Helsinki, 21 January 2021

Addressees
Registrant(s) of JS_94-46-2_[redacted] as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
15/10/2018

Registered substance subject to this decision ("the Substance")
Substance name: Isopentyl benzoate
EC number: 202-334-4
CAS number: 94-46-2

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 January 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. Water solubility (Annex VII, Section 7.7.; test method: EU A.6./OECD TG 105/OECD GD 29)

2. Skin sensitisation (Annex VII, Section 8.3.)

   i. *in vitro/in chemico* skin sensitisation information on molecular interactions with skin proteins (OECD TG 442C), inflammatory response in keratinocytes (OECD TG 442D) and activation of dendritic cells (EU B.71/OECD TG 442E)(Annex VII, Section 8.3.1.); and

   ii. Only if the *in vitro/in chemico* test methods specified under point 2.i.) are not applicable for the Substance or the results obtained are not adequate for classification and risk assessment, *in vivo* skin sensitisation (Annex VII, Section 8.3.2.; test method: EU B.42./OECD TG 429);

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

4. Only if study under section A.1 shows the substance is not poorly water soluble, Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: EU C.2./OECD TG 202)

5. Only if study under section A.1 shows the substance is poorly water soluble, Long-term toxicity testing on aquatic invertebrates (triggered by Annex VII, Section 9.1.1., column 2; test method: EU C.20./OECD TG 211)

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

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

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

- Appendix entitled "Reasons common to several requests";
- Appendix entitled "Reasons to request information required under Annexes VII of REACH".

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;

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.

Authorised[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 information requirements for the following standard information requirements by grouping substances in the category and applying a read-across approach in accordance with Annex XI, Section 1.5:

- Skin sensitisation (Annex VII, Section 8.3.)
- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Ready biodegradability (Annex VII, Section 9.2.1.1.)

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

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

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

Grouping of substances and read-across approach

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

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance[2] and related documents[3, 4].

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 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]

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

You have provided studies conducted with other substances than your Substance in order to comply with the REACH information requirements. In your registration dossier, you have not provided documentation as to why this information is relevant for your Substance.

In your comments to the draft decision you submitted a read-across justification document describing how the read-across analogues with data for ecotoxicological, toxicological and ready biodegradability endpoints were identified following the strategy for structuring and reporting a read-across prediction of toxicity by using the OECD QSAR toolbox v3.4. and publicly available information:

- Materials were clustered based on their structural similarity.
- Data availability and data quality on the selected cluster were examined.
- Appropriate read-across analogues from the cluster were confirmed by expert judgment
- Tanimoto structure similarity scores are calculated using FCFC4 fingerprints.
- The physical–chemical properties of the target substance and the read-across analogues were obtained from dossier disseminated at ECHA website.
- Protein binding, DNA binding, mutagenicity, genotoxicity alerts, and oncologic classification predictions were generated using OECD QSAR Toolbox v 3.4.
- Acute aquatic toxicity predictions were generated using MOA by OASIS, ECOSAR and Bioaccumulation – metabolism half-lives.

You have provided the following reasoning for the prediction of (Eco)toxicological properties:

"There is insufficient toxicity data on target chemical Isopentyl benzoate (CAS: 94-46-2; EC number: 202-334-4). Hence, in silico evaluation was conducted to determine read-across analogues for this chemical. Based on structural similarity, reactivity, physical–chemical properties, organic functional groups and general mechanistic approach, Benzyl isovalerate (CAS 103-38-8; EC number: 203-106-7); Phenethyl salicylate(CAS 87-22-9; EC number: 201-732-5); Phenyl acetate (CAS 122-79-2; EC number: 204-575-0); phenethyl benzoate (CAS: 94-47-3; EC number: 202-336-5); methyl benzoate (CAS: 93-58-3; EC number: 202-259-7); Benzyl propionate (CAS: 122-63-4; EC number: 204-559-3); Methyl phenylacetate (CAS No. 101-41-7; EC number: 202-940-9); Benzyl acetate (CAS No. 140-11-4; EC number: 202-399-7); benzyl butyrate (CAS No. 103-37-7; EC number: 203-105-1) and 2-phenylethyl 3-methylbutanoate (CAS No. 140-26-1; EC number: 205-406-3) were identified as read-across analogues with sufficient data for ecotoxicological, toxicological endpoints."

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 properties.

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"*[6]. The set of supporting

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

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 structural alerts for toxicological endpoints were consistent between the target substance and the read-across analogues. You used the OECD QSAR Toolbox v3.4 to identify target chemical and the read-across analogues that were structurally and functionally similar according to Tanimoto score, and share Aryl and Carboxylic acid ester groups in common or belong to the class of carboxylic acid esters.

For skin sensitisation, the read-across analogue, benzyl propionate (EC No. 204-559-3) has protein binding alerts for skin sensitization by OASIS V1.4 which was not found for the target substance. You consider that, according to these predictions, the read-across analogues are expected to be more reactive compared to the target chemical.

For genotoxicity, in vitro mutagenicity (Ames test) alerts by ISS and the DNA alerts for AMES test by OASIS v1.4 according to OECD QSAR v 3.4 were consistent between the target and read across analogues.

For acute aquatic toxicity classification by Verhaar and acute aquatic toxicity by MOA by OASIS were consistent between the target substance and the read-across analogues methyl benzoate (CAS No. 93-58-3, EC No. 202-259-7), benzyl propionate (CAS No. 122-63-4, EC No. 204-559-3), methyl phenylacetate (CAS No. 101-41-7, EC No. 202-940-9), benzyl acetate (CAS No. 140-11-4, EC No. 202-399-7), benzyl isovalerate (CAS No. 103-38-8, EC No. 203-106-7), benzyl butyrate (CAS No. 103-37-7, EC No. 203-105-1) and 2-phenylethyl 3-methylbutanoate (CAS No. 140-26-1, EC No. 205-406-3).

For ready biodegradation, both the target chemical and structural analogues, methyl benzoate (EC 202-259-7), benzyl propionate (EC No. 204-559-3), and benzyl acetate (EC 202-399-7) were readily biodegradable in water and hydrolysis half-life obtained fromQSAR V 3.4 were consistent between target and read-across analogues.

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 does not include relevant, reliable and adequate information investigating specifically the properties ((eco)toxicological endpoints) under consideration for your Substance, e.g. bridging studies of comparable design and, in the case of ecotoxicological endpoints, 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 - that relevant properties of the Substance can be predicted from data on the analogue substance. Therefore, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected.

2. 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:

- Water solubility (Annex VII, Section 7.7.)
- Skin sensitisation (Annex VII, Section 8.3.)
- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- Short-term toxicity testing on invertebrates (Annex VII, Section 9.1.1.)
- Ready biodegradability (Annex VII, Section 9.2.1.1.)

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

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

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.

- 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.

- Reliability of the QSAR information

While an adaptation was not specifically indicated by you, ECHA has evaluated the provided QSAR information sources under the rules set in Annex XI, Section 1.3. Qualitative or quantitative structure-activity relationship (QSAR).

- 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.

- 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.);

However, for these additional source studies, you do not provide information on when the studies are performed nor whether they are GLP compliant. Accordingly, it is not possible to conclude on reliability of these studies.

- Relevance of the provided information

Additional issues related to weight of evidence are addressed under the endpoint A2, A4, A6 and A7.

3. Rule for Annex XI, Section 1.3 adaptation

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 water solubility information requeriment, you have provided i) a reference to the Interface Suite™ QSAR predictions V4.11 and ii) a reference to the Danish QSAR predictions database.

  You did not provide QMRFs and QPRFs in the dossier for the Danish QSAR predictions database for the prediction applied. Furthermore, you did not establish the scientific validity of the model, verify that the Substance falls within the applicability domain of the model, or assess the adequacy of the prediction for the purposes of classification and labelling.

- For skin sensitisation information requirement, you have provided i) a reference to the Danish QSAR predictions database, and ii) prediction from the OECD QSAR Toolbox version 3.3 based on analogues.

  The predictions provided with the Danish QSAR database and OECD QSAR Toolbox were based on information on human and/or guinea pig maximisation tests, information on murine local lymph node assay (LLNA) were not included, albeit readily available in the database.

  You did not provide QMRFs and QPRFs in the dossier for the Danish QSAR predictions database for the prediction applied. Furthermore, you did not establish the scientific validity of the model, verify that the Substance falls within the applicability domain of the model, or assess the adequacy of the prediction for the purposes of classification and labelling.

  ECHA notes that in defining the applicability domain for the the analogues used in the category, you have excluded all substances having DNA and protein binding alerts which brings bias to the whole approach. By including additional data to the prediction i.e. LLNA data, analogues can be found having classification as skin sensitiser (Cat 1 or Cat 1A according to UN GHS/CLP).

- For *in vitro* gene mutation study in bacteria information requirement, you have provided a reference to the Danish QSAR predictions database. You have not provided QMRFs and QPRFs in the dossier.

  Based on the information provided it cannot be verified that the prediction is applicable for the information requirement (i.e. prediction performed for five strains in ames test, having or not having S9 metabolic activation).

  You did not establish the scientific validity of the model, verify that the Substance falls within the applicability domain of the model, or assess the adequacy of the prediction for the purposes of classification and labelling.

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

- For ecotoxicological information requirements, you have provided estimated toxicity values for the endpoints derived with OECD QSAR tool box version 3.3 and ECOSAR program version 1.11. You have provided summaries of the predictions and the outcome of the predictions. In your comments to the draft decision, you provide additional estimated toxicity values for algae endpoint with the Substance and analogue substances derived with OECD QSAR tool box version 3.4. You include the information on the prediction in the read-across justification document and state your intention to update the registration dossier with the information. However, the same deficiencies apply to these predictions provided in your comments as those identified under Section 1 above .

  For OECD QSAR toolbox, the predictions are performed on analogue substances. Overall, the use of Toolbox is considered invalid because the prediction should not come from the average of the closest analogue substances, but from a trend between log Kow and LC_{50}.

  For ECOSAR prediction, 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]).

  For environmental fate and pathways requirements, you have provided estimated toxicity values for the endpoints derived with OECD QSAR tool box version 3.3 and BIOWIN, version 4.10. You have provided summaries of the predictions and the outcome of the predictions.
  For OECD QSAR toolbox, the predictions are performed on analogue substances.

  For BIOWIN prediction, 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[10]).

- In your comments to the draft decision, you provide additional estimated toxicity values for biodegradation potential of the Substance and analogue substances derived with EPI Suite and OECD QSAR tool box version 3.4 respectively. For the predictions with analogue substances, you include the information on the prediction in the read-across justification document. You indicate your intention to update the registration dossier with the information. However, the same deficiencies identified under Section 1 above apply to these predictions provided in your comments.

[9] ECHA Guidance R.6, Section R.6.1.5
[10] ECHA Guidance R.6, Section R.6.1.5

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

1. Water solubility

Water solubility is a standard information requirement in Annex VII to REACH.

For Annex VII, 7.7., for your supporting information, you have adapted the standard information requirement mentioned above according to Annex XI, Section 1.2. (weight of evidence) of REACH.

You have provided the following :

- An OECD TG 105 study (2017) (Key study)
- One study summary which mentions four distinct references (Supporting study):
    - Interface Suite™ QSAR predictions V4.11 (2017)
    - Danish QSAR predictions database (2017)
    - A handbook data (1996)
    - CHEMID Plus Database (2017)

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

To comply with this information requirement, an OECD TG 105 (for the flask method) study must include adequate and reliable coverage of key parameters of the corresponding TG (Article 13(3) of REACH), which include (among others):

- the results of the preliminary test,
- precise specification of the substance (identity and impurities),
- the individual analytical determinations and the average where more than one value was determined for each flask,
- the pH of each sample,
- the average of the value for the different flasks which were in agreement,
- the test temperature,
- the analytical method employed,
- evidence of any chemical instability of the substance during the test and the method used,
- all information relevant for the interpretation of the results, especially with regard to impurities and physical state of the substance.

You claimed that the substance is insoluble in water, and you did not provide further explanation or supporting information for this conclusion.

Therefore, the key parameters are not covered. Based on the above, the information you provided do not fulfil the information requirement.

Although you do not explicitly claim an adaptation, ECHA understands that all the four distinct references listed further above were submitted in order to meet the required information by way of adaptation under Annex, Section XI 1.2.

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.

You have not submitted any explanation why the sources of information provides 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 nevertheless assessed the validity of your adaptation.

1. Reliability of the QSAR information

While an adaptation was not specifically indicated by you, ECHA has evaluated the provided QSAR information sources under the rules set in Annex XI, Section 1.3. Qualitative or quantitative structure-activity relationship (QSAR).

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)[11] and a QSAR Prediction Reporting Format (QPRF)[12] 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 provided i) a reference to the Interface Suite™ QSAR predictions V4.11 (2017) and ii) a reference to the Danish QSAR predictions database (2017)

We have assessed this information and identified the following issues:

You have not provided any documentation for your QSAR predictions. In particular, while you have provided SMILES notation used for your predictions and the outcome of the predictions, you did not specify which model was used if any to derive the obtained outcome as follows: "is slightly soluble in water" "13.7 mg/L at at 25 C".

[11] ECHA Guidance R.6, Section R.6.1.9
[12] ECHA Guidance R.6, Section R.6.1.10

In addition, 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[13]). You did not verify that the Substance falls within the applicability domain of the model, or assess the adequacy of the prediction for the purposes of classification and labelling and/or risk assessment.

2. Adequate and reliable documentation of the handbook data (1996) and CHEMID Plus Database (2017)

As indicated above for the key study, to comply with this information requirement, an OECD TG 105 (for the flask method) study must include adequate and reliable coverage of key parameters of the corresponding TG (Article 13(3) of REACH).

The obtained outcome was as follows: "is slightly soluble in water" "13.7 mg/L at at 25 C".

You did not provide further explanation for this conclusion.

The aforementioned conditions of the guideline are not covered.

In your comments to the draft decision, you agree that key information is missing in the robust study summary of the OECD TG 105 study. However you have now provided a new OECD TG 105 study on the Substance and you consider that the information provided is sufficient to fulfill the information requirement. In addition, you indicate that you intend to update the technical dossier to include this data. ECHA agrees that the submitted information is sufficient to fulfil the information requirement, however it is not in the technical dossier. You are responsible to provide the necessary information to comply with the decision by the set deadline.

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

2. Skin sensitisation

Skin sensitisation is a standard information requirement in Annex VII, Section 8.3. to the REACH Regulation. Column 1 of Section 8.3. requires the registrants to submit information allowing a conclusion whether the substance is a skin sensitiser and whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A), and risk assessment, where required.

For Annex VII, 8.3., you have adapted the standard information requirement mentioned above according to Annex XI, Section 1.2. (weight of evidence) and Annex XI 1.5 (read-across) of REACH.

In addition, you provided an adaptation for skin sensitisation stating that "*an in vivo skin sensitisation study does not need to be conducted because adequate data from an in vivo skin sesitisation study are available.*" ECHA interpreted the statement as an adaptation according to column 2 of Annex VII, Section 8.3.2.

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

[13] ECHA Guidance R.6, Section R.6.1.5

In support of your adaptation, you have provided the following sources of information (type of information indicated as weight of evidence):

i. a QSAR prediction for skin sensitisation with the Substance (OECD QSAR toolbox)
ii. a QSAR prediction for skin sensitisation with the Substance (Danish QSAR toolbox)
iii. a human maximisation test (1979a) with the Substance
iv. a human maximisation test (1979b) with analogue substance ethyl benzoate (EC 202-284-3)
v. a human maximisation test (1979c) with analogue substance isobutyl benzoate (EC 204-401-3)

In your comments to the draft decision you indicated that two additional sources of information are available:

vi. a human maximization test (2012) with the analogue substance benzyl propionate (EC 204-559-3)
vii. a guinea pig maximization test (1985) with the analogue substance methyl benzoate (EC 202-259-7)

You also provided further details on study iii) in your comments to the draft decision and request ECHA to remove the testing requirements for "*skin sensitisation, in vitro/in chemico studies (OECD TG 442C, 442D and 442E)*" from the draft decision, because "*a sufficient reliable information covering all the key aspects outlined in section 8.3.2 of Annex VII were provided.*"

You initially concluded in the registration dossier that "*based on the above predictions on 3-methylbutyl benzoate (94-46-2) as well as its read across and applying weight of evidence, it can be concluded that3-methylbutyl benzoate is not a skin sensitizer. Thus comparing the above annotations with the criteria of CLP regulation, 3-methylbutyl benzoate (94-46-2) can be considered as not classified for skin sensitization.*"

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.

The sources of information must provide sufficient weight of evidence to conclude that the information requirement for skin sensitisation, as specified in all of the available test guidelines (*in vitro* and *in vivo*[14]), is fulfilled by integrating and weighing the evidence e.g. the following aspects are covered: A) whether the substance causes skin sensitisation, and

[14] OECD TGs 442C, 442D, 442E, 429, 442A, 442B and 406

B) whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A), in case, the substance is considered to be a skin sensitiser.

ECHA has assessed to what extent the sources of information submitted enables a conclusion on these properties A) and B) and identified the following deficiencies:

You have provided the above seven sources of information to address whether the Substance causes skin sensitisation.

Source(s) of information i) and ii) does not provide reliable information for an adaptation according to Annex XI 1.2. on skin sensitisation information requirement 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 2 Assessment of your weight of evidence adaptation under Annex XI, Section 1.2.

While the source of information iii) and vi provide relevant information on skin sensitisation, the information has the following deficiencies affecting its reliability.

To fulfil the information requirement, the study iii) has to meet the general requirements for human studies. Among others, the key elements of these studies (i.e. human maximization study) include [15,16]:

a) information on number of induction and challenge exposure,
b) information on duration of induction and challenge exposures including potential rest period
c) information on pre-treatment with sodium lauryl sulfate (SLS), if applied
d) information on test volume and patch size or a direct statement of the dose per square area
e) information on justification for dose level selection for induction and challenge

While you provided further details on the study iii) key elements a) to d) in your comments to draft decision, the studies iii) – as well as the source of information vi) indicated in your comments to the draft decision – still do not cover the above key element e) needed in a human maximization test, and therefore they cannot be used to fulfil the information requirement.

While the source of information vii) indicated in your comments to the draft decision provides relevant information on *in vivo* skin sensitisation, the information has the following deficiencies affecting its reliability.

Insufficient study provided:

For *in vivo* skin sensitisation studies to be considered reliable, the study shall follow the specifications of the test method (OECD TG 406):

a) Concentration used for induction should be the highest to cause mild-to-moderate skin irritation and concentration used for challenge should be the highest non-irritant concentration.

The reported data for the study you indicated in your comments to the draft decision did not include:

[15] ECHA Guidance R.7a, Section R.7.3.5.2
[16] Kligman AM, The identification of contact allergens: III: The Maximization test: A procecure for screening and rating contact sensitisers (1966). The journal of investigative dermatology, Vol. 47, No. 5.

a) Concentration causing mild-to-moderate skin irritation and concentration used for challenge concentration.

The study vii) does not cover the above key element a) needed in *in vivo* skin sensitisation studies, and therefore its reliability is significantly affected.

Sources of information iii) to v) – as well as the source of information vi) and vii) indicated in your comments to the draft decision - do not provide reliable information on the above listed key elements needed.

Therefore, the sources of information i) to vii) cannot be considered as reliable and relevant sources of information for an adaptation according to Annex XI 1.2. as explained above, and 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 2 Assessment of your weight of evidence adaptation under Annex XI, Section 1.2.

The currently available data does not allow to conclude whether the Substance causes skin sensitisation. Thereby, an assessment whether the Substance can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A) cannot be performed.

Taken together, the provided sources of information are not reliable and relevant. Testing the Substance at appropriate duration and doses, as indicated above, is required in order to assess whether the Substance has a hazardous property.

Therefore, it is not possible to conclude whether your Substance causes skin sensitisation or not. Consequently, your adaptation is rejected and the information requirement is not fulfilled.

You have sought to adapt this information requirement based on Annex VII, Section 8.3.2., Column 2.

As explained above you have not provided reliable data to conclude whether the Substance causes skin sensitisation, therefore the Annex VII, section 8.3.2, column 2 adaptation is rejected and the information requirement is not fulfilled.

Therefore, your adaptations are rejected, and the information requirement is not fulfilled.

To fulfil the information requirement for the Substance for skin sensitisation, *in vitro/in chemico* studies (OECD TG 442C, 442D and 442E) are considered suitable. In case *in vitro/in chemico* methods are not suitable for the Substance or the results cannot be used for classification and risk assessment an *in vivo* skin sensitisation study (OECD TG 429) must be performed.

3. In vitro gene mutation study in bacteria

An *in vitro* gene mutation study in bacteria is a standard information requirement in Annex VII to REACH.

For Annex VII, 8.4.1., 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 (type of information indicated as weight of evidence):

i. a bacterial reverse mutation assay equivalent or similar to OECD TG 471 (1992a) with *S. typhimurium* strains TA97, TA98, TA100, TA1535, TA1537 with analogue substance methyl benzoate (EC 202-259-7)
ii. a bacterial reverse mutation assay equivalent or similar to OECD TG 471 (1992b) with *S. typhimurium* strains TA98, TA100, TA1535, TA1537 with analogue substance cyclohexyl 3-phenylacrylate (EC 231-921-8)
iii. a bacterial reverse mutation assay (1958) without a guideline reference with strain E. coli Sd-4-73 with the Substance
iv. QSAR prediction for gene mutation with the Substance (Danish QSAR database using the battery approach)

In your comments to the draft decision you indicated additional sources of information are available:

v. a bacterial reverse mutation assay according to OECD TG 471 (1997) with analogue substance phenethyl benzoate (EC 202-336-3)

You also provided further details on study i) in your comments to the draft decision, and consider that the information provided cover all the requirements as requested by ECHA to satisfy the regulatory obligations for *in vitro* gene mutation study in bacteria. You request ECHA to remove the testing requirements for *in vitro* gene mutation study in bacteria (OECD TG 471) from the draft decision.

You initially concluded in the registration dossier that "*based on the weight of evidence data available for the target chemical and its read across, Isoamyl benzoate does not induce gene mutation in vitro. Hence the chemical is not likely to classify as a gene mutant in vitro.*"

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.

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:

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

information requirement of Section 8.4.1. at Annex VII includes similar information that is produced by the OECD TG 471 (Bacterial Reverse Mutation Assay).

Neither the source(s) of information i) and ii) nor the source of information v) indicated in your comments to the draft decision - provide relevant and reliable information on gene mutation. More specifically, as explained under the Appendix on Reasons common to several requests your adaptations under Annex XI, Sections 1.2 and 1.5 are rejected. The studies are therefore not considered as reliable sources of information for an adaptation according to Annex XI 1.2. In addition, studies i) and ii) are both conducted without the appropriate 5th strain as required by the OECD TG 471 which is either S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). Your comments on source of information i) do not change that conclusion.

The source(s) of information iii) does not generally meet the requirements of OECD TG 471 (1997) and is therefore not considered as reliable source of information for an adaptation according to Annex XI 1.2. for the information requirement of *in vitro* gene mutation study in bacteria.

The source of information iv) does not provide reliable information on gene mutation, key element or key investigation(s) because the predicted values are uncertain, and cannot be used for replacing experimental data, as explained under the Appendix on Reasons common to several requests, section 2 Assessment of your weight of evidence adaptation under Annex XI, Section 1.2. The source of information iv) is therefore not considered as reliable source of information for an adaptation according to Annex XI 1.2.

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 471 study.

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

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

4. Only if study under section A.1 shows the substance is not poorly water soluble, Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: EU C.2./OECD TG 202)

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

You have adapted the standard information requirement mentioned above according to Annex XI, Section 1.2. of REACH (weight of evidence).

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 QSAR prediction OECD QSAR tool box version 3.3 on analogue substances;
(ii) a QSAR prediction ECOSAR program version 1.11;
(iii) an OECD TG 202 study (1996) with analogue substance Benzoic acid, methyl ester, EC number 93-58-3;
(iv) Data from HPVIS on analogue substance 1-[2-(benzoyloxy)propoxy]propan-2-yl

benzoate, EC number 248-258-5;

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;

(v) an OECD TG 202 study with the Substance;
(vi) an OECD TG 202 study with analogue substance Benzyl isovalerate (EC 203-106-7);
(vii) a short-term (48hr) aquatic toxicity study (no specification of TG) with analogue substance methyl benzoate (EC 202-259-7).

For these additional source studies, you did not specify when the studies are performed nor are the studies GLP compliant.

You initially concluded in the registration dossier that: *"Based on the prediction done using the OECD QSAR toolbox version 3.3 with log kow as the primary descriptor and considering the five closest read across substances, the short term toxicity on aquatic invertebrates was predicted forIsopentyl Benzoate (94-46-2). EC50 value was estimated to be 18.3 mg/l for Daphnia magna for 48 hrs duration."*

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 substances 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.

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 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. Therefore, they provide information that would contribute to the conclusion on this key parameter.

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 additional source studies provided by you in your comments to the draft decision, the information has the following additional deficiencies affecting its reliability.

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 of OECD TG 202 specifies that:

1. young daphnids, aged less than 24 hours at the start of the test, are used;
2. 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;
3. the pH variation is < 1.5 units;
4. 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;
5. 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 1-3 above, you do not provide information on these parameters. Regarding point 4 and 5, you do not specify whether the analytical monitoring was performed during the test and how the effect concentrations are derived.

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

In addition, 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, the additional information on the source substances benzyl isovalerate and methyl benzoate submitted with your comments is not sufficient to justify your read-across approach because similar properties of the Substance and the source substance have not been demonstrated, as discussed under the Appendix Reasons common to several requests, Section 1.

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.

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

However, Annex VII, section 9.1.1, column 2, requires to perform a long-term toxicity study on aquatic invertebrates (Annex IX, Section 9.1.5) instead of an acute test when the substance concerned is poorly water soluble. In that respect, as explained under request A.1, your dossier currently does not include reliable value on the water solubility of the substance. However, based on the information currently contained in the dossier it might be poorly water soluble. Therefore, a short-term toxicity testing on aquatic invertebrates must only be conducted if the data generated under request A.1 do not confirm that the substance is poorly water soluble (i.e. water solubility below 1 mg/L).

5. Only if study under section A.1 shows the substance is poorly water soluble, Long-term toxicity testing on aquatic invertebrates (triggered by Annex VII, Section 9.1.1., column 2; test method: EU C.20./OECD TG 211)

Short-term toxicity testing on aquatic invertebrates is a standard information requirement in Annex VII to REACH. However, pursuant to Annex VII, section 9.1.1, column 2, for poorly

water soluble substances (i.e. water solubility below 1 mg/L) long-term toxicity study on aquatic invertebrates (Annex IX, Section 9.1.5) must be considered instead of an acute test.

You have adapted the standard information requirement on toxicity testing on aquatic invertebrates according to Annex XI, Section 1.2. of REACH (weight of evidence).

You have not provided any data on long-term toxicity to aquatic invertebrates.

In your comments to draft decision, you request ECHA to remove the requirement of long-term toxicity to aquatic invertebrates from the draft decision, as additional information on the water solubility showing that the Substance is not poorly water soluble is provided in your comments to the draft decision.

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

As explained under request A.1, your dossier currently does not include reliable value on the water solubility of the substance. However, based on the information currently contained in the dossier, it might be poorly water soluble.

Poorly water soluble substances require longer time to reach steady-state conditions. Hence, the short-term tests may not give a true measure of toxicity for this type of substances.

Therefore, if the information requested on water solubility (request A.1) confirms that the substance is poorly water soluble (i.e. water solubility below 1 mg/L), a long-term test must be conducted.

The study (an OECD TG 105) on the Substance you provided in your comments to the Substance show that the Substance is not poorly water soluble (WS=15.650 mg/L). As stated above in the request A.1 on water solubility, ECHA considers that you have now addressed the request on water solubility with your newly submitted information. Hence long-term toxicity to aquatic invertebrates is not required for this Substance. However you must provide this information on water solubility in your updated dossier by the deadline of this decision. You are responsible to provide the necessary information to comply with the decision by the set deadline.

6. Growth inhibition study aquatic plants

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

You have provided a key study performed according to OECD TG 201 (2018) 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. of REACH (weight of 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 support of your adaptations, you indicate that the following sources of information are available;

(i) an OECD TG 201 study with the Substance;
(ii) an OECD TG 201 study with analogue substance 2-phenylethyl 3-methylbutanoate (EC 205-406-3);

(iii) an OECD TG 201 study with analogue substance benzyl isovalerate (EC 203-106-7);
(iv) a QSAR prediction (OECD QSAR toolbox v.3.4) with the analogue substance benzyl propionate (EC 204-559-3);
(v) a QSAR prediction (OECD QSAR toolbox v.3.4) with the analogue substance methyl phenylacetate (EC 202-940-9).

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 substances 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):

The provided key study (2018) was not performed according to GLP.

Tests on substances must be conducted in accordance with the OECD test guidelines or other internationally recognised test method (Article 13(3) of REACH).

OECD TG 201 in combination with the revised OECD Guidance 23, ENV/JM/MONO(2000)6/REV1 require(s) that the following conditions are met (among others):

- effect concentrations based on the measured values rather than nominal values unless the test concentrations are maintained within 20% of the measured initial concentrations throughout testing.
- For difficult to test substances, including poorly water soluble substance and/or unstable substance, the substance which degrades in the test medium, a sufficiently sensitive analytical method is particularly necessary due to the likelihood of losses of the Substance from the test medium. The possibility of losses during sampling, sample treatment and analysis must be considered and documented.

As explained under request A.1 above, your dossier currently does not include reliable value on the water solubility of the substance. However, based on the information currently contained in the dossier, it might be poorly water soluble. Based on the information provided in your comments to draft decision, ECHA understands that the Substance is water soluble. Furthermore, although there is currently no reliable studies for the ready biodegradability endpoint (as explained under request A.5 below), you concluded in the endpoint summary that the Substance is readily biodegradable. Thus, the substance potentially has low water solubility and/or has potential to degrade in the test system. Therefore it is expected that considerable losses will occur during the exposure period.

You did not provide any analytical monitoring of exposure concentrations and did not demonstrate that the test substance concentration during the test was maintained within the required 20% of the measured initial concentrations.

The aforementioned conditions of the guidelines are not met, therefore the information provided does not fulfil the information requirement.

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.

Regarding the experimental source studies (i), (ii), (iii), 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.

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

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.

The conditions of exposure in OECD TG 201 specify that:

1. exponential growth in the control cultures is observed over the entire duration of the test;
2. at least 16-fold increase in biomass is observed in the control cultures by the end of the test;
3. the mean coefficient of variation for section-by-section specific growth rates (days 0-1, 1-2 and 2-3, for 72-hour tests) in the control cultures is ≤ 35%;
4. the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures is ≤ 7% in tests with [Pseudokirchneriella subcapitata / Desmodesmus subspicatus]. For other less frequently tested species, the value is ≤ 10%;
5. the pH of the control medium does not increase by > 1.5 units;
6. three replicates at each test concentration and at least three replicates for controls (including solvent controls, if applicable) are included;
7. 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;
8. if the concentration of the test material has not been maintained within 20 % of the nominal or measured initial concentration throughout the test, results must be based on the geometric mean of measured concentrations during exposure or on a model describing the decline of the concentration of the test material.

Reagarding points 1-4 above, you indicate that the validity criteria were fulfilled for all the provided source studies (i), (ii) and (iv). However no raw data are provided to verify these validity criteria outlined in the points 1-4.

Regarding points 5 and 6, no information are provided in your comments for all the source studies.

Regarding points 7 and 8, you do not specify whether the analytical monitoring was performed during the tests nor if the concentrations of the test material have been maintained within 20 % of the nominal or measured initial concentration throughout the test for all the source

studies. However, the effect concentrations are reported based on nominal concentrations for all the source studies.

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

In addition, 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.

As a conclusion, sources of information as indicated above, provide relevant information on the 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.

7. Ready biodegradability

In your registration dossier, you have adapted the standard information requirement mentioned above according to Annex XI, Section 1.2. (weight of evidence).

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 QSAR prediction OECD QSAR tool box version 3.3 on analogue substances;
(ii) a QSAR prediction BIOWIN program version 4.10;
(iii) Data from peer reviewed journal on analogue substance Butyl benzoate, EC number 205-252-7;
(iv) data from HSDB database on analogue substance Butyl benzoate, EC number 205-252-7;
(v) data from HSDB database on analogue substance methyl benzoate, EC number 202-259-7;

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), and Annex XI, Section 1.3 (Qualitative or quantitative structure-activity relationship (QSAR)) of REACH.
In support of your adaptations, you indicate that the following sources of information are available;

(vi) QSAR prediction on the biodegradation potential with the Substance;
(vii) an OECD TG 301F study with analogue substance benzyl propionate (EC 204-559-3);
(viii) an OECD TG 301B study with analogue substance methyl benzoate (EC 202-259-7);
(ix) information from a data base (2018) on analogue substance benzyl acetate (EC 202-399-7);
(x) QSAR predictions (OECD QSAR toolbox v.3.4) with the Substance and analogue substances

For these additional experimental source studies (vii) and (viii), you did not specify when the studies are performed nor are the studies GLP compliant.

You initially concluded in the registration dossier that: *"Biodegradability of 3-methylbutyl benzoate (CAS no. 94 -46 -2) is predicted using QSAR toolbox version 3.3 with logKow as the primary descriptor (2017). Test substance undergoes 81.08% degradation by BOD in 28 days. Thus, based on percentage degradation, the test chemical 3 -methylbutyl benzoate was estimated to be readily biodegradable in water."*

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., section 2 Assessment of your weight of evidence adaptation under Annex XI, Section 1.2., and Section 3 : Assessment of your Qualitative or quantitative structure-activity relationship (QSAR) adaptation under Annex XI, Section 1.3, your adaptations under Annex XI, Sections 1.5, 1.2, 1.3 are 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 202 study.

In your comments to the draft decision, you indicate your intention to update the registration dossier with a QSAR Model Reporting Format (QMRF) report for QSAR prediction with the Substance. This information was not provided in your dossier nor your comment and thus cannot be taken into account. You are responsible to provide the necessary information to comply with the decision by the set deadline.

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

Appendix B: 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[17].

B. Test material

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 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.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[18].

[17] https://echa.europa.eu/practical-guides
[18] https://echa.europa.eu/manuals

Appendix C: Procedure

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

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

The compliance check was initiated on 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.

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

Appendix D: List of references - ECHA Guidance[19] 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)[20]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[21]

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.

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

OECD Guidance documents[22]

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.

[22] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix E: 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]

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.