~~Confidential~~

Helsinki, 23 July 2021

**Addressees**
Registrant(s) of JS_15721-78-5_[redacted] as listed in the last Appendix of this decision

**Date of submission of the dossier subject to this decision**
20 February 2019

**Registered substance subject to this decision ("the Substance")**
Substance name: Bis(4-(1,1,3,3-tetramethylbutyl)phenyl)amine
EC number: 239-816-9
CAS number: 15721-78-5

**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 ***28 October 2024***.

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

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

1. Partition coefficient n-octanol/water (Annex VII, Section 7.8.; using an appropriate test method);

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

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

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

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

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

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

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

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

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

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

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

5. Soil simulation testing (Annex IX, Section 9.2.1.3.; test method: EU C.23./OECD TG 307) at a temperature of 12 °C;

6. Sediment simulation testing (Annex IX, Section 9.2.1.4.; test method: EU C.24./OECD TG 308) at a temperature of 12 °C;

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

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

9. Effects on soil micro-organisms (Annex IX, Section 9.4.2.; test method: EU C.21./OECD TG 216);

10. Long-term toxicity on terrestrial invertebrates (Annex IX, Section 9.4.1., column 2; test method: Earthworm reproduction test (OECD TG 222) or Enchytraeid reproduction test (OECD TG 220) or Collembolan reproduction test (OECD 232);

11. Long-term toxicity to terrestrial plants (Annex IX, Section 9.4.3. column 2.; test method: Terrestrial plant test: seedling emergence and seedling growth test, OECD TG 208 with at least six species tested (with as a minimum two monocotyledonous species and four dicotyledonous species) *or* Soil Quality – Biological Methods – Chronic toxicity in higher plants, ISO 22030).

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 IX of REACH", respectively.

**Information required depends on your tonnage band**

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

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

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

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

**How to comply with your information requirements**

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

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

The studies relating to biodegradation and bioaccumulation are necessary for the PBT assessment. However, to determine the testing needed to reach the conclusion on the persistency and bioaccumulation of the Substance you should consider the sequence in which these tests are performed and other conditions described in Appendix E.

**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 provide 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 weight of evidence adaptations under Annex XI, Section 1.2**

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

- *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- *In vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study (Annex VIII, Section 8.4.2.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.);
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

In the comments to the draft decision you have provided information seeking to adapt, by applying weight of evidence approaches, also the following standard information requirements:

- Long-term toxicity testing on aquatic invertebrates (triggered by Annex VII, Section 9.1.1., Column 2, and Annex IX, Section 9.1.5.)
- Long-term toxicity testing on fish (triggered by Annex VIII, Section 9.1.3., Column 2, and Annex IX, Section 9.1.6.)
- Bioaccumulation in aquatic species (Annex IX, Section 9.3.2.).

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

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

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

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

In your comments to the draft decision, you have summarised the sources of information for the endpoints *in vitro* gene mutation study in bacteria, screening for reproductive/developmental toxicity, sub-chronic toxicity study (90-day), long-term toxicity testing on aquatic invertebrates, long-term toxicity testing on fish and bioaccumulation in aquatic species, in relation to the reliability, coverage of key parameters, consistency and results and concluded that as a weight of evidence based on the available sources of information, no further studies are needed.

For the endpoints *in vitro* cytogenicity study and pre-natal developmental toxicity, you have not included a justification for your weight of evidence adaptations, which would include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Irrespective of this principle deficiency on the documentation, which in itself could lead to the rejection of the adaptations, ECHA has assessed the provided sources of information with a view to their relevance and reliability for the endpoints in question.

In the following, ECHA gives the reasons why it considers in general a deficiency with regard to the reliability of information provided on analogue substances, while the specific deficiencies of the weight of evidence are set out in the reasons given for the individual information requirements in the Appendices below.

Reliability of the provided information with analogue substances

ECHA understands that you intend to predict the (eco)toxicological properties of the Substance for the listed above endpoints, from data obtained with analogue substances in a read-across approach as part of your weight-of-evidence approach.

**Grouping of substances and read-across approach**

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

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

**Read across documentation for (eco)toxicological properties**

For (eco)toxicological properties you read-across between the following substances, reported in the comments on the draft decision, as source substances and the Substance as target substance:

| Source/analogue | Human health endpoints | Environmental endpoints |
|---|---|---|
| 1,4-benzenediamine, n-(dimethylphenyl)-n'-(methylphenyl)- (CAS: 70290-05-0) | | Bioaccumulation in aquatic species |
| 4-(2,4,4-trimethylpentan-2-yl)phenol (EC: 205-426-2; CAS: 140-66-9) | In vitro gene mutation study in bacteria | Long-term toxicity testing on aquatic invertebrates and long-term toxicity testing on fish |

[2] ECHA Guidance R.6

| | | |
|---|---|---|
| N-1,3-dimethylbutyl-N'-phenyl-p-phenylenediamine (EC: 212-344-0; CAS: 793-24-8) | | Long-term toxicity testing on fish |
| 2,2-bis(4'-hydroxyphenyl)-4-methylpentane (EC: 401-720-1; CAS: 6807-17-6) | | Long-term toxicity testing on aquatic invertebrates |
| Phenol, 4-(1,1-dimethylethyl)- (EC: 202-679-0; CAS: 98-54-4) | In vitro gene mutation study in bacteria | |
| Bis(4-octylphenyl)amine (EC: 202-965-5; CAS: 101-67-7) | Combined repeated dose and reproductive toxicity study | |
| Diphenylamine (EC: 204-539-4; CAS: 122-39-4) | Two generation reproductive toxicity study | |
| Benzenamine, N-phenyl-, styrenated (EC: 270-485-3; CAS: 68442-68-2) | Combined repeated dose and reproductive toxicity study | |
| Benzenamine, N-phenyl-, reaction products with isobutylene and ,4,4-trimethylpentene (EC: 606-029-0; CAS: 184378-08-3) | Combined repeated dose and reproductive toxicity study<br><br>14 days toxicity study | |

In your comments to the draft decision you have provided a document entitled "[redacted] With this document you intend to justify the use of information obtained on the aforementioned analogue substances in your WoE adaptation.

In your justification document you have indicated that 'Scenario 2' was selected for the analogue approach. You provided the following reasoning for the prediction of (eco)toxicological properties: "*read-across of environmental fate, ecotoxicological and toxicological data from an analogue may be justified on the basis of:*

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

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

Based on the above, ECHA understands that you used the QSAR Toolbox for the identification of analogues and use information on these analogues to predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted to be quantitatively equal to those of the source substance(s).

You have provided the following information to support your hypothesis:

- Structural information on the Substances and analogues
- Information on structural alerts
- Information on physicochemical, degradation and bioaccumulation properties
- Bridging data to compare the toxicological properties of the substances

- Bridging data to compare the ecotoxicological properties of the substances

The detailed description and the assessment of the supporting information is provided further below.

ECHA notes the following deficiencies with regards to predictions of (eco)toxicological properties. The common deficiencies are set out here, while the specific ones, which also add to the overall conclusion, are set out under Appendices A-C below.

### *I.1* Predictions for toxicological properties

*I.1.1 Missing documentation for the predictions from EC 606-029-0*

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).[3]
For the substance with EC 606-029-0 you have not provided documentation on the justification for the read-across, including explanation of the rationale for the prediction of properties from the analogue substance and why this information is reliable and relevant for your Substance to be used, as part of weight-of-evidence.

In the absence of such documentation, ECHA cannot verify that the properties of your Substance can be predicted from the data on the source substance with EC 606-029-0. Therefore, the information from the analogue substance submitted under your weight-of-evidence adaptation is not considered reliable.

*I.1.2 Missing 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*"[4]. The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance(s).

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

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

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

[3] ECHA Guidance R.6, Section R.6.2.6.1
[4] ECHA Guidance R.6, Section R.6.2.2.1.f

- Alert profiles using the QSAR Toolbox

You have provided target and source substances which have [redacted] as common constituent. However, there are differences in other functional groups contained in the target and the analogue substances.
More specifically, for the analogue substances with EC 205-426-2 and EC 202-679-0 there is not an amine group but instead there is a phenol group. For the substance with EC 202-965-5 there is is a similar secondary aromatic amine "core" but there are alkyl ring substituent which are not branched and longer that the ones from target substance. For the substance with EC 204-539-4 there is a similar secondary aromatic amine "core" but there are no ring constituents like in the target substance. For the substance with EC 270-485-3 there is a similar secondary aromatic amine "core" but there are no additional [redacted] rings.

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

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

- Information from Experimental studies

In order to support your claim that the Substance and source substances have similar properties for the endpoints under consideration in the read-across approaches, you referred to experimental results from acute toxicity, irritation and skin sensitisation.

We have assessed this information provided with your comments and identified the following issue(s):

- Regarding alerts obtained from the QSAR toolbox

    - In vitro gene mutation study in bacteria

The profiles of structural alerts for the analogue substances EC: 205-426-2; CAS: 140-66-9 and EC: 202-679-0; CAS: 98-54-4 and the Substance have structural differences. In particular, for the endpoint gene mutation study in bacteria, the structural alerts obtained from the QSAR Toolbox for protein binding, estrogen receptor binding and DART indicate that the substances may have differences in the reactivity. This is related to the structural differences of the amine and/or secondary amine and/or secondary aromatic amine and/or methyl moieties. You have not explained why these differences do not influence the toxicological properties.

    - Repeated dose toxicity, reproductive and developmental toxicity

While the similarity in presence or absence of structural alerts may indicate that the structural differences between the Substance and the source substances do not influence the reactivity of the substances e.g. on the protein or DNA, this information does not confirm, on its own, that these substances have similar repeated dose toxicity, reproductive and developmental toxicity properties. In fact, the complexity of the systemic interactions and the reproductive process and the large number of targets/mechanisms associated with those broad areas of toxicity cannot be covered exclusively by information obtained from computational tools. Therefore, the structural alerts reported in the justification document do not constitue on their

own a reliable basis to establish that the the Substance and the source substances have similar repeated dose toxicity, reproductive and developmental toxicity properties.

Similarly regarding the predicted physicochemical and degradation properties, while this information might be relevant to support similarity in toxicokinetics, this information does not establish similarity in properties for the complex information requirements that you intend to cover with your adaptation, as indicated above.

- Regarding the experimental studies

According to the ECHA Guidance[5] "*it is important to provide supporting information to strengthen the rationale for the read-across approach. Thus, in addition to the property/endpoint being read-across, it is also useful to show that additional properties, relevant to the endpoint, are also (qualitatively or quantitatively) similar between the source and target chemicals*".

While the information on acute toxicity, irritation and skin sensitisation of the substances may provide support that the substances have similar properties for these toxicological properties, these studies do not inform on the sexual function and fertility properties of the target and source substances. Therefore, this information does not provide relevant information for the Substance and of the source substance(s) to support your read-across hypothesis for the endpoints screening for reproductive/developmental toxicity, sub-chronic toxicity study (90-day) and pre-natal developmental toxicity study.

Based on above, the available data set do not provide reliable supporting information to support your claim of similarity in toxicological properties for these endpoints. On the basis of the above, based on the information provided, no reliable comparison of the properties of the Substance and the analogues can be made.

*I.1.2 Conclusion for prediction of toxicological properties*

Based on the information in the dossier and provided in the comments, the information from the analogue substances submitted under your weight of evidence adaptation is not considered reliable. Additional issues related to weight of evidence are addressed under the corresponding information requirement.

## *I.2* Predictions for ecotoxicological properties

### I.2.1 Predictions for aquatic toxicity

*I.2.1.1 Missing 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 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).

[5] ECHA Guidance R.6, Section R.6.2.2.1.f
[6] ECHA Guidance R.6: Section R.6.2.2.1.f

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

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

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

- Alert profiles using the QSAR Toolbox

In your comments you have provided a target and a source substance (CAS No 793-24-8) which have [redacted] as common structural element. In addition, you have identified two source substances CAS No. 140-66-9 and 6807-17-6, which do not contain the common [redacted] constituent. With respect to these source substances you argue that they share functional groups like alkyl arenes (CAS No 140-66-9, and 6807-17-6), aryl (CAS No 140-66-9, 793-24-8 and 6807-17-6), aromatic amine (CAS No. 793-24-8), tert-butyl (CAS No. 140-66-9) and alkane branched with quaternary carbon (CAS No. 140-66-9) groups common with the target substance. However, two of these source substances (CAS No 140-66-9 and 6807-17-6) also have a hydroxyl functional group that is not shared by the target substance.

You have assessed the impact of these structural differences using a set of physico-chemical and (abiotic and biotic) degradation properties, structural characteristics and mechanistic alerts obtained from the QSAR Toolbox v3.4 for the Substance and for each of the source substances.

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

- Experimental studies

In the read-across justification you argue that the target and source substances "*share comparable properties with regard to their ecotoxicological parameters*". In your dossier you have not provided any experimental aquatic toxicity data neither on the Substance nor on the analogue substances. In your comments to the draft decision, you have provided the following information on experimental data for aquatic toxicity on the analogue substances indicated in the table below:

| **Study** | **EC 205-426-2 / CAS: 140-66-9** | **EC 401-720-1 / CAS 6807-17-6** | **EC 212-344-0 / CAS: 793-24-8** |
|---|---|---|---|
| **Long-term toxicity to invertebrates** | - EPA OPPTS 850.1300, 21d: NOEC = unknown and EC50 = 0.34 mg/L (measured) | - OECD TG 211, 21d: NOEC = 0.5 mg/L and EC50 = 5.3 mg/L (measured) | |

| | | | |
|---|---|---|---|
| **Long-term toxicity to fish** | - OECD TG 210, 30d: NOEC= 0.033 mg/L (nominal) and LC50 = unknwon | | - EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians (1975), 28d: NOEC = 0.066 mg/L and LC50 = 0.15 mg/L (nominal) |

We have assessed this information and identified the following issues:

- Regarding alerts obtained from the QSAR toolbox

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

Similarly regarding the predicted physicochemical and degradation properties, while this information might be relevant to support similarity in behaviour in aquatic compartment, this information does not allow the prediction of complex information requirements that you intend to cover with your adaptation, as indicated above.

- Regarding experimental studies

ECHA has identified shortcomings with the reliability of the experimental studies provided as supporting information:

Regarding long-term invertebrate and fish data, as described in the appendices below (sections C.3 and C.4, respectively), the studies are not considered reliable and therefore they cannot be used to compare the ecotoxicological properties of the substances.

Furthermore we note that for both long term toxicity on aquatic invertebrates and fish you have provided information on analogues but no information on the Substance

*I.2.1.2 Conclusion for prediction of aquatic toxicity*

Based on the information provided, no reliable comparison of the properties of the Substance and the analogue substances can be made.

Therefore, based on the information in the dossier and provided in the comments, the information from the analogue substances submitted under your weight of evidence adaptation is not considered reliable. Additional issues related to weight of evidence are addressed under the corresponding information requirement.

### ***I.2.2*** **Predictions for bioaccumulation**

*I.2.2.1 Missing supporting information*

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

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

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

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

- Alert profiles using the QSAR Toolbox

You have provided a target and a source substance (CAS No. 70290-05-0) which have [redacted] as common structural element. In addition, you argue that the source substance shares functional groups like aryl and aromatic amine groups common with the target substance.

You have assessed the impact of the structural differences using a set of physico-chemical and (abiotic and biotic) degradation properties, structural characteristics and mechanistic alerts obtained from the QSAR Toolbox v3.4 for the Substance and for the source substances.

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

- Experimental studies

In your dossier you have not provided any experimental data neither on the Substance nor on the analogue substances. In your comments to the draft decision, you have provided the following information on experimental data on bioaccumulation (bioconcentration factor) on the analogue substance indicated in the table below:

| Study | CAS 70290-05-0 |
|---|---|
| OECD 305 C | Conc. 0.1 mg/L<br>BCF (Peak A) = 3760 to 9800 L/Kg<br>BCF (Peak B) = 4210 to 9950 L/Kg<br>BCF (Peak C) = 3340 to 8530 L/Kg<br>Conc. 0.01 mg/L |

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

| | |
|---|---|
| | BCF (Peak A) = 5290 to 14600L/Kg<br>BCF (Peak B) = 6330 to 15200 L/Kg<br>BCF (Peak C) = 7710 to 14600 L/Kg |

In your comments to the draft decision, you have not provided any experimental data on the Substance but only a QSAR prediction for BCF (>2000 L/kg).

We have assessed this information and identified the following issues:

- Regarding alerts obtained from the QSAR toolbox

There are structural differences between the target and source substances. While the similarity in presence or absence of structural alerts may indicate that the differences do not influence the reactivity of the substance e.g. on the protein or DNA, this information does not confirm, on its own, that the Substance and the source substances have similar bioaccumulation properties. Therefore, the structural alerts reported in the justification document do not represent adequate information on the above mentioned properties of the Substance and the source substances, e.g. bridging studies of comparable design and duration.

Regarding the predicted physicochemical and degradation properties, while this information might be relevant to support similarity in behaviour in aquatic compartment, this information does not allow the prediction of complex information requirement that you intend to cover with your adaptation, as indicated above.

- Regarding experimental studies

ECHA has identified shortcomings with the reliability of the experimental study provided as supporting information:

Regarding bioaccumulation study, as described in the appendices below (section C.8), provided study is not considered reliable and therefore it cannot be used to compare the bioaccumulation properties of the substances.

Furthermore we note that there is currently no reliable information on the bioaccumulation of the Substance, since the QSAR prediction you provided for the BCF Substance is not reliable, as described in the appendices below (section C.8).

*I.2.2.2 Conclusion for prediction of bioacummulation property*

Based on the information provided, no reliable comparison of the properties of the Substance and the analogue substance can be made.

Therefore, based on the information in the dossier and provided in the comments, the information from the analogue substance submitted under your weight of evidence adaptation is not considered reliable. Additional issues related to weight of evidence are addressed under the corresponding information requirement.

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

You have provided (Q)SAR adaptations in accordance with Annex XI, Section 1.3 for the following standard information requirements:

- Partition coefficient n-octanol/water (Annex VII, Section 7.8.)
- Soil simulation study (Annex IX, Section 9.2.1.3.).
- Sediment simulation testing (Annex IX, Section 9,2,1,4,)
- Bioaccumulation in aquatic species (Annex IX. Section 9.3.2)

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

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

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

You have not provided any documentation for the QSAR predictions. In particular, you have not included a QMRF and a QPRF in your technical dossier for the relevant endpoints.

In your comments on the draft decison, you stated that a QSAR Model Reporting Format (QMRF) for the QSAR predictions on partition coefficient n-octanol/water, soil simulation study and sediment simulation study are available and that you will provide this information in an update of your registration dossier. However no additional documentation for the QSAR predictions is available in your comments. Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation)."

Therefore, ECHA cannot establish whether the model is scientifically valid, whether the Substance falls within the applicability domain of the model, and whether the results are adequate for classification and labelling and/or risk assessment.

Based on the information in your dossier and provided in the comments, the adaptations you provided do not fulfil the criteria specified in Annex XI, Section 1.3. and they are therefore rejected.

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 1 to 10 tonnes or more per year must contain, as a minimum, the information specified in Annex VII to the REACH Regulation.

## 1. Partition coefficient n-octanol/water

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

You have sought to adapt this information requirement based on Annex XI, Section 1.3 and you have provided:

- QSAR estimate based on KOWWIN v1.67 ((RAPA) Panel of the American Chemistry Council, 2001);
- QSAR estimate based on KOWWIN v1.68 ([redacted] – estimated, 2018).

However, for the reasons explained in the *Appendix on Reasons common to several requests* regarding the assessment of the QSAR adaptations (section 2) your adaptation is rejected.

In your comments to the draft decision, you:

A. claim you have additionally provided a QSAR Model Reporting Format (QMRF) for the two above mentioned QSAR estimates;

B. have provided a brief summary of an additional OECD TG 117 study on the Substance

ECHA has assessed the information provided and has identified the following issue(s):

A. QSAR prediction

As indicated under the *Appendix on Reasons common to several requests*, in your comments on a draft decison, you stated that a QSAR Model Reporting Format (QMRF) for the QSAR prediction on partition coefficient n-octanol/water is available and that you will provide this information in an updated of your registration dossier. However no additional documentation for the QSAR predictions is available in your comments.

As explained under the the *Appendix on Reasons common to several requests* regarding the assessment of the QSAR adaptations (Section 2), your adaptation is rejected.

B. OECD TG 117 study

EU A.8 and OECD TG 117 establish the requirements for the data to be reported for a partition coefficient study. For the HPLC method, especially the following is required:

- If determined the preliminary estimate of the partition coefficient, the estimated values and the method used; and if a calculation method was used, its full description including identification of the data base and detailed information on the choice of fragments;
- Purity of the test substance;
- Reference substances: purity, structural formula and CAS number,

- Elution profiles (chromatograms);
- Deadtime and how it was measured;
- Retention data and literature log Pow values for reference substances used in calibration;
- Details on fitted regression line (log k versus log Pow) and the correlation coefficient of the line including confidence intervals;
- Average retention data and interpolated log Pow value for the test substance;
- log Pow values relative to area % of the log Pow peak;
- Calculation using a regression line;
- Calculated weighted average log Pow values, when appropriate.

In your comments, you stated that a new OECD TG 117 study using the HPLC method is available and that you will provide this information in an update of your registration dossier. You have provided in your comments a brief summary of the study, including information on preparation of test solutions, names and log Pow ranges of reference substances and determined log Pow value for the Substance (i.e. log Pow = 7.472). However, the information in your comments is not sufficient for ECHA to make an assessment, because you have not reported all the parameters listed above. In the absence of the information to be reported, you have not demonstrated that the study complies with OECD TG 117. Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation).

Based on the above, the information you provided does not fulfil the information.

Possibility for data sharing for studies not involving vertebrate animals

The registrants of the jointly submitted registration for the Substance (lead registrant [redacted] have data available that is relevant for this endpoint. In accordance with Title III of the REACH Regulation, you may request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs[8].

## 2. 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.

You have adapted this information requirement by using a weight of evidence approach under Annex XI, Section 1.2.

In support of your adaptation, you have provided the following study records with analogue substances:

(i) OECD 471 In vitro gene mutation study in bacteria. Nite, 2018 on the substance 4-(1,1,3,3-tetramethylbutyl)phenol. EC 205-426-2

(ii) OECD 471 In vitro gene mutation study in bacteria. Nite, 2018 on the substance 2-(p-Hydroxyphenyl)-2-methylpropane. EC 202-679-0

In your comments you have provided documentation to support the read-across from the

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

aforementioned analogue substances. Based on the presented sources of information, you argue that the available data gives sufficient information to conclude that the Substance does not induce gene mutations in bacteria.

As explained under *Appendix on Reasons common to several requests* (section 1, weight of evidence), the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Relevant information that can be used to support a weight of evidence adaptation for the information requirement of Section 8.4.1 at Annex VII must include similar information as obtained in a study in accordance with OECD TG 471: Detection and quantification of gene mutations (base pairs, substitution or frame shift) in cultured bacteria including data on the number of revertant colonies; and data provided on 5 bacterial strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101).

The sources of information (i. and ii.) provide relevant information on detection and quantification of gene mutation in 5 bacterial strains (TA1535, TA1537, TA 100, TA 98 and *E. coli* WP2 uvrA).

In general, the reliability of sources of information (i) and (ii) is significantly affected by the deficiencies identified and explained in the above *Appendix on Reasons common to several requests, section 1, subsection I.1*.

In addition, sources of information (i) and (ii) have the following deficiencies:

According to Article 13(4) of REACH, toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP). According to Article 141(2), Article 13 applies from entry into application of the REACH Regulation on 1 June 2008, thus ensuring this quality and reliability standard for the evaluation of data for REACH registration purposes. The studies you provided were conducted according to the OECD TG 471, but the GLP compliance is not specified. In the absence of this information, ECHA must consider the reliability of the data for the conclusions on *in vitro* gene mutation study in bacteria compromised.

In summary, the sources of information (i) and (ii) have significant reliability issues and cannot contribute to the conclusion on the potential of the Substance to cause genotoxicity in bacteria.

*Conclusion*

It is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in *in vitro* gene mutation study in bacteria. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

<u>Possibility for data sharing for studies not involving vertebrate animals</u>

The jointly submitted registration for the Substance (lead registrant [redacted]) contains data which is relevant for this endpoint. In accordance with Title III of the

REACH Regulation, you may request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs[9].

### 3. Growth inhibition study aquatic plants

Growth inhibition study aquatic plants (Annex VII, Section 9.1.2) is a standard information requirement in Annex VII to REACH.

You have adapted this information requirement according to Annex VII, Section 9.1.2, Column 2 with the following justification:"*There are mitigating factors indicating that aquatic toxicity is unlikely to occur as the substance is highly insoluble in water also having the partition coefficient Log Kow value 10.8.*

We have assessed this information and identified the following issue:

Under Section 9.1.2., Column 2, Annex VII to REACH, the study may be omitted if aquatic toxicity is unlikely, for instance if the Substance is highly insoluble in water. ECHA Guidance R.7.8.5 explains that there is no scientific basis to define a cut off limit for solubility below which toxicity is unlikely. Therefore, the justification must demonstrate very low water solubility and low likelihood to cross biological membranes. For the latter, the indicators used for low likelihood of a high bioaccumulation potential (ECHA Guidance R.11, Figure R.11-4) must be considered, including:

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

Unless it can reliably be demonstrated that aquatic toxicity is unlikely to occur, the Substance must be considered as poorly water soluble.

You have provided a water solubility estimate for the Substance of 0.052 mg/L (based on a non-GLP compliant spectrophotometric method).

You have however not provided in your dossier:

- reliable information to show that log Kow > 10;
- any other physico-chemical indicators as listed above to support hindered uptake;
- relevant toxicokinetic studies in mammals or toxicity studies in mammals and birds or aquatic species to support that no significant uptake occurs following exposure to the Substance.

Therefore you have not demonstrated that toxicity is unlikely to occur and your adaptation is rejected. The Substance must be considered as poorly water soluble.

In your comments to the draft decision you have continued to rely on the adaptation of column 2 Annex VII.

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

In addition, to strengthen the justification you have used a high log Kow (> 10) and low water solubility to indicate low likelihood of the Substance to cross the biological membranes.

We have assessed this information against the criteria indicated in the original draft decision and identified the following issue:

As already explained in Section A.1 above, the predicted log Kow value >10 you reported is not reliable as the QSAR documentation supporting this prediction has not been provided. Moreover, in your comments you provide an additional brief summary of an experimental study with the Substance according to OECD TG 117 indicating log Kow of 7.4, which refutes your claim that Substance has a high log Kow value > 10. Additionally, no new data on other physico-chemical indicators to support hindered uptake or relevant toxicokinetic data to indicate that no significant uptake of the Substance occurs have been provided.

In conclusion, you have not reliably demonstrated the low likelihood of Substance to cross biological membranes, as explained previously, and therefore your adaptation is rejected.

*Study design*

The substance is difficult to test due to the low claimed water solubility (0.052 mg/L) and adsorptive properties (log Koc in range of 4.5550 – 6.7). OECD TG 201 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 201. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solutions.

<u>Possibility for data sharing for studies not involving vertebrate animals</u>

The registrants of the jointly submitted registration for the Substance (lead registrant [redacted] have data available that is relevant for this endpoint. In accordance with Title III of the REACH Regulation, you may request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs[10].

## 4. Long-term toxicity testing on aquatic invertebrates as requested in C.3.

Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.) is a standard information requirement in Annex VII to REACH. However, for poorly soluble substances, a long-term aquatic toxicity study on aquatic invertebrates (Annex IX, Section 9.1.5) must be considered (Annex VII, section 9.1.1, Column 2).

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

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

test material (ECHA Guidance R.7b, Section 7.8.5).

The Substance is poorly water soluble, because the water solubility is below 1 mg/L (you report the water solubility as 0.052 mg/L at 25 °C).

Therefore, long-term toxicity testing is needed to accurately define the hazard of the Substance.

The examination of the information provided, as well as the selection of the requested test and the test design are addressed under Section C.3.

Your comments on the draft decision are also addressed in that section.

## 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.

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

In support of your adaptation, you have provided the following study records with analogue substances:

(i) OECD 473 *In vitro* cytogenicity / chromosome aberration study in mammalian cells. Nite, 2018 on the substance 4-(1,1,3,3-tetramethylbutyl)phenol. EC 205-426-2

(ii) OECD 473 *In vitro* cytogenicity / chromosome aberration study in mammalian cells. OECD, 2000 on the substance 2-(p-Hydroxyphenyl)-2-methylpropane. EC 202-679-0

As explained in the above *Appendix on Reasons common to several requests* (section 1, weight of evidence), the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.4.2. at Annex VIII must include: Detection and quantification of cytotoxicity and the frequency of cells with structural chromosomal aberration(s) or the frequency of micronuclei in cultured mammalian cells *(in vitro*) or in mammals (*in vivo*). A level of information on these aspects similar to that obtained from in vitro/in vivo chromosomal aberration tests (OECD TG 473/OECD TG 474) or in vitro/in vivo micronucleus tests (OECD TG 487/OECD TG 475) is required.

The sources of information provide relevant information on detection and quantification of gene mutation in cultured mammalian cells. However, these sources of information have the following deficiencies affecting their reliability.

In general, the reliability of sources of information (i) and (ii) is significantly affected by the deficiency identified and explained in the above *Appendix on Reasons common to several requests*.

In addition, sources of information (i) and (ii) have the following deficiencies:

Regarding source of information (i), testing in accordance with OECD TG 473 or OECD TG 487, respectively[11], requires that among others the following specifications/conditions have to be met:

- Data on the cytotoxicity and the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures must be reported.

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

In your dossier you have the following information regarding source of information (i):

- There is no data on cytotoxicity for the treated and control cultures.

Without this information it is not possible to conclude if the cells were exposed to the analogue substance nor what was the real exposure concentration.

According to Article 13(4) of REACH, toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP). According to Article 141(2), Article 13 applies from entry into application of the REACH Regulation on 1 June 2008, thus ensuring this quality and reliability standard for the evaluation of data for REACH registration purposes. The study (ii) you provided was conducted according to the OECD TG 473, but the GLP compliance is not specified. In the absence of this information, ECHA must consider the reliability of the data for the conclusions on in vitro cytogenicity compromised.

Moreover, in your dossier, regarding source of information (ii), the documentation provided does not allow to assess its reliability, and therefore ECHA agrees with your assessment that the information has to be disregarded in the assessment (Klimisch score 4).

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

*Conclusion*

It is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated *in vitro* cytotoxicity study in mammalian cells or in vitro micronucleus study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

*Information on the study design*

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

In your comments to the draft decision you agreed to perform the *in vitro* cytogenicity study.

Possibility for data sharing for studies not involving vertebrate animals

The jointly submitted registration for the Substance (lead registrant: [redacted]) contains data which is relevant for this endpoint. In accordance with Title III of the REACH Regulation, you may request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs[12].

## 2. 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

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

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. of REACH (weight of evidence).

In support of your adaptation, you have provided the following study records with analogue substances:

(i) OECD 416. Two-generation reproductive toxicity. TOXICOLOGY AND APPLIED PHARMACOLOGY 10, 362-374, 1967 on the substance Benzenamine, N-phenyl- EC 204-539-4

(ii) OECD 422. Combined Repeat Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test in the Rat. [redacted], 2006 on the substance: Benzenamine, N-phenyl-, reaction products with isobutylene and ,4,4-trimethylpentene. EC 270-485-3

(iii) OECD 422. Combined Repeat Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test in the Rat. [redacted], 2007 on the substance: Benzenamine, N-phenyl-, reaction products with 4-octyl-N-(4-octylphenyl)aniline. EC 202-965-5

(iv) OECD 422. Combined Repeat Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test in the Rat. [redacted], 2006; SPL Project Number [redacted] on the substance: Benzenamine, N-phenyl-, reaction products with isobutylene and ,4,4-trimethylpentene. EC 606-029-0

Based on the presented sources of information, you argue that the available data gives sufficient information to conclude that the substance does not induce reproductive toxicity.

As explained in the above *Appendix on Reasons common to several requests* (section 1, weight of evidence), the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.7.3 at Annex VIII includes similar information that is produced by the OECD TG 421/422. At general level, it includes information on the following key elements: 1) sexual function and fertility, 2) toxicity to offspring, and 3) systemic toxicity.

*Sexual function and fertility*

Sexual function and fertility on both sexes must include information on mating, fertility, gestation (length), maintenance of pregnancy (abortions, total resorptions), parturition, lactation, organ weights and histopathology of reproductive organs and tissues, litter sizes, nursing performance and other potential aspects of sexual function and fertility.

The sources of information (i.-iv.) provide relevant information on all aspects of the sexual function and fertility. However, the reliability of sources of information is significantly affected by the deficiency identified and explained in the above *Appendix on Reasons common to several requests* (*section 1, subsection I.1*) and cannot contribute to the conclusion on this key element.

*Toxicity to offspring*

Information on pre- and perinatal developmental toxicity reflected by litter sizes, postimplantation loss (resorptions and dead foetuses), stillborns, and external malformations, postnatal developmental toxicity reflected by survival, clinical signs and body weights of the pups (or litters), and other potential aspects related to pre-, peri- and postnatal developmental toxicity observed up to postnatal day 13.

The sources of information (i.-iv.) provide relevant information on toxicity to the offspring. However, they are affected by significant reliability issues as explained above under *Sexual function and fertility.* Therefore, they cannot contribute to the conclusion on this key element.

*Systemic toxicity*

Systemic toxicity must include information on clinical signs, survival, body weights, food consumption, haematology, clinical chemistry, organ weights and histopathology of non-reproductive organs and other potential aspects of systemic toxicity in the parental generation up to postnatal day 13.

The sources (i.-iv.) provide relevant information on systemic toxicity. However, they are affected by significant reliability issues as explained above under *Sexual function and fertility*. Therefore, they cannot contribute to the conclusion on this key element.

Taken together, the studies (i.-iv.) provide relevant information on the key elements: sexual function and fertility, toxicity to offspring and systemic toxicity . However, due to significant reliability issues, they cannot contribute to the conclusion on the potential of the Substance to cause reproductive toxicity.

*Conclusion*

It is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in OECD TG 421/422. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

*Information on study design*

A study according to the test method OECD TG 421/422 should be performed in rats with oral[13] administration of the Substance.

<u>Information on data sharing for studies involving vertebrate animals</u>

The jointly submitted registration for the Substance (lead registrant: [redacted]) contains data which is relevant for this endpoint. In accordance with Title III of the REACH Regulation, you must request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs[14].

[13] ECHA Guidance R.7a, Section R.7.6.2.3.2.
[14] https://echa.europa.eu/regulations/reach/registration/data-sharing

### 3. Long-term toxicity testing on fish as requested in C.4.

Short-term toxicity testing on fish is a standard information requirement in Annex VIII to REACH. However, for poorly soluble substances, a long-term aquatic toxicity study on fish (Annex IX, Section 9.1.6) must be considered (Annex VIII, section 9.1.3, Column 2).

Poorly water soluble substances require longer time to reach steady-state conditions. As a result, short-term tests do not give a true measure of toxicity for this type of substances and long-term testing is required. A substance is regarded as poorly water soluble if, for instance, it has a water solubility below 1 mg/L or below the detection limit of the analytical method of the test material (ECHA Guidance R.7b, Section 7.8.5).

The Substance is poorly water soluble, because the water solubility is below 1 mg/L (you report the water solubility as 0.052 mg/L at 25 °C).

Therefore, long-term toxicity testing is needed to accurately define the hazard of the Substance.

The examination of the information provided, as well as the selection of the requested test and the test design are addressed under Section C.4.

Your comments on the draft decision are also addressed in section C.4.

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

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

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

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

In support of your adaptation, you have provided the following study records with analogue substances:

(i) OECD 422. Combined Repeat Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test in the Rat. [redacted] 2006 on the substance: Benzenamine, N-phenyl-, reaction products with isobutylene and ,4,4-trimethylpentene, EC 270-485-3;

(ii) 14d Repeated dose oral toxicity study in rats. Dhinsa et al, 2006 on the substance: Benzenamine, N-phenyl-, reaction products with 4-octyl-N-(4-octylphenyl)aniline, EC 606-029-0.

In addition, in your comments, you refer also to the following study records, which are included in your technical dossier for a different information requirement (i.e. screening for reproductive/developmental toxicity):

(iii) OECD 422. Combined Repeat Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test in the Rat. [redacted] 2007 on the substance: Benzenamine, N-phenyl-, reaction products with 4-octyl-N-(4-octylphenyl)aniline. EC 202-965-5

(iv) OECD 422. Combined Repeat Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test in the Rat. [redacted], 2006; SPL Project Number [redacted] on the substance: Benzenamine, N-phenyl-, reaction products with isobutylene and ,4,4-trimethylpentene. EC 606-029-0

(v) OECD 422. Combined Repeat Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test in the Rat. [redacted], 2006; SPL Project Number [redacted] on the substance: Benzenamine, N-phenyl-, reaction products with isobutylene and ,4,4-trimethylpentene. EC 606-029-0

Moreover, in your comments to the draft decision you have invoked also an adaptation of Annex IX, Section 8.6.2, Column 2, based on the proposed classification as STOT RE "H373".

We have assessed all information and identified the following issues:

A. As explained in the above *Appendix on Reasons common to several requests* (section 1, weight of evidence), the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.6.2 at Annex IX includes, at general level, information on systemic toxicity in intact, non-pregnant and young adult males and females from: 1) in-life observations, 2) blood chemistry, 3) organ and tissue toxicity. Information should address effects on the following physiological systems: circulatory system, digestive/excretory system, endocrine system, immune system, integumentary system, musculoskeletal system, nervous system, renal/urinary system, reproductive system, and respiratory system.

*In-life observations*

In life observations must include information on survival, body weight development, clinical signs, functional observations, food/water consumption and other potential aspects of in life observations on the relevant physiological systems (circulatory, digestive/excretory, integumentary, musculoskeletal, nervous, renal/urinary, and respiratory).

The sources of information (i) to (v) do include relevant information on in life observations. The lack of sensory reactivity to various stimuli and functional observations of the animals in study (ii) limits the relevance of this source for conclusions similar to those from investigations under OECD TG 408.

However, the reliability of the studies (i) to (v) is significantly affected by a number of essential shortcomings: Primarily, in both studies the exposure duration was significantly shorter than that of 90 days required by OECD TG 408. You indicated an exposure duration of 54 and 14 days respectively. The exposure duration is an essential element for the conclusions drawn, because the effects observed in a long-term study provide more certainty compared to a shorter term study.

In addition, in study (ii) less than 10 animals per sex per test dose group were used. The statistical power of the information therefore does not meet the standard for each test group set by OECD TG 408, that is 20 animals (10 males + 10 females) for each test group.

Finally, ECHA agrees to your assessment regarding sources of information (i) to (iv) that the documentation provided in fact does not allow to assess its reliability (Klimisch score 4).

Because of the significant shortcomings regarding the reliability of the information (exposure duration, statistical power of study (ii) and the deficient documentation of the studies) the sources of information cannot contribute to conclusions on the key element In life observations similar to investigations in accordancd with OECD TG 408.

*Blood chemistry*

Information on blood chemistry must include haematological (full-scale) and clinical chemistry analysis (full-scale), and other potential aspects related to blood chemistry to address relevant physiological systems (circulatory digestive/excretory, endocrine, immune, musculoskeletal, and renal/urinary)

Source of information (ii) cannot contribute relevant information on blood chemistry similar to information from a study according to OECD TG 408, because information on hematology and clinical biochemistry is missing.

In any case, all sources of information are affected by significant reliability issues as explained above under *in-life observations.* Therefore, they cannot reliably contribute to the conclusions on this key element either.

*Organ and tissue toxicity*

Organ and tissue toxicity must include information on terminal observations on organ weights, gross pathology and histopathology (full-scale) and other potential aspects related to organ and tissue toxicity to address relevant physiological systems (circulatory, digestive/excretory, endocrine, immune, integumentary, musculoskeletal, nervous, renal/urinary system, reproductive, and respiratory).

Both sources of information lack relevant information to allow for conclusions similar to those from investigations under OECD TG 408: The source of information (i) to (v) does not include ophthalmological examination. The source of information (ii), in addition, does not include pathology of sexual (male and female) organs, full detailed gross necropsy and subsequent histopathology of both types tissues.

All sources of information are further affected by significant reliability issues as explained above under *In-life observations.* Therefore, they cannot contribute to the conclusions on organ and tissue toxicity.

*Conclusion*
Considering all the above, the sources of information as indicated above provide information with limited relevance in particular to organ and tissue toxicity, and all of them are affected by significant reliability issues.

It is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 408 study with a design described in this decision. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

B. As provided in Annex IX, Section 8.6.2, Column 2, you may adapt the information requirement, provided you fulfil the following criterion, including:

- a reliable short-term toxicity study (28-day) is available and shows severe toxicity effects leading to the classification of the Substance, and where the NOAEL-90 days can be extrapolated for the same route of exposure.

In your comments you conclude ,based on the aforementioned repeated dose toxicity studies provided on the analogue substances, that the classification of the Substance should be changed from no classification to STOT RE "H373: may cause damage to organs through prolonged or repeated exposure". You indicate that this will be reflected in an upcoming dossier update. You consider that "*performing an OECD 408 study with the registered substance is not considered to be justifiable for animal welfare reasons (please refer to Annex IX, Section 8.6.2 of the REACH regulation)*".

For the reasons explained in the *Appendix on Reasons common to several requests* (section 1, *subsection I.1*), information provided with the analogue substances cannot be considered as reliable. Therefore, the proposed classification that you propose to apply, based on the repeated dose toxicity studies with these analogue substances, does not fulfil conditions of the adaptation under Annex IX, Section 8.6.2, Column 2, for the registered substance Consequently your adaptation is rejected.

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

*Information on the study design*

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

Referring to the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity, because there is no evidence that internal exposure would be higher via other routes.

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

Information on data sharing for studies involving vertebrate animals

The jointly submitted registration for the Substance (lead registrant: [redacted] contains data which is relevant for this endpoint. In accordance with Title III of the REACH Regulation, you must request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs[15].

## 2. Pre-natal developmental toxicity study in one species

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

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

In support of your adaptation, you have provided the following study records:

(i) OECD 414. Prenatal Developmental Toxicity Study in rabbits. Edwards, J.A. et al. 1984 on the substance: Benzenamine, N-phenyl. EC 204-539-4

(ii) OECD 422. Combined Repeat Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test in the Rat. [redacted], 2006 on the substance: Benzenamine, N-phenyl-, styrenated / 4-(1-phenylethyl)-N-[4-(1-phenylethyl)phenyl]aniline. EC 270-485-3

(iii) OECD 422. Combined Repeat Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test in the Rat. [redacted] 2007 on the substance: Benzenamine, N-phenyl-, reaction products with 4-octyl-N-(4-octylphenyl)aniline. EC 202-965-5

Based on the presented sources of information, you argue that the available data gives sufficient information to conlude on the 1st species prenatal developmental toxicity.

As explained in the above *Appendix on Reasons common to several requests* (section 1, weight of evidence) the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

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

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

*Prenatal developmental toxicity*

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

Sources of information (ii) and (iii) provide information on some of the elements of developmental toxicity, such as litter sizes, postnatal survival and growth of pups. However, they do not inform on structural malformations and variations (external, visceral and skeletal) as foreseen to be investigated in OECD TG 414. Therefore, they only provide limited information on this key element in general.

The source of information (i) covers all relevant aspects of the prenatal developmental toxicity aspect.

However, the reliability of these sources of information is significantly affected by the deficiencies identified and explained in the above *Appendix on Reasons common to several requests* (section 1, weight of evidence), and cannot contribute to the conclusion on this key investigation.

Finally, ECHA agrees to your assessment regarding sources of information (i) and (ii) that the documentation provided in fact does not allow to assess its reliability (Klimisch score 4), and that therefore it cannot contribute to the conclusion on this key element.

*Maternal toxicity*

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

All sources of information provide relevant information on maternal toxicity. However, the reliability of the sources of information (i-iii) is significantly affected by the deficiencies identified and explained in the above *Appendix on Reasons common to several requests* (section 1, weight of evidence), and therefore cannot contribute to the conclusion on this key investigation.

*Maintenance of pregnancy*

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

All sources of information provide relevant information on maintenance of pregnancy.

However, the reliability of the sources of information (i-iii) is significantly affected by the deficiencies identified and explained in the above *Appendix on Reasons common to several requests* (section 1, weight of evidence), and cannot contribute to the conclusion on this aspect.

*Conclusion*

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

to be investigated in OECD TG 414, prenatal developmental toxicity study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

*Information on the study design*

A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species with oral[13] administration of the Substance.

In your comments to the draft decision you agreed to perform the Pre-natal developmental toxicity (PNDT) study.

Information on data sharing for studies involving vertebrate animals

The jointly submitted registration for the Substance (lead registrant: [redacted] contains data which is relevant for this endpoint. In accordance with Title III of the REACH Regulation, you must request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs[16].

### 3. Long-term toxicity testing on aquatic invertebrates

Long-term toxicity testing on aquatic invertebrates is a standard information requirement in Annex IX to the REACH Regulation.

You have provided the following information:

*A.* In your dossier, you have provided an adaptation where you consider that testing for this endpoint is scientifically unjustified since "*there are mitigating factors indicating that aquatic toxicity is unlikely to occur as the substance is highly insoluble in water also having the partition coefficient Log Kow value 10.8".*

*B.* In your comments to the draft decision you have provided an adaptation according to Annex XI, Section 1.2. of REACH (weight of evidence).

In support of your adaptation, you have provided the following study records with analogue substances:

i. EPA OPPTS 850.1300 (Daphnid Chronic Toxicity Test) study on an analogue substance 4-(1,1,3,3-Tetramethylbutyl)phenol, CAS: 140-66-9, EC: 205-426-2;

ii. OECD TG 211 study on an analogue substance 2,2-bis(4'-hydroxyphenyl)-4-methylpentane, CAS: 6807-17-6, EC: 401-720-1.

In your comments you conclude that: "*Considering above studies of read across analogues [..] using weight of evidence approach, the Substance it is likely to be toxic to aquatic invertebrates, and hence, considered to be classified in ''aquatic chronic category 2'' as per CLP classification criteria.* You consider that "*the results were found to be comparable and enough to support the classification of the target chemical*" and in consequence "*the information requirement for the long term toxicity to aquatic invertebrates (Annex IX) is fulfilled*".

We have assessed this information and identified the following issues:

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

*A. Adaptation with no legal basis*

In order to adapt this information requirement, an adaptation has to comply with specific rules for adaptation in accordance with column 2 of Annex IX, Section 9.1. or with the general rules of Annex XI to REACH.

The reasons that you provided for the waiving of the standard information requirement do not form any adaptation option as foreseen in the legal text.

As specified in Annex IX, Section 9.1., Column 2, a long-term toxicity study on aquatic invertebrates must be performed unless the Chemical Safety Assessment (CSA) demonstrates that risks towards the aquatic compartment arising from the manufacture and use of the Substance are controlled (Annex I, Section 0.1). The justification must be documented in the Chemical Safety Report (CSR).

In particular, the CSA must take into account the following elements to support that long-term aquatic toxicity testing is not required:

- all relevant hazard information from your registration dossier,
- the outcome of the risk characterisation in relation to the manufacture and/or uses of the Substance,
- the outcome of the assessment for identification of persistent, bioaccumulative and toxic (PBT) and/or very persistent and very bioaccumulative (vPvB) substances including information on relevant degradation products and constituents (Article 14 (3) in conjunction with Annexes I and XIII) present in concentration at or above 0.1% (w/w) (ECHA Guidance, Chapter R.11).

Poorly water soluble substances require longer time to reach steady-state conditions. As a result, short-term tests do not give a true measure of toxicity for this type of substances and the long-term test is required. A substance is regarded as poorly water soluble if, for instance, it has a water solubility below 1 mg/L or below the detection limit of the analytical method of the test material (ECHA Guidance R.7b, Section 7.8.5).

As the Substance is poorly water soluble, without the long-term toxicity studies your CSA does not demonstrate that the risks of the Substance are adequately controlled for the freshwater compartment.

*B. Adaptation according to Annex XI, Section 1.2. for Long-term toxicity testing on aquatic invertebrates*

As explained under *Appendix on Reasons common to several requests* (section 1, weight of evidence), 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.
Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 9.1.5 at Annex IX includes similar information that is produced by the OECD TG 211. This includes:

1. the reproductive output of *Daphnia sp.*, and

2. the survival of the parent animals during the test, and

3. the time to production of the first brood.

Concerning key investigation (1) *the reproductive output of Daphnia sp.*

Sources of information (i) and (ii) provide relevant information covering this key investigation by reporting the effect values based on reproduction. However, all these sources of information have the following deficiencies affecting their reliability.

The reliability of source of information (i) and (ii) is significantly affected by the deficiency identified and explained under *Appendix on Reasons common to several requests* (section 1, weight of evidence).

In addition, the reliability of sources of information (i) and (ii) is also affected by the following issue:

Testing in accordance with OECD TG 211 requires that the following specifications/conditions must be met:

- The full record of the daily production of living offspring during the test is provided;
- The number of deaths among the parent animals is provided and the day on which they occurred;
- Use of a reliable analytical method for the quantification of the test material in the test solutions with reported specificity, recovery efficiency, precision, limits of determination (i.e. detection and quantification) and working range must be available;
- 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;

In your comments to the draft decision you have provided/not provided the following information:

- You have not provided for any of the studies detailed information on the full record of the daily production of living offspring during the test;
- For none of the studies you provided the number of deaths among the parent animals and the day on which they occurred
- You have not provided details on the analytical methods used, such as LOQ and LOD, for any of the studies;
- For study (i) you have specified that analytical monitoring was performed and the results are reported based on measured concentrations. For study (ii) the results are reported based on nominal concentrations, but you did not specify that analytical monitoring was performed and no data has been provided on the measured concentration of the substance during the test.

The absence of information on living offspring and number of deaths among the parent animals does not allow an independent assessment of the validity criteria. Furthermore, although for study (i) you have reported results based on measured concentrations, you have not provided performance parameters of the analytical method, hence no independent assessment can be made. Furthermore, for study (ii) you have reported results based on nominal concentrations but you have not provided data on analytical monitoring to prove that the test material was maintained within 20 % during the test. Lacking all this information,

sources (i) and (ii) cannot be considered as reliable/or have low reliability.

Taken together, even though the sources of information (i) and (ii) as indicated above may provide relevant information, their reliability is affected significantly, therefore, they cannot contribute to the conclusion of the reproductive output of *Daphnia sp*.

Concerning key investigation (2) *survival of parent animal during the test*.

The sources of information (i) and (ii) do not provide any information covering this key investigation. Therefore, they do not provide information that would contribute to the conclusion on these key investigation.

Concerning key investigation (3) *the time to produe the first brood*.

Sources of information (i) and (ii) do not provide any information covering this key investigation. Therefore, they do not provide information that would contribute to the conclusion on these key investigation.

Taken together, sources of information as indicated above, provide information on reproductive output of *Daphnia sp.* but information on survival of parental animals and on time of production of first brood is not provided. Furthermore, the information provided on reproduction is not reliable. Therefore, your proposed conclusion that the substance is hazardous and should be classified *in ''aquatic chronic category 2'' as per CLP classification criteria* is unsupported.

*Conclusion*

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

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

*Study design*

The Substance is difficult to test, as already explained above. OECD TG 211 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. To this end, you must conduct chemical analysis to demonstrate that the selected approach permit to maximize exposure. In addition, due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. Methods capable of identifying gross changes in the composition of WAFs with time are required. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 211. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solutions.

## 4. Long-term toxicity testing on fish

Long-term toxicity testing on fish is a standard information requirement in Annex IX to the REACH Regulation.

You have provided the following information:

*A.* In your dossier, you have provided an adaptation where you consider that testing for this endpoint is scientifically unjustified since "*there are mitigating factors indicating that aquatic toxicity is unlikely to occur as the substance is highly insoluble in water also having the partition coefficient Log Kow value 10.8".*

B. In your comments to the draft decision you have provided an adaptation according to Annex XI, Section 1.2. of REACH (weight of evidence).

In support of your adaptation, you have provided the following study records with analogue substances:

i. OECD TG 210 study on an analogue substance 4-(1,1,3,3-Tetramethylbutyl)phenol, CAS: 140-66-9; EC: 205-426-2;

ii. EPA Methods for Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians (1975) study on an analogue substance N-1,3-dimethylbutyl-N'-phenyl-p-phenylenediamine, CAS: 793-24-8, EC: 212-344-0.

In your comments you conclude that: "*Considering above studies of read across analogues [..] using weight of evidence approach, the Substance it is likely to be toxic to fish, and hence, considered to be classified in ''aquatic chronic category 1'' as per CLP classification criteria.* You consider that "*the results were found to be comparable and enough to support the classification of the target chemical*" and in consequence "*the information requirement for the long term toxicity to aquatic fish (Annex IX) is fulfilled*".

We have assessed this information and identified the following issues:

*A. Adaptation with no legal basis*

In order to adapt this information requirement, an adaptation has to comply with specific rules for adaptation in accordance with column 2 of Annex IX, Section 9.1. or with the general rules of Annex XI to REACH.

The reasons that you provided for the waiving of the standard information requirement do not form any adaptation option as foreseen in the legal text.

As specified in Annex IX, Section 9.1., Column 2, a long-term toxicity study on fish must be performed unless the Chemical Safety Assessment (CSA) demonstrates that risks towards the aquatic compartment arising from the manufacture and use of the Substance are controlled (Annex I, Section 0.1). The justification must be documented in the Chemical Safety Report (CSR).

In particular, the CSA must take into account the following elements to support that long-term aquatic toxicity testing is not required:

- all relevant hazard information from your registration dossier,

- the outcome of the risk characterisation in relation to the manufacture and/or uses of the Substance,
- the outcome of the assessment for identification of persistent, bioaccumulative and toxic (PBT) and/or very persistent and very bioaccumulative (vPvB) substances including information on relevant degradation products and constituents (Article 14 (3) in conjunction with Annexes I and XIII) present in concentration at or above 0.1% (w/w) (ECHA Guidance, Chapter R.11).

Poorly water soluble substances require longer time to reach steady-state conditions. As a result, short-term tests do not give a true measure of toxicity for this type of substances and the long-term test is required. A substance is regarded as poorly water soluble if, for instance, it has a water solubility below 1 mg/L or below the detection limit of the analytical method of the test material (ECHA Guidance R.7b, Section 7.8.5).

As the Substance is poorly water soluble, without the long-term toxicity studies your CSA does not demonstrate that the risks of the Substance are adequately controlled for the freshwater compartment.

*B. Adaptation according to Annex XI, Section 1.2. for Long-term toxicity testing on fish*

As explained under *Appendix on Reasons common to several requests* (section 1, weight of evidence), 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.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 9.1.6 at Annex IX includes similar information that is produced by the OECD TG 210. This includes:

1. the stage of embryonic development at the start of the test, and
2. hatching of fertilized eggs and survival of embryos, larvae and juvenile fish, and
3. the appearance and behaviour of larvae and juvenile fish, and
4. the weight and length of fish at the end of the test.

Concerning key investigation (1) *the stage of embryonic development at the start of the test*, and key investigation (4) *the weight and length of fish at the end of the test*.

Sources of information (i) and (ii) do not provide any information covering these key investigations. Therefore, they do not provide information that would contribute to the conclusion on these key investigations.

Concerning key investigation (2) *hatching of fertilized eggs and survival of embryos, larvae and juvenile fish*.

Source of information (i) does not provide any information covering this key investigation. Source of information (ii) provides partial information on this key investigation as only survival of juvenile fish is reported. Information on hatching of fertilized eggs and survival of embryos and larvae is not provided, since the study was performed with developed fish (length 40.1 mm and weight 1.3 g). However, the reliability of source of information (ii) is significantly affected by the deficiency identified and explained under *Appendix on Reasons common to several requests*, (section 1, weight of evidence).

Altogether, the provided study (ii) cannot be considered a reliable source of information that could contribute to the conclusion on this key investigation.

Concerning key inverstigation (3) *the appearance and behaviour of larvae and juvenile fish*.

Source of information (i) does not provide any information covering this key investigation. For the source of information (ii), you mention that test fishes have been observed for abnormal behaviour but you do not specify neither the outcome of the observation nor the developmental stage of the fish.

However, as explained under point (2) above, the reliability of the source of information (ii), is significantly affected. Therefore, source of information (ii) cannot contribute to the conclusion on this key investigation.

Regarding source of information (i), as explained above it does not provide any information covering any of the key parameters investigated by the required study based on the information provided in your comments. Furthermore, the reliability of source of information (i) is significantly affected by the deficiency identified and explained under *Appendix on Reasons common to several requests* (section 1, weight of evidence).

Taken together, sources of information as indicated above, provide some information on long-term toxicity to fish (i.e. survival and behaviour of juvenile fish in source of information (ii)). However, essential parts of information of the dangerous property is lacking (stage of embryonic development at the start of the test, hatching of fertilized eggs and survival of embryos and larvae, appearance of larvae and juvenile fish, behaviour of larvae, weight and length of fish at the end of the test). Furthermore, the information provided on survival and behaviour of juvenile fish is not reliable. Therefore, your proposed conclusion that the substance is hazardous and should be classified *in ''aquatic chronic category 1'' as per CLP classification criteria* is unsupported.

*Conclusion*

Accordingly, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 210 study.

Therefore, your adaptation is rejected and the information requirements is not fulfilled.

*Study design*

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

The Substance is difficult to test as already explained above. OECD TG 210 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 210. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate

that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

5. **Soil simulation testing and**
6. **Sediment simulation testing**

Soil simulation testing and sediment simulation testing are standard information requirements at Annex IX to REACH.

You have adapted the standard information requirement by using a Qualitative or Quantitative structure-activity relationship ((Q)SAR) under Annex XI, Section 1.3.

You have provided a calculated values for these endpoints. You have reported an estimation of the half-life in soil and sediment based on EPISuite software ([redacted] – estimated, 2018). You report the half-life of the Substance to be 360 days in soil and 1620.833 days in sediment.

However, for the reasons explained in the *Appendix on Reasons common to several requests* regarding the assessment of the QSAR adaptations (section 2), your adaptation is rejected.

In your comments to the draft decision, you indicated your intention to update the dossier with a QSAR Model Reporting Format (QMRF) to support the EPI suite estimation for half-life in soil and sediment. Since you did not provide any such data in your comments, the data gaps remain.

Based on the above, the information you provided does not fulfil the information.

*Study design*

Under Annex XIII, the information must be based on data obtained under conditions relevant for the PBT/vPvB assessment. Therefore:

- You must perform the OECD TG 307 test using four soils representing a range of relevant soils (*i.e.* varying in their organic content, pH, clay content and microbial biomass).

- You must perform the OECD TG 308 test using two sediments. One sediment should have a high organic carbon content (2.5-7.5%) and a fine texture, the other sediment should have a low organic carbon content (0.5-2.5%) and a coarse texture.

- You must perform the tests at the temperature of 12 °C, the average environmental temperature for the EU (ECHA Guidance R.16, Table R.16-8). Performing the tests at this temperature is in line with the applicable test conditions of the OECD TG 309.

- The reference temperature for providing results is 12°C for surface water environment and 9°C for marine environment. Therefore, the degradation half-life for the Substance, even if measured in any other temperature, would still need to be corrected to the temperature of 12°C using Arrhenius equation (ECHA Guidance R.11 and R.7b, Section R.7.9.4.1).

Non-extractable residues (NER) must be quantified in all simulation studies. The reporting of results must include a scientific justification of the used extraction procedures and solvents. By default, total NER is regarded as non-degraded Substance. However, if reasonably justified and analytically demonstrated a certain part of NER may be differentiated and quantified as

irreversibly bound or as degraded to biogenic NER. Such fractions could be regarded as removed when calculating the degradation half-life(s) (ECHA Guidance R.11).

## 7. Identification of degradation products (Annex IX, Section 9.2.3.)

Identification of the degradation products is a standard information requirement at Annex IX of REACH.

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

Therefore, this information requirement is not met.

This information is required for the purpose of the PBT/vPvB assessment (Annex I, Section 4) and the risk assessment (Annex I, Section 6) of the Substance.

In your comments to the draft decision, you agree to perform the study with the Substance.

*Study selection and design*

You must obtain this information while performing the simulation studies requested in this decision (requests C.5 to C.7). You must provide a scientifically valid justification for any other method you have used for identification of the transformation/degradation products.

Identity, stability, behaviour, and molar quantity of the degradation/ transformation products relative to the Substance must be evaluated and reported, when analytically possible. In addition, degradation half-life, potential for bioaccumulation and toxicity of the transformation/degradation product must be investigated.

## 8. Bioaccumulation in aquatic species

Bioaccumulation in aquatic species, preferably in fish, is a standard information requirement at Annex IX to REACH.

You have sought to adapt this information requirement based on Annex XI, Section 1.3 and you have provided:

- QSAR prediction for the Substance based on Bioconcentration factor (v12.1.0.50374) (Bioconcentration factor (BCF) by ACD, 2018)
- QSAR prediction for the Substance based on PaDEL descriptors (BCF: The Fish Bioconcentration Factor from OPERA (OPEn saR App) models, 2017)
- QSAR prediction for the 4-(1,1,3,3-Tetramethylbutyl)phenol (EC 205-426-2) (Bioaccumulation- Aquatic or sediment, U.S. National Library of medicine, 2017)

However, for the reasons explained in the *Appendix on Reasons common to several requests* regarding the assessment of the QSAR adaptations (section 2), your adaptation is rejected.

Based on the above, the information you provided does not fulfil the information.

In your comments to the draft decision, you seek to adapt the above mentioned standard information requirements according to Annex XI, Section 1.2. of REACH (weight of evidence).

In support to your adaptation, you have referred to:

i. QSAR prediction for the Substance based on Bioconcentration Factor from the Chemspider database;
ii. an OECD TG 305 C study on a proposed analogue substance 1,4-benzenediamine, n-(dimethylphenyl)-n'-(methylphenyl) (CAS: 70290-05-0)

Based on this, you argue that this newly available data gives sufficient information to build the weight of evidence approach and to conclude on the bioaccumulation potential in aquatic species and to support classification of the Substance. Thus you request ECHA to remove this request from the decision.

We have assessed this information and identified the following issues:

As explained under *Appendix on Reasons common to several requests*, (section 1, weight of evidence), 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.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 9.3.2 at Annex IX must provide information on at least one of the following key parameters, obtained from an aquatic species and measured in whole body of the test organisms:

1. the uptake rate constant ($k_1$) and loss rate constants including the depuration rate constant ($k_2$),
2. the steady-state bioconcentration factor ($BCF_{SS}$),
3. the kinetic bioconcentration factor ($BCF_K$),
4. the dietary biomagnification factor (BMF).

Neither of the sources of information (i) and (ii) provide information on key parameters (1), (3) or (4) above.

*Concerning key parameter (2) the steady-state bioconcentration factor ($BCF_{SS}$):*

The sources of information (i) and (ii) may provide relevant information on steady-state bioconcentration factor ($BCF_{SS}$) .

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

*A. Regarding source of information (i) QSAR prediction:*

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) and a QSAR Prediction Reporting Format (QPRF) are required to establish the scientific validity of the model, to verify that the Substance falls within the

applicability domain of the model, and to assess the adequacy of the prediction for the purposes of classification and labelling.

You have not provided any documentation for the QSAR predictions. In particular, you have not included a QMRF and a QPRF in your technical dossier.

In the absence of documentation your prediction cannot be considered a reliable source of information that could contribute to the conclusion on the steady-state bioconcentration factor ($BCF_{SS}$).

*B. Regarding source of information (ii) OECD 305 C on analogue substance*

The reliability of source of information (ii) is significantly affected by the deficiency identified and explained under *Appendix on Reasons common to several requests*, section 1.

In addition, the reliability of this source of information is also affected by the following issue:

A study must fulfil the requirements of the corresponding OECD test guideline (Article 13(3) of REACH), in this case OECD TG 305. Therefore, the following must be documented:

- test conditions including:
  - information on test procedure and test design,
  - method of preparation of stock solutions and frequency of renewal,
  - description of any pre-treatment,
  - results of any demonstration of the ability of test fish to live in the water, water quality within test vessels;
- test results including:
  - information on mortality of the control fish and the fish in each exposure chamber,
  - information on any adverse effects observed,
  - the lipid content measured at least before the beginning and at the end of the uptake phase and the method used for its determination,
  - individual fish wet weights and total lengths for all sampling intervals are provided, and be linked to the analysed chemical concentration for that individual. The data are used to correct the BCF for growth dilution;
  - tabulated test material concentration data in individual fish and water (including mean values for test group and control, standard deviation and range, if appropriate) for all sampling times are provided;

In your comments, you have reported the results for 3 picks detected during the test and analysed by LC/MS method, but you have not reported any information on the parameters listed above. In the absence of the information to be reported the reliability of the test cannot be assessed.

Taken together, even if the sources of information (i) and (ii) may provide information on one of the key parameters necessary to be investigated for this information requirement (the steady-state bioconcentration factor ($BCF_{SS}$)), their reliability is affected significantly.

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 property foreseen to be under the corresponding endpoints. Therefore, your adaptation is rejected.

*Study design*

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

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

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

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

## 9. Effects on soil micro-organisms

Effects on soil micro-organisms is a standard information requirement in Annex IX to REACH.

You have provided an adaptation for this endpoint where you consider that: "*Based on the use pattern of the substance there will be no intentional release into the terrestrial compartment. According to Column 2 of Annex IX of the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) legislation if direct and indirect exposure of soil is unlikely, a toxicity to soil microorganisms study does not need to be conducted, therefore this endpoint has been waived*."

As specified in Annex IX Section 9.4, Column 2, testing for the effects on soil micro-organisms must be performed unless direct and indirect exposure of the soil compartment is unlikely.

Regarding the likelihood of exposure to soil, the substance has a low claimed water solubility of 0.052 mg/L and high adsorption coefficient (log Koc in range of 4.5550 – 6.7) indicating adsorptive properties. Furthermore, based on the uses reported in the technical dossier, ECHA considers that such uses are reported for which the likelihood of indirect soil exposure cannot be excluded e.g. Environmental Release Category (ERC) 8a and 8d. ECHA therefore considers that you have not demonstrated that indirect soil exposure is unlikely.

As the conditions for adapting this information requirement are not fulfilled - likelihood of indirect exposure of the Substance to the soil cannot be excluded – your adaptation is rejected.

In your comments to the draft decision, you agree to perform the study with the Substance.

Therefore, the information requirement is not fulfilled.

## 10. Long-term toxicity to terrestrial invertebrates

Short-term toxicity to terrestrial invertebrates is a standard information requirement in Annex IX to REACH.

You have adapted this information requirement based on Annex IX, Section 9.4., Column 2 with the following justification: "*Based on the use pattern of the substance there will be no intentional release into the terrestrial compartment. According to Column 2 of Annex IX of the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) legislation if direct and indirect exposure of soil is unlikely, a toxicity to soil microorganisms study does not need to be conducted, therefore this endpoint has been waived*".

As specified in Annex IX Section 9.4, Column 2, short-term toxicity testing on terrestrial invertebrates must be performed unless direct and indirect exposure of the soil compartment is unlikely. However, for substances that have a high potential to adsorb to soil or that are highly persistent, the effect of long-term exposures must be estimated for the hazard assessment (ECHA Guidance R.7c, Table R.7.11-2, and Column 2 of Section 9.4 of Annex IX).

Regarding the likelihood of exposure to soil, based on the uses reported in the techical dossier, ECHA considers that such uses are reported for which the likelihood of indirect soil exposure cannot be excluded, e.g., ERC 8a and 8d. ECHA therefore considers that you have not demonstrated that indirect soil exposure is unlikely. Moreover, based on the information you provided, the Substance is adsorptive (log Koc in range of 4.5550 – 6.7) and potentially P/vP (20% degradation in 28 days, OECD TG 301B).

As indicated above, due to the uses of the Substance for which likelihood of indirect exposure of the Substance to the soil cannot be excluded, and due to the properties of the Substance, long-term terrestrial toxicity studies are necessary to assess the hazards.

In your comments to the draft decision, you agree to perform the study with the Substance.

Therefore, the information requirement is not fulfilled.

### 11. Long-term toxicity to terrestrial plants

Short-term toxicity to terrestrial plants is a standard information requirement in Annex IX to REACH.

You have adapted this information requirement based on Annex IX, Section 9.4., Column 2 with the following justification: "*Based on the use pattern of the substance there will be no intentional release into the terrestrial compartment. According to Column 2 of Annex IX of the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) legislation if direct and indirect exposure of soil is unlikely, a toxicity to terrestrial plants study does not need to be conducted, therefore this endpoint has been waived*".

As specified in Annex IX, Section 9.4., Column 2, short-term toxicity to plants must be performed unless the direct and indirect exposure of the soil compartment is unlikely. However, for substances that have a high potential to adsorb to soil or that are highly persistent, the effect of long-term exposures must be estimated for the hazard assessment (ECHA Guidance R.7c, Table R.7.11-2, and Column 2 of section 9.4 of Annex IX). The effects on terrestrial organisms must be addressed for different taxonomic groups: invertebrates, soil micro-organisms and terrestrial plants.

Regarding the likelihood of exposure to soil, based on the uses reported in the techical dossier, ECHA considers that such uses are reported for which the likelihood of soil exposure cannot be excluded, e.g., ERC 8a and 8d. ECHA therefore considers that you have not demonstrated that indirect soil exposure is unlikely. Moreover, based on the information you

provided, the Substance is adsorptive (log Koc in range of 4.5550 – 6.7) and potentially P/vP (20% degradation in 28 days, OECD TG 301B).

As indicated above, due to the uses of the Substance for which the likelihood of indirect exposure of the Substance to the soil cannot be excluded, and due to the properties of the Substance, long-term terrestrial toxicity studies are necessary to assess the hazards.

In your comments to the draft decision, you agree to perform the study with the Substance.

Therefore, the information requirement is not fulfilled.

*Test design*

OECD TG 208 with six species or ISO 22030 is the preferred guideline to fulfil this information requirement. OECD guideline 208 (Terrestrial plants, growth test) considers the need to select the number of test species according to relevant regulatory requirements, and the need for a reasonably broad selection of species to account for interspecies sensitivity distribution. For long-term toxicity testing, ECHA considers six species as the minimum to achieve a reasonably broad selection. Testing shall be conducted with species from different families, as a minimum with two monocotyledonous species and four dicotyledonous species, selected according to the criteria indicated in the OECD 208 guideline.

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

### A. Test methods, GLP requirements and reporting

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

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

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[17].

### 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[18].

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

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

### A. Strategy for the PBT/vPvB assessment

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

In particular, you are advised to first conclude whether the Substance fulfils the Annex XIII criteria for P and vP, and then continue with the assessment for bioaccumulation. When determining the sequence of simulation degradation testing you are advised to consider the intrinsic properties of the Substance, its identified uses and release patterns as these could significantly influence the environmental fate of the Substance. You must revise your PBT assessment when the new information is available.

### B. Testing strategy for the terrestrial toxicity testing

You are advised to consult ECHA Guidance R.7c, (Section R.7.11.6) which describes the Integrated Testing Strategy for toxicity testing on terrestrial organisms.

**Appendix F: Procedure**

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

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

The compliance check was initiated on 4 September 2019.

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

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

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

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

**Appendix G: List of references - ECHA Guidance[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)[20]

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[21]

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

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

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

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

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

**Appendix H: Addressees of this decision and 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.