ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 21 January 2021

Addressees
Registrant(s) of JS_94-47-3_[redacted] as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
20/02/2019

Registered substance subject to this decision ("the Substance")
Substance name: Phenethyl benzoate
EC number: 202-336-5
CAS number: 94-47-3

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***28 April 2022***.

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

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

3. Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: OECD TG 301A/B/C/D/E/F or OECD TG 310)

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 test performed for the information requirement of 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 repeated dose toxicity (28 days; Annex VIII, Section 8.6.1.) to be combined with the Screening for reproductive/developmental toxicity below (request B.4)

4. Combined repeated dose toxicity study with the Reproduction/developmental toxicity screening test (Annex VIII, Section 8.7.1.; test method: EU B.64/OECD TG 422) by oral route, in rats

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

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 VIII of REACH", respectively.

Information required depends on your tonnage band

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

- the information specified in 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 and VIII to REACH, for registration at 10-100 tpa;

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". For references used in this decision, please consult the Appendix entitled "List of references".

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.

Approved[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

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

Appendix on Reasons common to several requests

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

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

i. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
ii. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
iii. Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)
iv. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
v. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: OECD TG 203)

In addition, in your comments to the draft decision, you indicate to adapt the following additional standard information requirements by applying read-across approache(es) in accordance with Annex XI, section 1.5:

vi. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1)
vii. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2)
viii. Ready biodegradation (Annex VII, Section 9.2.2.1)

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

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

1. Predictions for (eco)toxicological and environmental fate properties

Read-across documentation

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

[2] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals. 2008 (May) ECHA, Helsinki. 134. pp. Available online: https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf/77f49f81-b76d-40ab-8513-4f3a533b6ac9

[3] Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)

[4] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://doi.org/10.2823/794394

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).[5]

In your dossier you provided studies conducted with other substances than your Substance in order to comply with the REACH information requirements. You did not provide documentation as to why this information would be relevant for your Substance.

In your comments to the draft decision, you submitted a read-across justification document describing how the read across analogues were identified following different grouping methods including general mechanistic approach and empirics used in the OECD QSAR toolbox v3.4.:

1. Materials were clustered based on their structural similarity.
2. Data availability and data quality on the selected cluster were examined.
3. The structure similarity scores were calculated using QSAR toolbox 3.4.
4. Tanimoto structure similarity scores are calculated using FCFC4 fingerprints.
5. The physical–chemical properties of the target substance and the read-across analogues were calculated using EPI Suite v4.11.
6. OECD HPV Chemical Categories, US-EPA New Chemical Categories, DNA binding, Protein binding alerts, Mutagenicity, gene toxicity alerts and oncologic classification predictions were generated using OECD QSAR Toolbox v3.4.
7. Biodegradation ultimate (Biowin 3) and Aquatic toxicity classification by ECOSAR were predicted using OECD QSAR Toolbox v3.4.
8. ER binding, DART scheme v 1.0 and Repeated Dose (HESS) categorization were also generated using OECD QSAR Toolbox v 3.4.
9. Empiric method such as organic functional groups was also applied for the prediction using OECD QSAR Toolbox v3.4.

In your comments to the draft decision, you have provided the following reasoning for the prediction of (eco)toxicological and environmental fate properties:

"Based on structural similarity, physical-chemical properties, organic functional groups and several general and endpoint specific mechanistic approach using OECD QSAR toolbox v3.4, Benzyl phenylacetate (CAS no. 102-16-9), Benzyl propionate (CAS no. 122-63-4), Benzyl acetate (CAS no. 140-11-4), Benzyl 4-hydroxybenzoate (CAS no. 94-18-8), Benzyl salicylate (CAS No. 118-58-1), Methyl phenylacetate (CAS No. 101-41-7) and Phenethyl phenylacetate (CAS No.102-20-5) were identified as read-across chemical with sufficient data for environmental fate, ecotoxicological and toxicological evaluations used for the target chemical Phenethyl benzoate (CAS no. 94-47-3)."

ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted to be quantitatively equal to those of the source substance.

ECHA notes the following shortcoming(s) with regards to prediction(s) of (eco)toxicological and environmental fate properties.

Supporting information

[5] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.6.1

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*"[6]. 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 bridging studies to compare properties of the Substance and source substances.

According to Annex XI, Section 1.5 there needs to be structural similarity between substances resulting in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties.

In your read-across justification document submitted with your comments to the draft decision, you conclude that according to the OECD QSAR Toolbox v3.4, structural alerts and general mechanistic like OECD HVP Chemical Categories, US-EPA New Chemical Categories, DNA binding by OECD, Protein binding by OECD and by OASIS v.1.4, protein binding potency and Estrogen Receptor Binding for (eco)toxicological and environmental fate endpoints are consistent between the target substance and the read-across analogues.

For genotoxicity, according to the OECD QSAR Toolbox v3.4, endpoint specific alerts like DNA alerts for CA and MNT by OASIS v. 1.4 and Protein Binding Alerts for Chromosomal Aberration by OASIS v. 1.2 for toxicological endpoints are consistent between the target substance and the read-across analogues.

For repeated dose toxicity, the target substance and the read across analogues Benzyl propionate (CAS No. 122-63-4), Methyl phenylacetate (CAS No. 101-41-7) and Benzyl acetate (CAS No. 140-11-4) have consistency in Repeated Dose (HESS), respectively.

For reproductive toxicity, the target substance and the read across analogues Methyl phenylacetate (CAS No. 101-41-7) and Benzyl acetate (CAS No. 140-11-4) have consistency in DART scheme v.1.0, respectively.

For environmental fate (biodegradation), the target substance and the read across substances benzyl phenylacetate (CAS 102-16-9) and benzyl propionate (CAS 122-63-4) share common alerts in endpoint specific mechanisms which include biodegradation ultimate (BIOwin 3) for environmental fate endpoints.

For aquatic toxicities, the target substance and read across analogue substances benzyl acetate (CAS 140-11-4) and benzyl 4-hydroxybenzoate (CAS 94-18-8) share common alerts in endpoint specific mechanisms which include Aquatic toxicity classification by ECOSAR forecotoxicologicalendpoints.

Whilst this information may constitute a relevant indication in support of the read-across approach, it does not address the whole complexity and uncertainty of the endpoints under consideration and these QSAR and other *in silico* predictions cannot be seen, on their own, as evidence of similarity in the properties of these constituents. The data set reported in your registration dossier and in your comments to the draft decision does not include relevant, reliable and adequate information investigating specifically the properties ((eco)toxicological

[6] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

endpoints) under consideration for your Substance, e.g. bridging studies of comparable design and duration to those on the source substances are missing. The information provided does not allow to verify the crucial aspects of the read-across hypothesis, and, in the absence of such bridging information, you have not established that the Substance and of the source substance(s) are likely to have similar properties. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

Conclusions on the read-across approach

As explained above, you have not established – neither in your registration dossier nor in your comments to the draft decision that relevant properties of the Substance can be predicted from data on the analogue substances. Therefore, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5., and your grouping and read-across approach is rejected.

2. Assessment of your weight of evidence adaptation under Annex XI, Section 1.2.

You have adapted the following standard information requirements by applying weight of evidence (WoE) adaptation in accordance with Annex XI, section 1.2:

1. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
2. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
3. Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)
4. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

For these endpoints you provided studies with analogue substances.

In addition, in your comments to the draft decision, you indicate to adapt the following additional standard information requirements by applying weight of evidence (WoE) adaptation in accordance with Annex XI, section 1.2:

5. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
6. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2)
7. Ready biodegradation (Annex VII, Section 9.2.2.1)
8. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3).

For these endpoints you provided studies with the Substance and analogue substances.

Your weight of evidence adaptation raises the same decifiencies irrespective of the information requirement for which it is invoked. Accordingly, ECHA addressed these deficiencies in the present Appendix, 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 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.4.4, 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 of the information for the given regulatory information requirement. Subsequently, relevance, reliability, 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.

However, for each relevant information requirement, 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 spite of this critical deficiency, ECHA has have nevertheless assessed the validity of your adaptation.

These issues identified below are essential for all the information requirements in which you invoked a weight of evidence.

1. Relevance of the provided information

Deficiencies regarding the relevance of information submitted for your weight of evidence adaptation have been addressed under the section 4 of Appendix B.

2. Reliability of the read across approach

Section 1 of the present Appendix identifies deficiencies of the grouping and read across approach used in your dossier. These findings apply equally to the sources of information relating to analogue substances submitted under your weight of evidence adaptations.

3. Reliability of QSAR adaptation

Section 3 of the present Appendix identifies deficiencies of the QSAR adaptation(s) used in your dossier. These findings apply equally to the sources of information relating to QSAR submitted under your weight of evidence adaptations.

4. Study conducted after 2008 and GLP compliance

Since 1 June 2008, toxicological and eco-toxicological tests and analyses on substances must be carried out in compliance with the principles of good laboratory practice (GLP) (Article 13(4) and Article 141(2) of REACH).

In your comments to the draft decision, you provide additional source studies for the following endpoints.

- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Short-term toxicity testing on invertebrates (Annex VII, Section 9.1.1.);
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2);
- Ready biodegradability (Annex VII, Section 9.2.1.1.);
- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3).

However, for these additional source studies, you do not provide information on whether they are GLP compliant or the year of the study has not been indicated. Accordingly, it is not possible to conclude on reliability of these studies.

3. Rule for Annex XI, Section 1.3 adaptation

In your comments to the draft decision, you indicate to adapt the following additional standard information requirements by applying Qualitative or quantitative structure-activity relationship (QSAR) adaptation in accordance with Annex XI, section 1.3.

- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3).

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.

According to ECHA's Practical guide "How to use and report (Q)SARs", section 3.4, a QSAR Model Reporting Format (QMRF)[7] and a QSAR Prediction Reporting Format (QPRF)[8] 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.

- For short-term fish information requirements, you have provided estimated toxicity values for the endpoint derived with ECOSAR program version 1.11. The predictions are performed on the Substace and you have provided the outcome of the prediction.

However, you have not provided documentation establishing the scientific validity of the model for the QSAR predictions (i.e. QMRF and QPRF are not provided in the technical dossier, including identity of the compounds used during the parameterisation of the models, defined descriptor and structural fragment domains[9]).

In addition, as explained above in the Appendix on Reasons common to several requests, section 1 Assessment of your read-across approach under Annex XI, Section 1.5., and section 2 Assessment of your weight of evidence adaptation under Annex XI, Section 1.2., your adaptation under Annex XI, Sections 1.2 and 1.5 is rejected.

ECHA's Conclusion

The adaptation you provided does not fulfil the criteria specified in Annex XI, Section 1.3. and it is therefore rejected.

[7] ECHA Guidance R.6, Section R.6.1.9
[8] ECHA Guidance R.6, Section R.6.1.10
[9] ECHA Guidance R.6, Section R.6.1.5

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

1. Short-term toxicity testing on aquatic invertebrates

Short-term toxicity testing on aquatic invertebrates is a standard information requirement in Annex VII to REACH.

You have provided a key study and supporting study for this endpoint.

i. Key study: OECD TG 202 (2018) not GLP compliant, with the Substance
ii. Supporting study: OECD TG 202 (2018) not specified to be GLP compliant, with the Substance

In your comments to the draft decision, you indicate to adapt the standard information requirement mentioned above according to Annex XI, Section 1.2. (weight of evidence) as well as, Annex XI 1.5 (grouping of substances and read-across) of REACH.

In support of your adaptations, you indicate that the following additional sources of information are available;

iii. an OECD TG 202 study (2019) with the Substance;
iv. an OECD TG 202 study (2017) with the Substance;
v. a short-term (24hr) invertebrate study (2005) with the Substance;
vi. an OECD TG 202 study (2017) with analogue substance Benzyl 4-hydroxybenozoate (EC: 202-311-9).

For these additional source studies, you did not specify whether they are GLP compliant.

In the comments to the draft decision, you conclude that the information requirement for this endpoint is fulfilled by the studies on the Substance and analogue substance and you indicate your intension to update the registration dossier with the study records for the additional studies and read-across justification for analogue substances.

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

A: Reliability of the study

To comply with this information requirement, an OECD TG 202 study must fulfil the validity criteria and cover the key parameters of the corresponding TG (Article 13(3) of REACH), which include (among others):

1. The dissolved oxygen concentration at the end of the test should be ≥3 mg/l in control and test vessels
2. Analytical monitoring to verify initial concentrations and maintenance of these concentrations throughout the test as required in TG
3. If test concentrations are not maintained within 20% of initial measured concentrations throughout testing, effect concentrations must be reported based on measured values (see ECHA Guidance R7b, section R.7.8.4.1)
4. A full description of the analytical monitoring method (e.g. calibration, recovery and sensitivity determination) and of the preparation of the test samples for analysis (including the description of filtration and/or extraction steps, if any);

You have provided OECD TG 202 studies showing the following:

For key study (2018), you provided name of the test material, name of the test organism, the name of the test guideline followed, some information on test design and condition, test

results in nominal concentration, and conclusion. You specify that analytical monitoring was performed however, you did not provide any information on the analytical method used nor report the measured concentrations. Thus you do not demonstrate whether a stable exposure concentrations were maintained throughout the duration of the study. Despite this, you reported the result based on the nominal concentation.

For supporting study (2017), you did not specify whether the analytical monitoring was performed nor any vehicle was used for preparing the test solution. You provided the name of the test organism but no information on the acclimation was provided. You have provided nominal concentrations but no informaiton on measured concentrations are provided. However, you have reported EC50 based on measured concentration without specifying how it was derived.

You did not provide measured concentrations for both key and supporting study and thus did not demonstrate that the test concentrations were maintained within 20% of initial measured concentrations throughout testing.

In addition, you did not provide any raw data to verify that the validity criteria were fulfilled. In addition, key parameters are not covered.

B. Studies conducted after 1 August 2008 and not GLP

Toxicological and eco-toxicological tests and analyses on substances must be carried out in compliance with the principles of good laboratory practice (GLP) provided for in Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or ECHA and with the provisions of Directive 86/609/EEC, if applicable (Article 13(4) of REACH). According to Article 141(2), Article 13 applies from 1 June 2008.

The provided key study was indicated as not being performed according to GLP. You did not specify GLP compliance of the supporting study, hence you did not demonstrate that these studies are performed according toGLP.

C. Read-across

As explained in Section 1 of the Appendix common to several requests, your adaptation is rejected.

D. Weight of the evidence

ECHA has assessed to what extent the sources of information submitted in your comments to the draft decision enables a conclusion on *short-term toxicity to daphnia* as investigated in the information requirement proposed to be adapted and identified the following deficiencies:

As explained in Section 2 of the Appendix common to several requests, the weight of evidence 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.

All the sources of information you provided investigate immobilisation of aquatic invertebrate, the key element for this endpoint. Therefore, they provide information that would contribute to the conclusion on this key element.

However, the reliability of these sources of information is significantly affected by the deficiencies identified in Section 2 of the Appendix on Reasons common to several requests.

In addition, the reliability of the sources of information is also affected by the following additional issues.

To fulfil the information requirement, normally a study according to OECD TG 202 must be provided. The key parameter investigated by this test is immobilisation of aquatic invertebrate. The conditions in OECD TG 202 specifies that:

1. the test duration is 48 hours or longer;
2. Daphnia magna (or other suitable Daphnia species) is used as test species;
3. at least 20 animals are used at each test concentration and for the controls;
4. young daphnids, aged less than 24 hours at the start of the test, are used;
5. the test medium fulfils the following condition(s): particulate matter ≤ 20 mg/L, total organic carbon (TOC) ≤ 2 mg/L, hardness between 140 and 250 mg/L (as CaCO3), pH between 6 and 9;
6. the test medium fulfils the following condition(s): particulate matter ≤ 20 mg/L, total organic carbon (TOC) ≤ 2 mg/L, hardness between 140 and 250 mg/L (as CaCO3), pH between 6 and 9;
7. the pH variation is < 1.5 units;
8. the concentrations of the test material are measured at least at the highest and lowest test concentration, at the beginning and end of the test;
9. the effect values can only be based on nominal or measured initial concentration if the concentration of the test material has been satisfactorily maintained within 20 % of the nominal or measured initial concentration throughout the test (see also ECHA Guidance R.7b, Section R.7.8.4.1).

Regarding points 1-2 above, the test duration is 24 hrs and Artemia salina (Brine shrimp) was used as test species for the source study v (2005).

Regarding point 3 above, only 10 daphnids per test concentration and for control were used for the source study iii (2019). For source study iv (2017), you mention that 5 organisms per vessel/replicates was used. However number of replicate used per test concentration is not reported. For the source study vi (2017), you do not provide this information.

Regarding points 4-7 above, you do not provide information on these parameters for all the provided source studies.

Regarding points 8 and 9 above, test chemical concentrations are not verified analytically for the source study iv (2017) with the Substance and vi (2017) with analogue substance, thus it is not demonstrated that the concentrations of the Substance were maintained during the study. However the effect concentrations are reported based on nominal concentrations. Therefore the provided source studies cannot be considered a reliable source of information.

Further, you did not specify GLP compliance of the source studies provided in your comments, hence it is not possible to assess their reliability.

Finally, the reliability of the studies i. and ii. is significantly affected by the deficiencies identified under sections A and B. above.

As a conclusion, sources of information as indicated above, provide information on immobilisation of aquatic invertebrate but the information provided 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 property foreseen to be investigated in an OECD TG 202 study.

Therefore, the data provided are rejected and the information requirement is not fulfilled.

2. Growth inhibition study aquatic plants

Growth inhibition study aquatic plants is a standard information requirement in Annex VII to REACH.

You have provided a key study study for this endpoint.

i. Key study: OECD TG 201 (2017) not GLP compliant, with the Substance

In your comments to the draft decision, you indicate to adapt the standard information requirement mentioned above according to Annex XI, Section 1.2. (weight of evidence) as well as, Annex XI 1.5 (grouping of substances and read-across) of REACH.

In support of your adaptations, you indicate that the following additional sources of information are available;

ii. an OECD TG 201 study (2019) with the Substance;
iii. an OECD TG 201 study (2017) with the Substance;
iv. an OECD TG 201 study (2017) with analogue substance Benzyl 4-hydroxybenozoate (EC: 202-311-9).

For these additional source studies, you did not specify whether they are GLP compliant.

In the comments to the draft decision, you conclude that the information requirement for this endpoint is fulfilled by the studies on the Substance and analogue substance and you indicate your intension to update the registration dossier with the study records for the additional studies and read-across justification for analogue substances.

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

A. Reliability of the study

To comply with this information requirement, an OECD TG 201 study must fulfil the validity criteria and cover the key parameters of the corresponding TG (Article 13(3) of REACH), which include (among others):

- The mean coefficient of variation for section-by-section specific growth rate in the control cultures not exceeding 35%
- The biomass in the control cultures should increase exponentially by a factor of at least 16 within the 72-hour test period
- The coefficient of variation of average specific growth rates during the whole test period in replicate control cultures must not exceed 7% in tests with Desmodesmus subspicatus
- Analytical monitoring to verify initial concentrations and maintenance of these concentrations throughout the test a full description of the analytical monitoring method (e.g. calibration, recovery and sensitivity determination) and of the preparation of the test samples for analysis (including the description of filtration and/or extraction steps, if any);

For key study (2017), you provided name of the test material, name of the test organism, the name of the test guideline followed, some infomartion on test design and condition, test

results in nominal concentration, and conclusion. You did not specify whether analytical monitoring was performed nor did you provide any information on the analytical method used nor measured concentrations. Thus you do not demonstrate whether a stable exposure concentrations were maintained throughout the duration of the study. Despite this, you reported the result based on the nominal concentation.

Furthermore, you stated that validity criteria were fulfilled and provided calculated values. However, you did not provide any raw data to demonstrate the fulfilment of the validity criteria. For example, you provided the initial biomass concentration but you did not provide the biomass concentration at the end of the test. Therefore, it is not possible for ECHA to verify the fulfilment of the validity criteria.

Therefore you did not demonstrate that the valifity criteria were met. In addition, key parameters are not covered.

B. Studies conducted after 1 August 2008 and not GLP

Toxicological and eco-toxicological tests and analyses on substances must be carried out in compliance with the principles of good laboratory practice (GLP) provided for in Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or ECHA and with the provisions of Directive 86/609/EEC, if applicable (Article 13(4) of REACH). According to Article 141(2), Article 13 applies from 1 June 2008.

The provided key study was not performed according to GLP. For the additional source studies, you did not specify whether they are GLP compliant, hence you did not demonstrate that all these studies are performed according to GLP.

Therefore, the provided studies are rejected and the information requirement is not fulfilled.

C. Read-across

As explained in Section 1 of the Appendix common to several requests, your read-acoss adaptation is rejected.

D. Weight of evidence

ECHA has assessed to what extent the sources of information submitted in your comments to the draft decision enables a conclusion on growth inhibition on aquatic plants as investigated in the information requirement proposed to be adapted and identified the following deficiencies:

As explained in Section 2 of the Appendix common to several requests, the weight of evidence 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.

All the sources of information you provided investigate growth rate, the key element for this endpoint. Therefore, they provide information that would contribute to the conclusion on this key element.

However, the reliability of these sources of information is significantly affected by the deficiencies identified in Section 2 of the Appendix on Reasons common to several requests.

In addition, the reliability of the sources of information is also affected by the following additional issues.

To fulfil the information requirement, normally a study according to OECD TG 201 must be provided. The key parameter investigated by this test is growth rate of algal cultures.
The conditions in OECD TG 201 specifies that:

1. the pH of the control medium does not increase by > 1.5 units;
2. three replicates at each test concentration and at least three replicates for controls (including solvent controls, if applicable) are included;
3. the concentrations of the test material are measured at least at the beginning and end of the test:
4. the results can be based on nominal or measured initial concentration only if the concentration of the test material has been maintained within 20 % of the nominal or measured initial concentration throughout the test;

Regarding points 1 and 2 above, no information are provided in your comments to the draft decision for all the source studies.

Regarding points 3 and 4 above, test chemical concentrations are not verified analytically for the source study iii (2017) with the Substance and iv (2017) with analogue substance, thus it is not demonstrated that the concentrations of the Substance were maintained during the study. However the effect concentrations are reported based on nominal concentrations.

In addition, as already explained section A above for the key study (2017), although you state that validity criteria were fulfilled and provided calculated values for all the source studies. However, you do not provide any raw data to demonstrate the fulfilment of the validity criteria. Therefore, it is not possible for ECHA to verify the fulfilment of the validity criteria.

Finally, the reliability of the study i. (key study) is significantly affected by the deficiencies identified under sections A and B. above.

Therefore the provided source studies cannot be considered a reliable sources of information.

As a conclusion, sources of information as indicated above, provide information on growth rate of algal cultures but the information provided 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 property foreseen to be investigated in an OECD TG 201 study.

Therefore, the provided data do not fulfil the information requirement.

3. Ready biodegradability

Ready biodegradability is a standard information requirement in Annex VII to REACH.

You have provided a key study study for this endpoint.

i. Key study: OECD TG 301D (2018) not GLP compliant, with the Substance

In addition, in your comments to the draft decision, you indicate to adapt the standard information requirement mentioned above according to Annex XI, Section 1.2. (weight of evidence) as well as, Annex XI 1.5 (grouping of substances and read-across) of REACH.
In support of your adaptations, you indicate that the following sources of information are available;

ii. an OECD TG 301D study (2018) with analogue substance Benyl phenylacetate (EC 203-008-4);
iii. an OECD TG 301D study (2016) with analogue substance Benzyl propionate(EC: 204-559-3).
iv. QSAR predictions (OECD QSAR toolbox v.3.4) with the Substance and analogue substances

For these additional experimental source studies, you did not specify whether they are GLP compliant.

In the comments to the draft decision, you conclude that the information requirement for this endpoint is fulfilled by the studies on the Substance and analogue substance and you indicate your intension to update the registration dossier with the study records for the additional studies and read-across justification for analogue substances.

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

A. Reliability of the study

To comply with this information requirement, an OECD TG 301 A, B, C, D, E, F, 310 study must fulfil the validity criteria and cover the key parameters of the corresponding TG (Article 13(3) of REACH), which include (among others):

- Acceptable source of inocula
- The test conducted in aerobic condition

You have provided an OECD TG 301D showing the following:

You did not specify oxygen conditions therefore you did not demonstrate that the test was conducted in aerobic conditions.You stated that mixed inoculum was used. However you did not specify the source of inoclula, any pre-conditioning and concentrations used, as specified in the TG.

Therefore you did not demonstrate that the valifity criteria were met. In addition, key parameters are not covered.

- In your comments to the draft deicision additional information on the key study was provided. Provided new information includes: The study was performed at a temperature of 20°C under aerobic conditions;
- The test system included control, test chemical and reference substance;
- Polyseed capsule (mixed culture) was used as a test inoculum for the study;
- No pretreatment / preconditioning was given to the test inoculum;
- concentration of test inoculum used for the study was 32 ml/l which corresponds to $10E^7$ to $10E^8$ CFU/ml;
- The concentration of test and reference substance (Sodium Benzoate) chosen for both the study was 4 mg/L;
- The degradation of the reference compound has reached the pass level by day 14;

However, you still do not provide information on the difference of extreame replicate values of the removal of the test material, oxygen depletion in the inoculum blank and the residual concentration of oxygen in the test bottle. Therefore you still do not demonstrate that the valifity criteria were met with the additional information provided in your comments to the draft decision.

The concentration of the test inoculum added (32 mg/L) and the bacterial cell density ($10E^7$ to $10E^8$ CFU/ml) are higher than allowed for the OECD TG 301D study (≤ 5 mg/L and 10^4 to 10^6 cells/L respectively). You did not provide a justification for these deviations from the OECD 301D.

B. Studies conducted after 1 August 2008 and not GLP

Toxicological and eco-toxicological tests and analyses on substances must be carried out in compliance with the principles of good laboratory practice (GLP) provided for in Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or ECHA and with the provisions of Directive 86/609/EEC, if applicable (Article 13(4) of REACH). According to Article 141(2), Article 13 applies from 1 June 2008.

The provided key study was not performed according to GLP and you still do not address this point in your comments to the draft decision.

Therefore, the key study provided do not fulfil the information requirement.

C. Read-across

As explained in the Appendix on Reasons common to several requests, section 1, your adaptations under Annex XI, Sections 1.5 is rejected.

D. Weight of evidence

ECHA has assessed to what extent the sources of information submitted in your comments to the draft decision enables a conclusion on ready biodegradation as investigated in the information requirement proposed to be adapted and identified the following deficiencies.

As explained in Section 2 of the Appendix common to several requests, the weight of evidence 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.

All the sources of information you provided investigate ultimate aerobic biodegradation, the key element for this endpoint. Therefore, they provide information that would contribute to the conclusion on this key element.

However, the reliability of these sources of information is significantly affected by the deficiencies identified in Section 2 of the Appendix on Reasons common to several requests.

Finally, the reliability of key study i. is significantly affected by the deficiencies identified under section A. above.

As a conclusion, sources of information as indicated above, provide information on ready biodegradation but the information provided 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 property foreseen to be investigated in an OECD TG 301 study.

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

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 a standard information requirement in Annex VIII to REACH.

For Annex VIII, 8.4.2., you have adapted the standard information requirement mentioned above according to Annex XI, Section 1.2. (weight of evidence) and Annex XI 1.5 (grouping of substances and read-across) of REACH.

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

In support of your adaptation, you have provided the following sources of information:

(i) an *In vitro* Mammalian Chromosome Aberration Test (1987) according to OECD TG 473 with analogue substance benzyl acetate (EC 205-399-7)
(ii) an *In vitro* Mammalian Chromosome Aberration Test (1996) according to OECD TG 473 with analogue substance benzyl acetate (EC 205-399-7)

You conclude that "*on the basis of available data for the test chemicals and applying the weight of evidence approach, the test chemical is not likely to classify as a gene mutant in vitro. Hence the test chemical is not likely to classify as a gene mutant as per the criteria mentioned in CLP regulation.*"

In your comments to the draft decision, you indicated additional sources of information are available and included a summary of an *In vitro* Mammalian Chromosome Aberration Test with the analogue substance benzyl salicylate, CAS: 118-58-1 (EC 204-262-9).

ECHA has assessed to what extent the sources of information submitted enables a conclusion on these properties as investigated in the information requirement(s) proposed to be adapted and identified the following deficiencies:

As explained in the Appendix on Reasons common to several requests, section 1 Assessment of your read-across approach under Annex XI, Section 1.5., and section 2 Assessment of your weight of evidence adaptation under Annex XI, Section 1.2., your adaptation under Annex XI, Sections 1.2 and 1.5 is rejected. Furthermore, as described in these sections, the additional information on the source substance benzyl salicylate submitted with your comments to the draft decision is not sufficient to justify your read-across approach because similar properties of the Substance and the source substance have not been demonstrated.

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 property foreseen to be investigated in an OECD TG 473 study.

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

To fulfil the information requirement for the Substance, both *in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) and *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 a standard information requirement in Annex VIII to REACH in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

Your dossier contains (i) a negative result for *in vitro* gene mutation study in bacteria, and (ii) inadequate data for the other study (*in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study).

The information for the *in vitro* cytogenicity studies in mammalian cells or *in vitro* micronucleus study provided in the dossier are rejected for the reasons provided in section B1.

For Annex VIII, 8.4.3., you have not provided any study in your dossier. However, you provided an adaptation according to the general rules for adaptation of Annex XI, Section 1.2. and Section 1.5.

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

In support of your adaptation, you have provided the following sources of information:

(i) an *In Vitro* Mammalian Cell Gene Mutation Test (2015a) according to OECD TG 476 with analogue substance 2-phenylethyl 2-phenylacetate (EC 203-013-1)
(ii) an *In Vitro* Mammalian Cell Gene Mutation Test (2015b) according to OECD TG 476 with analogue substance methyl phenylacetate (EC 202-940-9)

You conclude that "*on the basis of available data for the test chemicals and applying the weight of evidence approach, the test chemical is not likely to classify as a gene mutant in vitro. Hence the test chemical is not likely to classify as a gene mutant as per the criteria mentioned in CLP regulation.*"

In your comments to draft decision you request ECHA to remove the requirement of *in vitro* gene mutation study in mammalian cells as per OECD 476 or OECD 490, from the draft decision while no additional source studies were provided or indicated.

ECHA has assessed to what extent the sources of information submitted enables a conclusion on these properties as investigated in the information requirement(s) proposed to be adapted and identified the following deficiencies:

As explained in the Appendix on Reasons common to several requests, section 1 Assessment of your read-across approach under Annex XI, Section 1.5., and section 2 Assessment of your weight of evidence adaptation under Annex XI, Section 1.2., your adaptation under Annex XI, Sections 1.2 and 1.5 is rejected.

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 property foreseen to be investigated in an OECD TG 476 study.

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

The result of the request for information in section B1 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.

Consequently, you are required to provide information for this endpoint, if the *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study provide a negative result.

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

3. Short-term repeated dose toxicity (28 days)

A Short-term repeated dose toxicity study (28 days) is a standard information requirement in Annex VIII to REACH.

You have adapted the standard information requirement mentioned above according to Annex XI, Section 1.2. (weight of evidence) and Annex XI 1.5 (grouping of substances and read-across) of REACH.

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

In support of your adaptation, you have provided the following sources of information:

(i) a screening study (2016) according to guideline 422 with the with the analogue substance methyl phenylacetate (EC 202-940-9);
(ii) a sub-cronic toxicity study (2017), no guideline, with the analogue substance diethylene glycol dibenzoate (EC 204-407-6);

You conclude that "*based on the data available for the test chemical 2-phenylethyl benzoate (94-47-3) not likely to exhibit toxic nature upon repeated exposure by oral, inhalation and dermal route of exposure and hence is not likely to classify as per the criteria mentioned in CLP regulation.*"

In your comments to the draft decision, you indicated that additional sources of information are available and included a summary of a repeated oral 28-days toxicity study (OECD TG 407) with the analogue substance benzyl propionate, CAS No. 122-63-4 (EC No. 204-559-3), and a combined chronic toxicity / carcinogenicity study (OECD TG 453) with the analogue substance benzyl acetate, CAS No. 140-11-4 (EC No. 205-399-7).

You also ask ECHA to consider the fact that the substance is used in cosmetics and new animal testing is in conflict with provisions of Cosmetic Regulation (EC) No 1223/2009.

In addition to the use in cosmetic products, the Substance has formulation use as an intermediate ([redacted]). Moreover, the Substance has a consumer use in pharmaceuticals and in washing and maintenance products (including [redacted]). Exposure scenario 6: Use at industrial sites – Use in Pharmaceuticals, contributing scenario 5 (PROC 5), for example shows an RCR of [redacted] for combined routes, systemic, long-term exposure. Exposure scenario 3: Use at industrial sites – Use in perfumes and Fragrances, contributing scenario 9 (PROC 9) shows an RCR of [redacted] for combined routes, systemic, long-term exposure.

On that basis, uses other than cosmetics exist. For those non-cosmetic uses there may be both potential consumer and worker exposure to the Substance. In any case, potential worker exposure may exist (eg, PROC 5 excluding demonstration of strictly controlled conditions). In addition, potential worker exposure may exist for the use of the substance at industrial sites for the manufacture of perfumes and fragrances (PROC 9). Therefore, testing information is

necessary to at least assess the risks from exposure to workers and therefore in order to fulfil the relevant REACH requirements.

This is in accordance with ECHA's factsheet on the interface between REACH and Cosmetics Regulations, 10 which was developed jointly with the European Commission. According to that fact sheet further, animal testing performed to meet the REACH information requirements for human health endpoints is permitted for substances that have cosmetic uses either (1) in case the substance also has non-cosmetic uses or (2) in case the substance only has cosmetic uses where there is a need to assess the risks from exposure to the workers involved in the manufacture of the cosmetic product.

Such testing would not trigger the testing and marketing bans under the Cosmetics Regulation as the testing is to be performed for the purposes of meeting the requirements of the REACH Regulation; see Commission Communication of 11 March 2013 on the animal testing and marketing ban and on the state of play in relation to alternative methods in the field of cosmetics (COM(2013)135))4.[11]

ECHA has assessed to what extent the sources of information submitted enables a conclusion on these properties as investigated in the information requirement(s) proposed to be adapted and identified the following deficiencies:

As explained in the Appendix on Reasons common to several requests, section 1 Assessment of your read-across approach under Annex XI, Section 1.5., and section 2 Assessment of your weight of evidence adaptation under Annex XI, Section 1.2., your adaptation under Annex XI, Sections 1.2 and 1.5 is rejected. Furthermore, as discussed in these sections, the additional information on the source substance benzyl propionate and benzyl acetate submitted with your comments to the draft decision is not sufficient to justify your read-across approach because similar properties of the Substance and the source substance have not been demonstrated.

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 property foreseen to be investigated in an OECD TG 407 study.

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

Study design

Further information on the study design is provided under Section B.4. below.

4. Screening for reproductive/developmental toxicity

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

You have adapted the standard information requirement mentioned above according to Annex XI, Section 1.2. (weight of evidence) and Annex XI 1.5 (grouping of substances and read-across) of REACH.

[10] https://echa.europa.eu/documents/10162/13628/reach_cosmetics_factsheet_en.pdf
[11] see Commission Communication of 11 March 2013 on the animal testing and marketing ban and on the state of play in relation to alternative methods in the field of cosmetics (COM(2013)135))4, in particular page 8.

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

In support of your adaptation, you have provided the following sources of information:

(i) a screening study (2016) according to guideline 422 with the analogue substance methyl phenylacetate (EC 202-940-9);
(ii) a sub-acute study (2014) according to OECD TG 407 with the analogue substance benzyl propionate (EC 204-559-3);
(iii) a two-generation reproductive toxicity study (2017) according to OECD TG 416 with the analogue substance diethylene glycol dibenzoate (EC 204-407-6);

You conclude that "*based on the data available from different studies, test material did not showed reproductive toxicity at dose concentration 556.0 mg/kg /day. When male and female rats were treated with test material orally, thus, comparing this value with the criteria of CLP regulation test materialis not likely to classify as reproductive toxicant.*"

In your comments to the draft decision, you indicated additional source of information is available and included a summary of a pre-natal developmental toxicity study (OECD TG 414) with the analogue substance benzyl acetate, CAS No. 140-11-4 (EC No. 205-399-7.

You also ask ECHA to consider the fact that the substance is used in cosmetics and new animal testing is in conflict with provisions of Cosmetic Regulation (EC) No 1223/2009.

As explained under section 3 of this Appendix, the requested vertebrate tests are justified for the purposes of meeting REACH information requirement(s).

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. Annex XI, 1.2. requires that the source(s) of information provide sufficient weight of evidence to conclude that the information requirement(s) for OECD TG 421/422 is fulfilled for the properties screening for reproductive/developmental toxicity if by integrating and weighing the evidence, e.g. the following aspects are covered: Information on sexual function and fertility (mating, fertility, gestation, parturition and lactation) including histopathology of gonads and accessory sex organs for reproductive/developmental toxicity.

ECHA has assessed to what extent the sources of information submitted enables a conclusion on these properties as investigated in the information requirement(s) proposed to be adapted and identified the following deficiencies:

Source studies (i) and (iii) provide information on sexual function and fertility. This information is fully relevant for the (dangerous) property reproductive toxicity as investigated by OECD TG 421/422. Source study (ii) contains information on reproductive organs but does not provide information on sexual function and fertility. Therefore this source of information is only partly relevant for the (dangerous) property reproductive toxicity as investigated by OECD TG 421/422.

The pre-natal developmental toxicity study indicated in your comments to the draft decision provides information on gestation.

The sources of information provided investigate the above mentioned key parameters.

However, while the source(s) of information ((i)-(iii))), as well as the pre-natal developmental toxicity study submitted in your comments to the draft decision, provide (partly) relevant information on reproductive toxicity, these sources of information have the following deficiencies affecting their reliability:

As explained in the Appendix on Reasons common to several requests, section 1 Assessment of your read-across approach under Annex XI, Section 1.5., your adaptation under Annex XI, Section 1.5 is rejected. Therefore, studies i-iii cannot be used as part of a weight of evidence adaptation according to Annex XI, Section 1.2. Furthermore, as discussed in these sections, the additional information on the source substance benzyl acetate submitted with your comments to the draft decision is not sufficient to justify your read-across approach because similar properties of the Substance and the source substance have not been demonstrated.

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 property foreseen to be investigated in a screening for reproductive/developmental toxicity study.

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

Study design

In a proposal for amendment (PfA), submitted by one of the Member States competent authorities, it was indicated that when there is no information available neither for the 28-day repeated dose toxicity endpoint (EU B.7, OECD TG 407) (as explained above under section B.3.), nor for the screening study for reproductive/ developmental toxicity (OECD TG 421 or TG 422), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to ensure that unnecessary animal testing is avoided. Such an approach offers the possibility to avoid carrying out a 28-day study according to OECD TG 407, because the OECD TG 422 can at the same time fulfil the information requirement of REACH Annex VIII, 8.6.1 and that of REACH Annex VIII, 8.7.1.[12] ECHA agrees with this approach.

In your comments you agree with the PfA.

Therefore, a study according to the test method EU B.64/OECD TG 422 must be performed in rats with oral[13] administration of the Substance.

5. Short-term toxicity testing on fish

Short-term toxicity testing on fish is a standard information requirement in Annex VIII to REACH.

You have provided a key study and supporting study for this endpoint.

i. Key study: OECD TG 203 (2018) not specified to be GLP compliant, with the Substance
ii. Supporting study: OECD TG 203 (2017) not specified to be GLP compliant, with an analogue substance, benzyl 4-hydroxybenzoate (EC number 202-311-9)

Furthermore, in your comments to draft decision, you indicate to adapt the standard information requirement mentioned above according to Annex XI, Section 1.2. (weight of

[12] ECHA Guidance R.7a, Section R.7.6.2.3.2., pages 484 to 485 of version 6.0 – July 2017. (https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf)
[13] ECHA Guidance R.7a, Section R.7.6.2.3.2.

evidence) as well as, Annex XI 1.5 (grouping of substances and read-across), and Annex XI, Section 1.3 (Qualitative or quantitative structure-activity relationship (QSAR)) of REACH.

In your comments to the draft decision, you provide the following additional information:

iii. additional OECD TG 203 study (2019) on the Substance;
iv. QSAR prediction (ECOSAR version 1.11) with the Substance;
v. A data from a review article (2019) on the Substance.

In support of your WoE adaptations, you indicate that the following sources of information are available;

vi. A study record of an OECD TG 203 study (1995) with analogue substance Benzyl acetate (EC: 205-399-7).
vii. A study record of an OECD TG 203 study (2017) with analogue substance Benzyl 4-hydroxybenozoate (EC 202-311-9)

For these additional experimental (source) studies performed after 2008, you did not specify whether they are GLP compliant.

A. Reliability of the studies

To comply with this information requirement, an OECD TG 203 study must fulfil the validity criteria and cover the key parameters of the corresponding TG (Article 13(3) of REACH), which include (among others):

1. Analytical monitoring to verify initial concentrations and maintenance of these concentrations throughout the test as required in guideline
2. [Appropriate reporting of the test results] If test concentrations are not maintained within 20% of initial measured concentrations throughout testing, effect concentrations must be reported based on measured values (see ECHA Guidance R7b, section R.7.8.4.1)
3. all fish are held in the laboratory for at least 9 days before being used for testing (including a 48 hours settling-in period and a 7 days acclimation period). Only batches showing mortalities below 5% of the population in seven days and with no diseases or abnormalities are used;
4. the test is conducted on juveniles of similar age (or size);
5. the test medium fulfils the following condition(s): particulate matter ≤ 5 mg/L, total organic carbon (TOC) ≤ 2 mg/L or carbon oxygen demand (COD) ≤ 5 mg/L.
6. the fish-to-water loading rate is ≤ 0.8 g of fish (wet weight) per litre of water for static and semi-static tests / the fish-to-water loading rate is ≤ 0.5 g of fish (wet weight) per litre of water per day and 5 g/L at any time for flow-through tests

You have provided three OECD TG 203 studies (studies i-iii listed above) and one study record from a review article (study v, 2019 listed above) with the Substance, showing the following:

For key study you indicated that the analytical monitoring was performed and provided test concentrations. However, you did not indicate the reported values are nominal or measured concentrations. You did not provide the information on the analytical method used such as sample preparation, recovery, limit of detection and limit of quantification.

For supporting study you stated that the analytical monitoring was not required as the Substance is stable. For the additional study (study v, 2019) provided in your comments to

the draft decision, you state that test chemical concentrations were not verified analytically.

For both key and supporting study, you did not demonstrate that test concentrations are maintained within 20% of initial measured concentrations throughout testing. Despite this you reported the effect concentration based on nominal concentrations.

For the additional OECD TG 203 study (study iii, 2019) which you provide in your comments to the draft decision, you do not provide information outlined in the points 3-6 above.

Therefore the the validity criteria are not met and key parameter is not covered and the information provided is rejected.

The information requirement is not fulfilled.

Therefore, the studies provided do not fulfil the information requirement.

B. Studies conducted after 1 August 2008 and not GLP

Toxicological and eco-toxicological tests and analyses on substances must be carried out in compliance with the principles of good laboratory practice (GLP) provided for in Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or ECHA and with the provisions of Directive 86/609/EEC, if applicable (Article 13(4) of REACH). According to Article 141(2), Article 13 applies from 1 June 2008.

You did not demonstrate that the studies (i-iii) are performed according to GLP.

C. Read-across

Furthermore, with regard to supporting study (2017) and source studies provided in your comments to the draft decision as explained in the Appendix on general considerations your adaptation under Annex XI, Section 1.5 is rejected. Therefore, the information requirement is not fulfilled.

D. Qualitative or quantitative structure-activity relationship

Regarding to the QSAR prediction provided in your comments to the draft decision (study iv) as explained in the Appendix on Reasons common to several requests, section 3 your adaptation under Annex XI, Section 1.3 is rejected. Therefore, the information requirement is not fulfilled.

E. Weight of evidence

ECHA has assessed to what extent the sources of information submitted in your comments to the draft decision enables a conclusion on mortality of the juvenile fish as investigated in the information requirement proposed to be adapted and identified the following deficiencies:

As explained in Section 2 of the Appendix common to several requests, the weight of evidence 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.

All the sources of information you provided investigate mortality of fish, the key element for this endpoint. Therefore, they provide information that would contribute to the conclusion on this key element.

However, the reliability of these sources of information is significantly affected by the deficiencies identified in Section 2 of the Appendix on Reasons common to several requests.

Finally, the reliability of the studies i. to iii. are significantly affected by the deficiencies identified under sections A and B. above.

As a conclusion, sources of information as indicated above, provide information on mortality of fish but the information provided 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 property foreseen to be investigated in an OECD TG 203 study.

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

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

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[14].

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[15].

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

Appendix D: Procedure

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

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

The compliance check was initiated on 9 July 2019.

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

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

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

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

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

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

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-72 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix E: List of references - ECHA Guidance[16] 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)[17]

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]

[16] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[17] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[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 F: Addressees of this decision and the corresponding information requirements applicable to them

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]

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.