~~Confidential~~

Helsinki, 29 August 2022

**Addressees**
Registrant(s) of JS_242-894-7 as listed in the last Appendix of this decision

**Date of submission of the dossier subject to this decision**
22/07/2019

**Registered substance subject to this decision ("the Substance")**
Substance name: Propane-1,2-diyl dibenzoate
EC number: 242-894-7
CAS number: 19224-26-1

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

## DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***6 March 2025***.

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

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

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

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

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

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

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

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

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

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

**How to comply with your information requirements**

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

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

**Appeal**

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

**Failure to comply**

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Mike Rasenberg, Director of Hazard Assessment

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

**Appendix on Reasons common to several requests**

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

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

- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)
- Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)
- Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

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

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

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

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

A. **Predictions for (eco-)toxicological properties**

You have provided a read-across justification document in IUCLID Section 13.

In the dossier subject to this decision, you read-across between the structurally similar substance, oxydipropyl dibenzoate (Dipropylene Glycol Dibenzoate, DPGDB) EC 248-258-5 (CAS 27138-31-4) as source substance and the Substance (Propylene Glycol Dibenzoate, PGDB) as target substance.

In your comments to the draft decision, you attached an updated a read-across justification document with Appendices 1-7 covering structures and compositions, molecular descriptors and cheminformatics, physicochemical properties, ADME and toxicokinetics assessment, and comparison of the (eco)toxicological properties (based on summary matrices on the results).

In your comments to the draft decision, you propose additional source substances:

- Ethylene dibenzoate (Ethylene Glycol Dibenzoate, EGDB) EC 202-338-6 (CAS 94-49-5)
- Oxydiethylene Dibenzoate (Diethylene Glycol Dibenzoate, DEGDB) EC 204-407-6 (CAS 120-55-8)
- Benzoic acid (BA) EC 200-618-2 (CAS 65-85-0)

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

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

In line with the reasonings provided for (eco)toxicological predictions in the dossier subject to this decision, the updated read-across justification document provided the following reasoning for the prediction of (eco)toxicological properties:
*"Propane-1,2-diyl dibenzoate, Ethylene dibenzoate, Oxydiethylene dibenzoate and Oxydipropyl dibenzoate will exhibit similar environmental and (eco)toxicological effects due to their structural similarity and similar physicochemical properties."*

In your comments to the draft decision you also state that the main metabolite of the Substance is considered to be benzoic acid and that therefore a recently conducted OECD TG 443 study (with Cohort 1B extension to mate the Cohort 1B animals to produce the F2 generation, Cohorts 2A and 2B for developmental neurotoxicity, and Cohort 3 for developmental immunotoxicity) with benzoic acid is sufficient for addressing the reproductive toxicity potential of the Substance.

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

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

*Read-across hypothesis contradicted by existing data for reproductive and developmental toxicity*

Annex XI, Section 1.5. provides that "substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances. The ECHA Guidance[4] indicates that "*it is important to provide supporting information to strengthen the rationale for the read-across*". The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance. The observation of differences in the toxicological properties between the source substance(s) and the Substance would contradict the hypothesis that the properties of the Substance can be predicted from the data on the source substance. An explanation why such differences do not affect the read-across hypothesis needs to be provided and supported by scientific evidence.

As indicated above, your read-across hypothesis is based on the assumption that the structurally similar target and source substances cause the same type of effect(s).

The results of the information on reproductive toxicity obtained with the target and source substances vary. The OECD TG 422 study with the Substance indicates (slight) decrease in live birth index and a (small) increase in the number of offspring dying between birth and day 7 of age for the group receiving 1000 mg/kg/day, while no such effects on offspring were observed in the OECD TG 416 study on the source substances DPGDB and DEGDB.

In your comments you also indicate the availability of the OECD TG 443 study on the source substance BA. You did not attach any robust study summary or further details of this study in your comments to the draft decision but indicated your intention to spontaneously update your dossier to include the robust study summary of this study. In the absence of these information in your comments, ECHA cannot assess the study.

The available results from source substances DPGDB and DEGDB do not induce effects on

[4] Guidance on information requirements and chemical safety assessment (version 6.0, July 2017), Chapter R.6, Section R.6.2.2.1.f

fertility and offspring and therefore contradict the hypothesis because their toxicity profiles indicate lower toxicity than the Substance. However, the results of the lower tier OECD TG 422 study with the source substance EGDB appear not to contradict the hypothesis according to the data matrix summary attached to the comments to the draft decision.

In addition, the results of the information on repeated dose toxicity obtained with the target and source substances vary. OECD TG 422 and the OECD TG 408 studies on the target substance report myofibre degeneration/necrosis and increased relative and absolute pituitary weight in females, respectively. Neither of the effects were observed in the OECD TG 408 study conducted with the source substances DPGDB and DEGDB.

Neither your initial read-across justification with source substance DPGDB, nor the updated read-across justification attached to the comments to the draft decision and its additional source substances EGDB, DEGDB and BA, address these differences or explain why the differences would not be relevant in predicting properties of the Substance regarding reproductive toxicity and developmental toxicity.

ECHA acknowledges your comments to the draft decision noting there are adequate and robust OECD 414 studies for both rat and rabbit available for the source substances DEGDB and DPGDB that showed no developmental toxicity, and that there are no developmental toxicity studies available for the Substance.

Considering the above contradictions and incomplete information on the additional source studies, ECHA is unable to conclude its assessment on the updated read-across justifications and supporting information.

The available set of data on the target and source substances indicates differences in the toxicological properties of the substances. This contradicts your read-across hypothesis whereby the structurally similar target and source substances cause the same type of effect(s). Therefore you have not demonstrated and justified that the properties of the source substance(s) and of the Substance are likely to be similar despite the observation of these differences.

*Relevance of the supporting information for predictions of ecotoxicological properties*

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*".

In order to support your claim that your Substance and source substance(s) have similar properties for the ecotoxicological endpoints under consideration in the read-across approach, in the read-across justification document provided in the dossier subject to this decision, you refer to their physico-chemical and environmental fate properties and results of experimental studies available for the Substance and source substance on toxicity to algae and to micro-organisms (sludge).

Whilst this data set suggests that the substances may have similar physico-chemical and environmental fate properties, and toxicity to algae and to micro-organisms (sludge) these studies do not inform on the properties of the target and source substances that are relevant to short- and long-term toxicity to fish and aquatic invertebrates.

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

Accordingly, these pieces of information are not considered as relevant to support prediction of all the endpoints under consideration.

ECHA acknowledges your intentions to improve the ecotoxicological profile of the Substance and your plans to refine your read-across approach. As you indicated in the comments to the draft decision, this strategy relies essentially on data which is yet to be generated or still to be re-evaluate for its adequacy, therefore no conclusion on the compliance can currently be made.

Moreover, you should provide justification as to how information on short-term fish and aquatic invertebrates toxicity, and on algae toxicity is relevant for the prediction of toxicity to early life stages of fish (stage of embryonic development, hatching, abnormal appearance and behaviour, length and weight) and to the daphnids (the reproductive output of *Daphnia* sp. expressed as the total number of living offspring produced at the end of the test and the time to production of the first brood).

*Bias of the prediction*

In order to make an accurate prediction of ecotoxicological and toxicological properties all relevant information must be considered in the prediction. If not all information is considered in the read-across approach, bias can be introduced in the predictions which may result in an over/underestimation in the prediction (RAAF, 2017; Chapter 4.5.1.5.). Bias may be caused by incorrect/incomplete selection of source substance(s); or due to a particular selection of study(ies) performed on the source substance(s).

To justify the selection of source substances, you must provide documentation how the source substance(s) have been chosen, for example, what methods/tools have been used to map the field of potential source substance(s), which other substances have been considered and why they have been discarded (RAAF, 2017, Chapter 4.4.1.5 and 4.5.1.5). If there are structural analogue(s) not used as source substances and data show significantly different results for the properties to be predicted without any justification for setting aside these different results, then the proposed prediction are considered biased.

In the comments to the draft decision you propose results of the long-term toxicity studies with aquatic invertebrates and fish with source substance oxydipropyl dibenzoate (CAS 27138-31-4) to be read-across to the Substance. You have not provided any justification on the selection of this substance over other source substances noted in your justification document, including ethylene dibenzoate (CAS 202-338-6) for which information on long-term toxicity to fish and aquatic invertebrates is available, to be used to predict the properties of the Substance.

You have not justified why other source substances have not been considered.

Therefore, your predictions are biased and may underestimate the hazards of the Substance.

*Reliability of the supporting information for long-term aquatic toxicity*

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

Supporting information must include bridging studies to compare properties of the Substance and source substance.

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).

1. *(Q)SAR studies*

In the registration dossier you provided QSAR predictions of the short-term toxicity to fish for the Substance and for the source substance.

As noted below in the Section 2 of this Appendix, QSAR predictions of the short-term toxicity to fish for the Substance are not reliable, therefore they are not adequate to support your read-across hypothesis.

In the comments to the draft decision you note that actions, as listed in the sub-section on "*Relevance of the supporting information for predictions of ecotoxicological properties"* above*,* "*will negate the need for QSARs to be used to support the read-across*".

2. *Missing Robust Study Summaries*

For the time being, the data set reported in the technical dossier and the data you provided in the comments to the draft decision do not include relevant, reliable and adequate information for the Substance and of the source substances to support your read-across hypothesis.

In the comments to the draft decision, you refer to source studies done with the source substances by providing their respective results (i.e., effect concentrations derived from them for the test species and test duration used) as well as the test guideline numbers. You did not provide further information on them. Therefore, you have not provided detailed information on the methods, results and conclusions, allowing for an independent assessment of the reliability of the studies.

In the absence of such information outlined in points 1. and 2. above, the studies cannot be considered to provide an adequate and reliable coverage of the key parameters foreseen to be investigated in a study under to the corresponding OECD test guidelines.

You have not established that the Substance and the source substance are likely to have similar short-term aquatic toxicity. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

*Adequacy of source studies*

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

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

Where relevant adequacy of the studies with the source substance are addressed under endpoint specific requests in Appendices A-C below.

## B. Conclusions on the read-across approach

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

## 2. Assessment of your (Q)SAR adaptation under Annex XI, Section 1.3.

You seek to adapt the following standard information requirements by applying (a) (Q)SAR approach(es) in accordance with Annex XI, Section 1.3:

- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

ECHA has considered the scientific and regulatory validity of your (Q)SAR adaptation(s) in general before assessing the specific standard information requirements in the following appendices.

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

- results need to be adequate for the purpose of risk assessment or classification and labelling.

With regard to these conditions, we have identified the following issue:

Under ECHA Guidance R.6.1.3.4 a prediction is adequate for the purpose of classification and labelling and/or risk assessment when the model is applicable to the chemical of interest with the necessary level of reliability. ECHA Guidance R.6.1.5.3. specifies that, among others, the following condition must be met:

- the model predicts well substances that are similar to the substance of interest.

Your registration dossier provides the following information:

- the Substance is a multi-constituent with two stereoisomers present at equal concentrations;
- Short-term toxicity to fish and to aquatic invertebrates predictions by USEPA (Q)SAR ECOSAR (v1.11) for the Substance with prediction documentation (QPRF) attached for both;
- QPRF for the short-term toxicity to fish prediction indicating that "*the training set contains several alkyl monobenzoates and compounds with phenyl structures but no close structural analogues to propylene glycoldibenzoate(no alkyl dibenzoates)*" and that no stereochemical features were considered for the prediction;
- QPRF for the short-term toxicity to aquatic invertebrates prediction indicating that "*the training set contains compounds with phenyl and benzoate fragments (benzyl butyl phthalate) and propyl ester groups but no close structural analogues to propylene glycol benzoate (no aryl alkyl benzoates)*" and that no stereochemical features were considered for the prediction.

In respect of isomers the help file of ECOSAR v1.11 indicates the following: "***Isomers:*** *Three dimensional molecular properties or molecular conformation can be important as it relates to absorption, binding, and resulting toxicity potential of a chemical. Some QSAR models are unable to account for these three dimensional characteristics that in some cases can be important considerations since they can influence toxicokenetic (PBPK) processes. Often QSAR models do not distinguish between steroisomers, optical isomers, tautomers, or specific*

*conformations because they are built using simple one or two-dimensional descriptors only, as is the case with the ECOSAR model."*

The predictions for the Substance used as input are not reliable and you have not demonstrated that the model predicts well substances that are similar to the Substance because the used ECOSAR v1.11 cannot distinguish between stereoisomers of the Substance and there are no close structural analogues in the training sets of the used ECOSAR models. Therefore, you have not demonstrated that the prediction for the Substance is adequate for the purpose of classification and labelling and/or risk assessment.

Therefore, your adaptations are rejected.

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

### 1. Short-term toxicity testing on aquatic invertebrates

Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII to REACH (Section 9.1.1.).

You have provided the following information:

i. an adaptation under Annex XI, Section 1.3., supported by prediction of short-term toxicity to aquatic invertebrates by USEPA (Q)SAR ECOSAR (v1.11) for the Substance;

ii. an adaptation under Annex XI, Section 1.5., supported by OECD TG 202 study with the source substance (oxydipropyl dibenzoate, EC 248-258-5).

We have assessed this information and identified the following issues:

*Rejection of adaptation under Annex XI, Section 1.3.*

As explained in Appendix on Reasons common to several requests, Section 2 your adaptation under Annex XI, Section 1.3. is rejected.

*Rejection of adaptation under Annex XI, Section 1.5.*

As explained in Appendix on Reasons common to several requests, Section 1 your adaptation under Annex XI, Section 1.5. is rejected.

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

As mentioned in Appendix on Reasons common to several requests, if the grouping concept is applied then in all cases the results to be read-across should:

- have adequate and reliable coverage of the key parameters of the corresponding test methods, in this case OECD TG 202 and the OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test.

Therefore, the following specifications must be met:

- OECD GD 23 notes the option for estimation of results of aquatic toxicity studies on the basis of the 'loading rates' only for UVCB substances which are poorly soluble in water;
- the effect values can only be based on nominal or measured initial concentration if the concentration of the test material has been satisfactorily maintained within 20 % of the nominal or measured initial concentration throughout the test (see also ECHA Guidance R.7b, Section R.7.8.4.1).

Your registration dossier provides an OECD TG 202 study:

- with the following test material composition: source substance present at concentration of 89.4% and four impurities with concentrations from 4.98% to 0.28%;
- where the source substance, based on the results of analytical monitoring of exposure concentrations, was not maintained within 20% of the nominal concentration in all the test solutions and only the nominal concentration of 4.6 mg/l was maintained within 20 % of the measured initial concentration throughout the test;
- with results based on nominal loading rates/concentrations.

The Substance is difficult to test (solubility of 7.7 mg/L at 20 °C).

Based on the information provided in the registration dossier the source substance is not UVCB, therefore estimation of results of the study on the basis of the 'loading rates' is not acceptable. Furthermore, the results of the provided study should be based on the measured concentrations of the source substance.

Therefore, the provided study does not have adequate and reliable coverage of the necessary key parameters.

In the comments to the draft decision, you indicate that an OECD TG 202 study on the Substance is available and that you plan to provide this information in an update of your registration dossier. However, in your comments you have not included any new scientific information supported by adequate documentation (i.e., a robust study summary) that could address the information requirement.

On this basis the information requirement is not fulfilled.

*Study design*

The Substance is difficult to test due to the low water solubility (7.7 mg/L at 20 °C) and volatility (Henry's Law constant equal to 2.22 $Pa \cdot m^3/mol$). OECD TG 202 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e., measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 202. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

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

### 1. Short-term toxicity testing on fish

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

You have provided the following information:

i. an adaptation under Annex XI, Section 1.3., supported by prediction of short-term toxicity to fish by USEPA (Q)SAR ECOSAR (v1.11) for the Substance;
ii. an adaptation under Annex XI, Section 1.5., supported by:
    a. OECD TG 203 (key) study with the source substance (oxydipropyl dibenzoate, EC 248-258-5);
    b. OECD TG 203 (supporting) study with the source substance (oxydipropyl dibenzoate, EC 248-258-5);
    c. prediction of short-term toxicity to fish by USEPA (Q)SAR ECOSAR (v1.00) for the source substance (oxydipropyl dibenzoate, EC 248-258-5);
    d. prediction of short-term toxicity to fish by USEPA (Q)SAR ECOSAR (v1.11) for the Substance, as noted under point i. above.

We have assessed this information and identified the following issues:

*Rejection of adaptation under Annex XI, Section 1.3.*

As explained in Appendix on Reasons common to several requests, Section 2 your adaptation under Annex XI, Section 1.3. is rejected.

*Rejection of adaptation under Annex XI, Section 1.5.*

As explained in Appendix on Reasons common to several requests, Section 1 your adaptation under Annex XI, Section 1.5. is rejected.

On this basis, the information requirement is not fulfilled.

In the comments to the draft decision, you agree with the request.

*Study design*

OECD TG 203 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.1.

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

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

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

You have adapted the standard information requirement according to Annex XI, Section 1.5. Grouping of substances and read-across approach of REACH Regulation.

In support of this adaptation of the information requirement, you have provided the following information for this endpoint:

i. Prenatal developmental toxicity study in rat (2000) on source substance oxydipropyl dibenzoate (EC 248-258-5)
ii. Prenatal developmental toxicity study in rabbit (2018) on source substance oxydipropyl dibenzoate (EC 248-258-5)

In your comments to the draft decision you indicate the availability of further source study(ies) on oxydiethylene dibenzoate (EC 204-407-6) and a prenatal developmental toxicity study (in a first species) planned with ethylene dibenzoate (EC 202-338-6).

You provided an updated read-across justification document attached to your comments to the draft decision but did not provide further information (i.e. robust study summary for additional source studies).

ECHA assessed the above information according to the requirements of Annex XI, Section 1.5 of the REACH Regulation and identified the following issue(s):

As explained in the Appendix on Reasons common to several requests your adaptation under Annex XI, Section 1.5. is rejected and the information requirement is not fulfilled.

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral[6] administration of the Substance.

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

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

You have provided the following information:

i. an adaptation under Annex XI, Section 1.5., supported by OECD TG 211 study with the source substance (oxydipropyl dibenzoate, EC 248-258-5).

We have assessed this information and identified the following issues:

As explained in Appendix on Reasons common to several requests, Section 1 your adaptation under Annex XI, Section 1.5. is rejected.

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

As mentioned in Appendix on Reasons common to several requests, if the grouping concept is applied then in all cases the results to be read-across should have adequate and reliable coverage of the key parameters of the corresponding test methods, in this case OECD TG 211

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

and the OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test. Therefore, the following specifications must be met:

- the percentage of mortality of the parent animals (female *Daphnia*) in the control is ≤ 20% at the end of the test (validity criterion of OECD TG 211);
- the mean number of living offspring produced per surviving parent animal in the control is ≥ 60 at the end of the test (validity criterion of OECD TG 211);
- the full record of the daily production of living offspring during the test by each parent animal is provided;
- the number of deaths among the parent animals (if any) and the day on which they occurred is reported;
- the coefficient of variation for control reproductive output is reported.

The Substance is difficult to test (solubility of 7.7 mg/L at 20 °C).

Your registration dossier provides an OECD TG 211 with the source substance where information on the specifications, including fulfilment of validity criteria of OECD TG 211, listed above is not reported.

Based on the above, the reporting of the study is not sufficient to conduct an independent assessment of its reliability. Consequently, the results of the study are not adequate for the purpose of classification and labelling and/or risk assessment and cannot be used as the source study for the read-across approach.

In the comments to the draft decision, you indicate your intention to update the read-across adaptation submitted for the information requirement.

Your proposal for updating your read-across adaptation is addressed under Appendix on Reasons common to several requests.

Further, you indicate your intention to adapt this information requirement based on exposure considerations, according to Annex XI, Section 3 of REACH regulation.

In particular, you propose to conduct a full and comprehensive exposure assessment and risk characterisation to demonstrate lack of risk to the environment but provide no supporting information. You indicate your intention to provide it in the future update of your registration dossier.

The information in your comments is not sufficient for ECHA to make an assessment because you have only provided an intention to adapt without supporting information.

On this basis, the information requirement is not fulfilled.

*Study design*

OECD TG 211 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.1.

**2. Long-term toxicity testing on fish**

Long-term toxicity testing on fish is an information requirement under Annex IX to REACH (Section 9.1.6.).
ECHA understands that you have provided an adaptation under Annex XI, Section 1.5. with the following note "*This information will be submitted later based on ECHA communication/decision number TPE-D-2114465948-28-01/F received by the lead registrant*

*for Oxydipropyl dibenzoate (DPGDB; EC# 248-258-5) on April 10, 2019, requesting this study to be completed. This dossier for propylene glycol dibenzoate (PGDB) will be updated upon receipt of the final report from the lead registrant for Oxydipropyl dibenzoate (DPGDB; EC# 248-258-5). The justification for read across is presented as an attachment included in Section 13 of the IUCLID dossier."*

We have assessed this information and identified the following issues:

As explained in Appendix on Reasons common to several requests, Section 1 your adaptation under Annex XI, Section 1.5. is rejected.

In addition, the following endpoint-specific deficiency has been identified in your read-across adaptation:
You have provided no OECD TG 210 study with the source substance.

In the comments to the draft decision, you indicate your intention to update the read-across adaptation submitted for the information requirement.

Your proposal for updating your read-across adaptation is addressed under Appendix on Reasons common to several requests.

Further, you indicate your intention to adapt this information requirement based on exposure considerations, according to Annex XI, Section 3 of REACH regulation.

In addition, you propose a "*stepwise, tiered approach*" for generating further toxicity data. You provide the following information: "*if following completion the short-term endpoints, an Annex XI adaptation is not possible and there is still concern for the environment, an OECD 211 Daphnia reproduction study will be conducted. If the adaptation according to Annex XI is still not possible following conduct of the OECD 211, an OECD 210 Fish Early Life Stage test will be conducted as a last resort*".

In particular, you propose to conduct a full and comprehensive exposure assessment and risk characterisation to demonstrate lack of risk to the environment but provide no supporting information. You indicate your intention to provide it in the future update of your registration dossier.

The information in your comments is not sufficient for ECHA to make an assessment because you have only provided an intention to adapt without supporting information.

In the comments, you also refer to animal welfare considerations.

Minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under Column 2 nor under the general rules of Annex XI. Therefore, your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

*Study design*

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

OECD TG 210 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.1.

## 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[7].

### 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[8].

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

**Appendix E: 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 17 September 2020.

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

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

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment. No amendments were proposed.

Following tonnage band changes by registrants, the addressee list in Appendix G was updated and the corresponding requests to the highest REACH Annex were removed. The deadline was amended accordingly.

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 12 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

ECHA adopted the decision under Article 51(3) of REACH.

**Appendix F: List of references - ECHA Guidance[9] 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)[10]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[11]

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[12]

[9] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[10] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[11] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[12] 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.

ECHA Guidance on the Application of the CLP Criteria (Version 5.0 – July 2017), referred to as ECHA Guidance on the Application of the CLP Criteria

**Appendix G: Addressees of this decision and their corresponding information requirements**

You must provide the information requested in this decision for all REACH Annexes applicable to you.

| Registrant Name | Registration number | Highest REACH Annex applicable to you |
|---|---|---|
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

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.