] ECHA Guidance R.7a, Table R.7.7–2, p.557

negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test concentration must correspond to 10 mM, 2 mg/mL or 2 µl/mL, whichever is the lowest.
b) At least 300 well-spread metaphases must be scored per concentration.
c) One positive control must be included in the study. The positive control substance must produce a statistically significant increase in the response compared with the concurrent negative control.
d) The response for the concurrent negative control must be inside the historical control range of the laboratory.
e) Data on the cytotoxicity and the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures must be reported.

The reported data for the studies do not include:
a) a maximum tested concentration of 10 mM, 2 mg/mL or 2 µl/mL, or that induced 55+5% of cytotoxicity compared to the negative control, or the precipitation of the tested substance.
b) the scoring of at least 300 metaphases per concentration.
c) a positive control that produced a statistically significant increase in the response compared with the concurrent negative control.
d) a negative control with a response inside the historical control range of the laboratory.
e) data on the cytotoxicity and/or the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures.

In the absence of such information on those critical aspects of the specification/conditions of the provided studies, ECHA cannot evaluate the reliability of the conclusions on cytotoxicity and the frequency of cells with structural chromosomal aberration(s).

In summary, all three sources of information have significant reliability issues and cannot contribute to the conclusion on the potential of the Substance to cause cytotoxicity and cannot provide information on the frequency of cells with structural chromosomal aberration(s) or the frequency of micronuclei in cultured mammalian cells.

Finally, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 473 study because there are no reliable sources of infromation.

On this basis, your adaptation is rejected and the information requirement is not fulfilled.

In their comments to the draft decision, the lead registrant agrees with the request.

Other registrants have indicated in their own comments that a GLP study on the Substance conducted according to the OECD test guideline 487 exists. This study produced positive results in the absence and in the presence of metabolic activation. The registrants also declare that an *in vivo* Comet assay was conducted with the Substance "*to meet the requirements of a regulatory jurisdiction other than REACH*". They refer to this *in vivo* data in order to follow-up on the positive results obtained in the OECD TG 487 study. This Comet assay revealed a statistical increase in DNA damage in the stomach at the dose of 1000 mg/kg/d. These effects are considered by the registrants to be within the range of response observed in the historical control data, albeit at the high end of that range. These registrants state that they intend on submitting this *in vitro* and *in vivo* information either in an update of the jointly submitted dossier or in an opt-out in order to fulfil the information requirement.

The existing information referred to by some registrants in their comments has the potential to address the incompliances identified for this information requirement however, the information provided in your comments is not sufficient for ECHA to make an independent assessment of the adequacy and reliability of this experimental data. Therefore, the data gap remains.

Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation").

Study design

To fulfil the information requirement for the Substance, either *in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) or *in vitro* micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) are considered suitable.

2. In vitro gene mutation study in mammalian cells

An *in vitro* gene mutation study in mammalian cells is an information requirement under Annex VIII to REACH (Section 8.4.3.) in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

Triggering of the study

The result of the request for information in Appendix A, Section 1 and Appendix B, Section 1 will determine whether the present requirement for an *in vitro* mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3 is triggered.

Assessment of information provided the following

You have adapted this information requirement by using Weight of evidence under Annex XI, Section 1.2. based on the experimental data from various chemicals:

(i) in vitro gene mutation study in mammalian cells with the Substance ([redacted] 2015a)

(ii) in vitro gene mutation study in mammalian cells with the Substance ([redacted] 2015b)

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

As explained under Appendix on Reasons common to several requests, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.4.3 at Annex VIII includes similar information that is produced by the OECD TG 476/490 and OECD TG 488. This includes:

- Detection and quantification of gene mutations (point mutations, frame-shift mutations, small deletions, etc.) including data on the frequency of mutant colonies in cultured mammalian cells (*in vitro*) or mutant frequency for each tissue in mammals (*in vivo*).

The sources of information provide relevant information for the information requirement.

However, the reliability of these sources of information is significantly affected by the following deficiencies:

Insufficient level of reporting for an independent assessment of the information

In order to independently assess the reliability of the information obtained from a study and establish its contribution to a weight of evidence approach, a robust study summary must be provided (Art. 3(28) and 10(a)(vii) and Annex I, Section 1.1.4 of REACH).

Robust study summaries must provide a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study (Article 3(28)).

Information on the following key investigations required from the OECD TG 476 or OECD TG 490[10] are missing from the endpoint study records included in your dossier for studies (i) and (ii):

a) The maximum concentration tested must induce 80-90% of cytotoxicity compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test concentration must correspond to 10 mM, 2 mg/mL or 2 µl/mL, whichever is the lowest.
b) At least 4 concentrations must be evaluated, in each test condition.
c) One positive control must be included in the study. The positive control substance must produce a statistically significant increase in the response compared with the concurrent negative control.
d) The response for the concurrent negative control must be inside the historical control range of the laboratory.
e) Data on the cytotoxicity and the mutation frequency for the treated and control cultures must be reported.

The reported data for the studies do not include:

a) a maximum tested concentration of 10 mM, 2 mg/mL or 2 µl/mL, or that induced 80-90% of cytotoxicity compared to the negative control, or the precipitation of the tested substance.
b) the evaluation of at least 4 concentrations in each test condition.
c) one positive control that produced a statistically significant increase in the number of revertant colonies per plate compared with the concurrent negative control.
d) a negative control with a response inside the historical control range of the laboratory.
e) data on the cytotoxicity and the mutation frequency for the treated and control cultures.

In the absence of such information on those critical aspects of the specification/conditions of the provided studies, ECHA cannot evaluate the reliability of the conclusions on cytotoxicity and the frequency of gene mutations. Therefore this information must be considered as unreliable.

In summary, both sources of information have significant reliability issues and cannot contribute to the conclusion on the potential of the Substance to cause cytotoxicity and cannot provide information on frequency of gene mutations.

Finally, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 476 or OECD TG 490 study because there are no reliable sources of infromation.

[10] ECHA Guidance R.7a, Table R.7.7–2, p.557

On this basis, your adaptation is rejected and the information requirement is not fulfilled.

In their comments to the draft decision, the lead registrant agrees with the request and indicate that in case of negative results are obtained from the studies planned to be conducted according to the OECD TGS 471 and 473, they will perform an *in vitro* gene mutation study in mammalian cells according to the OECD TG 476.

Other registrants have indicated in their own comments that since the *in vitro* cytogenicity study on the Substance that they mentioned in their comments provided positive results, "*the requirement for an in vitro gene mutation study in mammalian cells is not required*".

As indicated above, an *in vitro* gene mutation study in mammalian cells is an information requirement under Annex VIII to REACH (Section 8.4.3.) in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test. Some registrants have referred to existing information on the Substance relevant for both *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test. In particular, they reported positive results for the *in vitro* cytogenicity test. However, as the information on the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test is currently not available in the registration dossier and since the information on these studies provided in the comments is not sufficient for ECHA to make an independent assessment of their adequacy and reliability, it is not possible to conclude on whether the information requirement for an *in vitro* gene mutation in mammalian cells is triggered or not. Therefore the data gap remains as per the conditions listed above.

Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation").

Study design

To fulfil the information requirement for the Substance, either the *in vitro* mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) or the thymidine kinase gene (OECD TG 490) are considered suitable.

3. Short-term toxicity testing on fish

Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH (Section 9.1.3.).

You have adapted this information requirement by using Weight of evidence under Annex XI, Section 1.2. Your weight of evidence is based on the following experimental data from various chemicals:

(i) OECD TG 236 fish embryo acute toxicity (FET) test with the analogue substance 2,2'-methylenebis(6-tert-butyl-4-methylphenol), EC No. 204-327-1 (Xiaoxi Yang et.al.,2018)
(ii) OECD TG 203 fish acute toxicity test with the analogue substance 2,2'-methylenebis(6-tert-butyl-4-methylphenol), EC No. 204-327-1 (J-check 2018)

In their comments to the draft decision, the lead registrant also provides the following additional study (iii):

(iii) DIN 38412, part L15 fish acute toxicity test with the analogue substance 2,3,5-Trimethylquinol, EC No. 211-838-3. According to the lead registrant, data are taken from different published literature/secondary source and the reliable handbook.

We have assessed this information and identified the following issues:

As explained under Appendix on Reasons common to several requests, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 9.1.3 at Annex VIII includes similar information that is produced by the OECD TG 203. This includes that the concentration of the test material leading to the mortality of 50% of the juvenile fish at the end of the test is estimated.

The provided source of information (i) provides information on fish embryo toxicity and therefore does not cover the key investigation required by OECD TG 203. Therefore, it does not provide relevant information for the information requirement.

The provided source of information (ii) in your dossier and the source of information (iii) in your comments provide relevant information for the information requirement.

However, the reliability of the information in study (ii) and the reliability of the information in the study (iii) provided in your comments is significantly affected by the deficiencies identified and explained under Appendix on Reasons common to several requests (Section 1. A).

ECHA concludes that the source of information (i) is not relevant. Furthermore, the source of information (ii) and (iii) do not provide reliable information on this key investigation.

Accordingly, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 203 study.

On this basis, your adaptation is rejected and the information requirement is not fulfilled.

Other registrants have indicated in their own comments to the draft decision that a study on the Substance conducted according an OPPTS guideline without analytical monitoring of test concentrations is available for the short-term toxicity to fish endpoint.

However, these registrants state that they intend to adapt the requested short-term toxicity study based on REACH Annex VIII section 9.1.3 column 2, if the long-term toxicity to fish study (OECD TG 210) requested in Appendix C. Section 4 remains in the final decision. They also conclude that the available OPPTS guideline test can be used as a supporting study for short-term toxicity endpoint and as a range finder for the long-term test, and they intend to submit this information either in an update of the jointly submitted dossier or in an opt-out in order to fulfil the information requirement.

REACH Annex VIII section 9.1.3 column 2 specifies that the short-term toxicity study does not need to be conducted if a long-term aquatic toxicity study on fish is available. However, as the information on short-term or long-term fish toxicity studies on the Substance is currently not available in the registration dossier and since the information provided in your comments is not sufficient for ECHA to make an independent assessment of the adequacy and reliability of the experimental short-term data, the data gap remains. Regarding any 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 VIII, Section 9.1.3, Column 2 or one of the general adaptation rules under Annex XI.

Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation").

Study design

OECD TG 203 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 A, Section 3.

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

1. Sub-chronic toxicity study (90-day)

A Sub-chronic toxicity study (90 day) is a standard information requirement in Annex IX to REACH.

You have provided:
(i) Short-term toxicity study (28-days) with the Substance ([redacted] 2014)

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

To fulfil the information requirement, the Sub-chronic toxicity study (90 day) has to meet the requirements of OECD TG 408. Therefore, the following specifications must be: at least 10 male and 10 female animals for each test and control group; and dosing of the Substance daily for a minimum of 90 days.

The reported data for the study provided indicates the following about the design of the study: 5 males and females in each test and control group; and an exposure duration of 28 days.

Based on the above, the information you provided do not fulfil the information requirement.

Specification of the study design

Following the criteria provided in Annex VIII, Section 8.6.1, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity of the Substance; Guidance on IRs and CSA, Section R.7.5.6.3.2.

According to the OECD TG 408, the rat is the preferred species.

Therefore, the study must be performed according to the OECD TG 408, in rats and with oral administration of the Substance.

Information on data sharing for studies involving vertebrate animals

The registration dossier of the registrant who opted-out from the joint submission for this information requirement contains data which is relevant for this endpoint (90-day sub-chronic toxicity study, OECD TG 408, 2017). In accordance with Title III of the REACH Regulation, you must request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs[11].

ECHA considers six months a sufficiently reasonable time for the registrant to seek permission to refer to the other registrant's full study report.

Information provided in the registrants' comments to the draft decision and to the proposal for amendment

In their comments to the draft decision, the lead registrant indicated that the registration dossier will be updated to include the results from an existing 90-day repeated-dose toxicity study performed using the Substance. Information derived from a scientific article describing the study and an executive summary of the study were provided in the comments.

[11] https://echa.europa.eu/regulations/reach/registration/data-sharing

ECHA has taken this information into account and notes the following issues.

In order to make an independent assessment of a key study, a robust study summary must be provided (Guidance on IRs and CSA, Section R.6.2.6; Art. 3(28) and 10(a)(vii) and Annex I, Section 1.1.4/3.1.5 of REACH).

Robust study summary (RSS) must provide a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study (Article 3(28)).

The information on the existing 90-day repeated-dose toxicity study, performed using the Substance and reported to be conducted according to OECD TG 408, provided in the comments by the lead registrant is not sufficient for ECHA to make an assessment of the reliability of this data because some elements of the study design required in a RSS are missing from your comments. This information includes, e.g. details on the scope of the gross necropsy, the set of organs for which an histopathological assessment was conducted. In the absence of such information, no conclusions on the reliability and adequacy of this study to fulfil the information requirement can be made.

During the period provided to comment on the amendment proposed by a Member State Competent Authority the lead registrant provided further information from the above mentioned publication. ECHA considers that elements of the study design required in a RSS are still missing. In particular, only an assumption regarding the scope of the gross necropsy and the set of organs for which an histopathological assessment was conducted is made without being actually reported in the provided information. In the absence of such information, from mere assumptions, no conclusions on the reliability and adequacy of this study to fulfil the information requirement can be made.

Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation").

Other registrants have indicated in their comments their agreement to provide the relevant study that is already available in the dossier of the registrant who opted-out from the joint submission for this information requirement by the set deadline suggested in the proposal for amendment submitted by a competent authorities of a Member State.

2. 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 adapted this information requirement by using Weight of evidence under Annex XI, Section 1.2. based on the experimental data from various chemicals:

(i) reproductive and developmental toxicity screening test with the Substance ([redacted] 1999a)
(ii) combined repeated dose toxicity study with the reproductive/developmental toxicity screening test with the analogue substance 6,6'-di-tert-butyl-2,2'-methylenedi-p-cresol, CAS No. 119-47-1 ([redacted] 1999b)
(iii) modified combined repeated dose toxicity study with the reproductive/developmental toxicity screening test with the analogue substance 2,4,6-trimethylphenol, EC No. 208-419-2 (Tyl, 2005)
(iv) investigation of fetal resorption in the rat with 2,2'-methylenebis(6-tert-butyl-4-methylphenol), EC No 204-327-1 and 6,6'-di-tert-butyl-2,2'-methylenedi-p-cresol, CAS No. 119-47-1 (Telford, 1962)

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

As explained under Appendix on Reasons common to several requests, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.7.2 at Annex IX includes similar information that is produced by the OECD TG 414 on one species. The following aspects are covered: 1) pre-natal developmental toxicity, 2) maternal toxicity, and 3) maintenance of pregnancy.

Pre-natal developmental toxicity

Pre-natal developmental toxicity includes information after prenatal exposure on embryonic/foetal survivial (number of live foetuses; number of resorptions and dead foetuses, postimplantation loss), growth (body weights and size) and structural malformations and variations (external, visceral and skeletal).

Maternal toxicity

Maternal toxicity includes information after gestational exposure on maternal survival, body weight and clinical signs and other potential aspects of maternal toxicity in dams.

Maintenance of pregnancy

Maintenance of pregnancy includes information on abortions and/or early delivery as a consequence of gestational exposure and other potential aspects of maintenance of pregnancy.

The sources of information provide relevant information for the information requirement which cover aspects 2) and 3). However, for aspect 1) the relevance of the sources of information is significantly affected by the following deficiency: none of the sources of information has investigated the most important aspects of developmental toxicity, i.e. skeletal and visceral malformations and variations as required by OECD TG 414.

In addition, the reliability of the sources of information (ii), (iii) and (iv) is significantly affected by the deficiency identified and explained under Appendix on Reasons common to several requests, Section 1.A.

Furthermore, the reliability of source of information (i) is significantly affected by the following deficiency: this study has a statistical power which is significantly less than that of the OECD TG 414. As a consequence, the results obtained on the aspects 1) (to the extent it is covered), 2) and 3) are associated with a significant uncertainty when compared to the OECD TG 414.

In summary, all of the sources of information have the same deficiency in the coverage the most critical investigations with regard to aspect 1), i.e. skeletal and visceral malformations and variations. In addition all sources of information have significant reliability issues and cannot reliably contribute to a robust conclusion on the potential of the Substance to be a developmental toxicant.

Finally, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen

to be investigated in an OECD TG 414.

On this basis, the information you provided do not fulfil the information requirement.

Specification of 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[1] administration of the Substance.

In their comments to the draft decision, the lead registrant agrees with the request and indicates that testing will be conducted in the rat.

Other registrants indicated in their comments their agreement with the request. They also indicated that "*It is likely that the rabbit will be selected as the initial test species as available test data indicate the substance is unlikely to be a developmental toxicant in rats.*"

As indicated in the decision, the test shall be conducted either in the rat or in the rabbit as first species. The selection of the species used to conduct this study between the rat or the rabbit is at the discretion of the registrants.

3. 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 Weight of evidence under Annex XI, Section 1.2. Your weight of evidence is based on the following QSAR estimated and experimental data from various chemicals:

(i) QSAR estimation based on ECOSAR Version 1.11 (class neutral organics) with the Substance ([redacted] 2018)
(ii) OECD TG 211 *Daphnia magna* reproduction test with the analogue substance tert-dodecanethiol, EC No. 246-619-1 (J-check 2018a)
(iii) OECD TG 211 *Daphnia magna* reproduction test with the analogue substance 2,2'-methylenebis(6-tert-butyl-4-methylphenol), EC No. 204-327-1 (J-check 2018b)

In their comments to the draft decision, the lead registrant also provides the following additional study (iv):

(iv) OECD TG 202 (1984) toxicity test with the analogue substance 6-tert-butyl-2,4-xylenol, EC no. 217-533-1. According to the lead registrant, data are taken from different published literature/secondary source and the reliable handbook.

We have assessed this information and identified the following issues:

As explained under Appendix on Reasons common to several requests, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 9.1.5 at Annex IX includes similar information that is produced by the OECD TG 211. This includes the reproductive output of *Daphnia sp.*, the survival of the parent animals during the test, and the time to production of the first brood.

The provided sources of information in your dossier and the source of information (iv) in your comments provide relevant information for the information requirement.

However, the reliability of all sources of information in your dossier and in your comments is significantly affected by the deficiencies identified and explained under Appendix on Reasons common to several requests (Section 1. A and B).

ECHA concludes that sources of information as indicated above provide information on long-term toxicity of daphnids, but the information provided on the key investigations is not reliable.

Accordingly, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 211 study.

On this basis, your adaptation is rejected and the information requirement is not fulfilled.

Other registrants indicated in their own comments to the draft decision their agreement with the request.

Study design

OECD TG 211 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 A, Section 3.

4. 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 adapted this information requirement by using the following QSAR estimated data under Annex XI, Section 1.3:

(i) QSAR estimation based on ECOSAR Version 1.11 (class neutral organics) with the Substance ([redacted] 2018)

We have assessed this information and identified the following issue:

> As explained under Appendix on Reasons common to several requests, your QSAR adaptation is rejected.

On this basis, the information requirement is not fulfilled.

In their comments to the draft decision, the lead registrant stated the following: "*As per ECHA's suggestion of target chemical (2E)-2-(phenylmethylidene)heptanal (CAS no. 78605-96-6; EC no. 800-696-3), we will consider the request of long term toxicity testing on fish and will perform the study according to the internationally accepted standard test guideline, thereby to support the classification of the substance*."

However, ECHA notes that your comment on the substance with EC No 800-696-3 is not related to the Substance (EC No 226-378-9) addressed in this decision.

Other registrants indicated in their own comments their agreement with the request.

Study design

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 A, Section 3.

5. 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 adapted this information requirement by using the following QSAR estimated data under Annex XI, Section 1.3:

(i) QSAR estimation based on level III Fugacity Model by EPI Suite estimation database with the Substance ([redacted] 2018)

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

Whilst your QSAR adaptation is rejected for the reasons explained under the Appendix on Reasons common to several requests, ECHA has also identified the following endpoint specific issue.

Under Section 1.3., first paragraph, third indent of Annex XI to REACH, a study may be omitted if QSAR results are adequate for the purpose of classification and labelling and/or risk assessment, including PBT assessment. Results obtained from biodegradation (Q)SAR models are only regarded as screening information on P/vP properties (Annex XIII, Section 3.1.). As further explained in ECHA Guidance R.11.4.1.1.4., such information is not considered sufficient on its own to conclude on non-persistence and must be supported by additional information (*e.g.* test data information, read-across).

You have provided the following QSAR prediction in your dossier:
- Level III fugacity model with the Substance, DT50 37.5 d

Based on these QSAR results, you conclude that the Substance does not meet the P/vP criteria. You have not provided additional information to support this conclusion.

As explained above, the provided QSAR results alone does not provide a robust approach to conclude that the Substance does not meet the P/vP criteria and thus are not adequate for PBT assessment. Therefore, you adaptation is rejected.

In their comments to the draft decision, the lead registrant indicated an intention to perform the biodegradation screening study "*by following the principles of OECD TG 301"* instead of performing an OECD TG 309 study as requested. If the result of the intended OECD TG 301 study would indicate that the Substance is readily biodegradable, the lead registrant proposes to potentially waive the study requested in this decision.

REACH Annex IX section 9.2.1.2. column 2 specifies that the simulation testing on ultimate degradation in surface water does not need to be conducted if the substance is readily biodegradable. At present there are no data in the IUCLID dossier to demonstrate that the Substance would be readily biodegradable and, to the contrary, the lead registrant concludes in the dossier that the Substance is not expected to be readily biodegradable.

Accordingly, your adaptation arguments cannot be accepted and the need to address the data gap with the appropriate study – OECD TG 309 - remains.

Please note that this decision does not consider updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation).

Therefore, this information requirement is not met.

Other registrants indicated in their own comments to the draft decision that on the basis of Mackay Fugacity Model Level III, the persistency of the Substance cannot be ruled out and the compartment of most concern is the sediment. As such, the most relevant simulation test (i.e. worst case for persistence concerns) is proposed to be the OECD 308 test which should be conducted initially. If the outcome of this test would be that the Substance is P/vP, they propose that no further simulation testing is necessary. If the outcome would be not P/vP, they propose to provide justifications as to why testing in other compartments of less concern is not required.

ECHA notes, that as described above, simulation testing on ultimate degradation in surface water is a standard information requirement at Annex IX of REACH for your Substance. This standard information requirement is separate and independent from simulation testing study in sediment.

Accordingly, your adaptation arguments cannot be accepted and the need to address the data gap remains.

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.).

6. 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 sediment.

The Substance has a high adsorption coefficient (Log K_{oc} 5.0)] and therefore has high potential for adsorption to sediment.

You have adapted this information requirement by using the following QSAR estimated data under Annex XI, Section 1.3:

(i) QSAR estimation based on level III Fugacity Model by EPI Suite estimation database with the Substance ([redacted] 2018)

We have assessed this information and identified the following issue:

Whilst your QSAR adaptation is rejected for the reasons explained under the Appendix on Reasons common to several requests, ECHA has also identified the following endpoint specific issue.

Under Section 1.3., first paragraph, third indent of Annex XI to REACH, a study may be omitted if QSAR results are adequate for the purpose of classification and labelling and/or risk assessment, including PBT assessment. Results obtained from biodegradation (Q)SAR models are only regarded as screening information on P/vP properties (Annex XIII, Section 3.1.). As further explained in ECHA Guidance R.11.4.1.1.4., such information is not considered sufficient on its own to conclude on non-persistence and must be supported by additional information (*e.g.* test data information, read-across).

You have provided the following QSAR prediction in your dossier:

- Level III fugacity model with the Substance, DT50 337.5 d

Based on these QSAR results, you conclude that the Substance does meet the P but not vP criteria. You have not provided additional information to support this conclusion.

As explained above, the provided QSAR results alone does not provide a robust approach to conclude that the Substance does not meet the vP criteria and thus are not adequate for PBT assessment. Therefore, you adaptation is rejected.

In their comments to the draft decision, the lead registrant indicated an intention to perform OECD TG 301 instead of performing an OECD TG 308 study as requested, to investigate whether the substance is readily biodegradable.

REACH Annex IX section 9.2.1.4. column 2 specifies that the sediment simulation testing does not need to be conducted if the substance is readily biodegradable. At present there are no data in the IUCLID dossier to demonstrate that the Substance would be readily biodegradable and, to the contrary, the lead registrant concludes in the dossier that the Substance is not expected to be readily biodegradable. Accordingly, your adaptation arguments cannot be accepted and the need to address the data gap with the appropriate study – OECD TG 308 - remains.

Please note that this decision does not consider updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation).

Therefore, this information requirement is not met.

Other registrants indicated in their own comments to the draft decision that on the basis of Mackay Fugacity Model Level III, the persistency of the Substance cannot be ruled out and the compartment of most concern is the sediment. On this basis they agree to conduct the requested test with the Substance.

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 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 308.

In accordance with the specifications of OECD TG 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 308; ECHA Guidance R.11.4.1.).

7. 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 high adsorption coefficient (log K_{oc} 5.0357)] and therefore has high potential for adsorption to soil.

You have adapted this information requirement by using the following QSAR estimated data

under Annex XI, Section 1.3:

(i) QSAR estimation based on level III Fugacity Model by EPI Suite estimation database with the Substance ([redacted] 2018)

We have assessed this information and identified the following issue:

Whilst your QSAR adaptation is rejected for the reasons explained under the Appendix on Reasons common to several requests, ECHA has also identified the following endpoint specific issue.

Under Section 1.3., first paragraph, third indent of Annex XI to REACH, a study may be omitted if QSAR results are adequate for the purpose of classification and labelling and/or risk assessment, including PBT assessment. Results obtained from biodegradation (Q)SAR models are only regarded as screening information on P/vP properties (Annex XIII, Section 3.1.). As further explained in ECHA Guidance R.11.4.1.1.4., such information is not considered sufficient on its own to conclude on non-persistence and must be supported by additional information (*e.g.* test data information, read-across).

You have provided the following QSAR prediction in your dossier:
- Level III fugacity model with the Substance, DT50 75 d

Based on these QSAR results, you conclude that the Substance does not meet the P/vP criteria. You have not provided additional information to support this conclusion.

As explained above, the provided QSAR results alone does not provide a robust approach to conclude that the Substance does not meet the vP criteria and thus are not adequate for PBT assessment. Therefore, you adaptation is rejected.

In their comments to the draft decision, the lead registrant indicated an intention to perform OECD TG 301 instead of OECD TG 307 study as requested, to investigate whether the substance is readily biodegradable.

REACH Annex IX section 9.2.1.3. column 2 specifies that the soil simulation testing does not need to be conducted if the substance is readily biodegradable. At present there are no data in the IUCLID dossier to demonstrate that the Substance would be readily biodegradable and, to the contrary, the lead registrant concludes in the dossier that the Substance is not expected to be readily biodegradable. Accordingly, your adaptation arguments cannot be accepted and the need to address the data gap with the appropriate study – OECD TG 307 - remains.

Please note that this decision does not consider updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation).

Therefore, this information requirement is not met.

Other registrants indicated in their own comments to the draft decision that on the basis of Mackay Fugacity Model Level III, the persistency of the Substance cannot be ruled out and the compartment of most concern is the sediment. As such, the most relevant simulation test (i.e. worst case for persistence concerns) is proposed to be the OECD 308 test which should be conducted initially. If the outcome of this test would be that the Substance is P/vP, they propose that no further simulation testing is necessary. If the outcome would be not P/vP, they propose to provide justifications as to why testing in other compartments of less concern is not required.

ECHA notes that, as described above, soil simulation testing is a standard information requirement at Annex IX of REACH for your Substance. This standard information requirement is separate and independent from simulation testing study in sediment.

Accordingly, your adaptation arguments cannot be accepted and the need to address the data gap remains.

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).

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.

In accordance with the specifications of OECD TG 307, 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; ECHA Guidance R.11.4.1.).

8. 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.

In their comments to the draft decision, the lead registrant indicated an intention to perform OECD TG 301 study instead of providing information on the identification of degradation products as requested.

At present there are no data in the IUCLID dossier to demonstrate that the Substance would be readily biodegradable and, to the contrary, the lead registrant concludes in the dossier

that the Substance is not expected to be readily biodegradable. Accordingly, your adaptation arguments cannot be accepted and the need to address the data gap by providing information on the identification of degradation products remains.

Please note that this decision does not consider updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation).

Therefore, this information requirement is not met.

This information 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.

Other registrants did not submit comments to the draft decision specifically related to the identification of degradation products.

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 Appendix C, Section 5-7. 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.

9. Bioaccumulation in aquatic species

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

You have adapted this information requirement by using Weight of evidence under Annex XI, Section 1.2. Your weight of evidence is based on the following QSAR estimated and experimental data from various chemicals:

(i) QSAR estimation based on BCFBAF (v3.01) model by EPI Suite with the Substance ([redacted] 2018)
(ii) QSAR estimation based on ACD/Bioconcentration factor (v12.1.0.50374) model with the Substance (ADC/I-Lab 2018)
(iii) Bioaccumulation study based on TG "Bioaccumulation test of a chemical substance in fish or shellfish" provided in "the Notice on the Test Method Concerning New Chemical Substances", with the analogue substance 2,4,6-trimethylphenol, EC No. 208-419-2 (J-check 2018)
(iv) Estimation of the BCF using a logKow 2.36 and a regression derived equation, with the analogue substance 2,6-dimethylphenol, EC No. 209-400-1 (HSDB 2017)

In their comments to the draft decision, the lead registrant provides also a short summary of the following additional study:

(v) OECD TG 305 C bioaccumulation test with the analogue substance 6,6'-di-tert-butyl-2,2'-methylenedi-p-cresol, EC no. 204-327-1. According to the lead registrant, data are taken from different published literature/secondary source and the reliable handbook.

We have assessed this information and identified the following issues:

As explained under Appendix on Reasons common to several requests, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 9.3.2 at Annex IX includes similar information that is produced by the OECD TG 305. This includes:

- the uptake rate constant (k_1) and loss rate constants including the depuration rate constant (k_2), and/or
- the steady-state bioconcentration factor (BCF_{SS}), and/or
- the kinetic bioconcentration factor (BCF_K), and/or
- the biomagnification factor (BMF).

The provided sources of information (i – iv) in your dossier and the source of information (v) in your comments provide relevant information (BCFs) for the information requirement.

However, the reliability of all sources of information in your dossier and in your comments is significantly affected by the deficiencies identified and explained under Appendix on Reasons common to several requests (Section 1. A and B).

ECHA concludes that sources of information as indicated above provide information on bioaccumulation, but the information provided on the key investigation is not reliable.

Accordingly, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 305 study.

On this basis, your adaptation is rejected and the information requirement is not fulfilled.

Other registrants indicated in their own comments to the draft devision that they intend to conduct the persistence assessment first. If the Substance is considered as meeting the P/vP criteria, they agree to conduct the bioaccumulation study in aquatic species as requested in the decision. If the Substance is not P/vP, they do not consider a need to follow up with assessing bioaccumulation in aquatic species. They also state in their comments that based on the QSAR (BCFBAF v3.01) estimated BCF value of 16.13, the Substance is considered to have a low bioaccumulation potential.

ECHA notes that as described above, bioacummulation is a standard information requirement at Annex IX of REACH for your Substance. At present, no definitive information on persistency nor bioaccumulation is provided in the IUCLID dossier. Therefore no conclusion on the compliance can currently be made and the data gap remains. The QSAR information referred to in your comments does not include a documentation to allow an assessment whether it complies with the conditions of Annex XI, section 1.3. Regarding any potential 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: Reasons to request information required under Annex X of REACH

1. Pre-natal developmental toxicity study in a second species

Pre-natal developmental toxicity (PNDT) studies (OECD TG 414) in two species is a standard information requirement under Annex X to REACH.

You have adapted this information requirement by using Weight of evidence under Annex XI, Section 1.2. based on the experimental data from various chemicals:

(i) reproductive and developmental toxicity screening test with the Substance [redacted] 1999a)
(ii) (combined repeated dose toxicity study with the reproductive/developmental toxicity screening test with the analogue substance 6,6'-di-tert-butyl-2,2'-methylenedi-p-cresol, CAS No. 119-47-1 ([redacted] 1999b)
(iii) modified combined repeated dose toxicity study with the reproductive/developmental toxicity screening test with the analogue substance 2,4,6-trimethylphenol, EC No. 208-419-2 (Tyl, 2005)
(iv) investigation of fetal resorption in the rat with 2,2'-methylenebis(6-tert-butyl-4 methylphenol), EC No 204-327-1 and 6,6'-di-tert-butyl-2,2'-methylenedi-p-cresol, CAS No. 119-47-1 (Telford, 1962)

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

As explained under Appendix on Reasons common to several requests, the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.7.2 at Annex X includes similar information that is produced by the OECD TG 414 on a second species (two species taking the first species into account to address the potential species differences). The following aspects are covered: 1) prenatal developmental toxicity in two species, 2) maternal toxicity in two species, and 3) maintenance of pregnancy in two species.

The sources of information provided are all provided information on one species (rat). No source of information provides information regarding the potential for developmental toxicity in a second species. All the sources of information provided in your dossier to fulfil this information requirement are considered as not relevant.

ECHA concludes that none of the sources of information alone or combined provide sufficient coverage of the aspects 1), 2) and 3) that is foreseen to be investigated in the OECD TG 414 in a second species. Therefore, the information provided in your dossier is not sufficient to conclude whether the Substance is a developmental toxicant in a second species.

On this basis, the information you provided do not fulfil the information requirement.

Specification of the study design

A PNDT study according to the OECD TG 414 study should be performed in the rabbit or rat as the preferred second species, depending on the species tested in the first PNDT study ,

depending on the species tested in the first PNDT study (request B.2 in this decision). The study shall be performed with oral[12] administration of the Substance.

In their separate comments to the draft decision, the lead registrant and the other registrants indicated that they would like to await the results of the pre-natal developmental toxicity in the first species before performing this study in a second species in order to assess whether testing in a second species can be waived in accordance with Annex X, Section 8.7, column 2.

The timelines set in the decision allow for sequential testing.

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

Appendix E: 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[13].

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[14].

[13] https://echa.europa.eu/practical-guides
[14] https://echa.europa.eu/manuals

Appendix F: 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 G: Procedure

You submitted a testing proposal for an Extended one-generation reproductive toxicity study (EOGRTS; Annex IX, 8.7.3.), however this testing proposal is on hold pending the receipt of the data requested under section C.1. of this decision. This is because the results of the Sub-chronic toxicity study (90-day) are considered crucial to inform on the study design of the EOGRTS. Therefore, you are required to submit the Sub-chronic toxicity study (90-day) first, and submit the results by the deadline indicated above.

Together with providing the results for the requested Sub-chronic toxicity study (90-day), you may also consider updating your EOGRTS testing proposal. You should include a justification for the study design according to ECHA Guidance R.7a, Section R.7.6., taking into account the results of the Sub-chronic toxicity study (90-day).

Similarly, the information requirement for a Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.) is not addressed in this decision; as the EOGRTS will cover the same parameters.

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 30 October 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 requests.

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 and referred the modified draft decision to the Member State Committee.

The lead registrant took this opportunity to provide comments on the draft decision instead of the proposed amendment. These comments were not considered by the Member State Committee, as they did not concern the proposal for amendment and thus are considered outside of the scope of Article 51(5).

Other registrants provided comments on the proposal for amendment and on the draft decision. The comments agreeing with the proposed amendment were taken into account by the Member State Committee.

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

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-77 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix H: List of references - ECHA Guidance[15] 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)[16]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[17]

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[18]

[15] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[16] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[17] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[18] 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 I: 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]
[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.